APPENDIX E. TOXICOLOGICAL SUMMARY SHEETS

Copies of all 37 of the Toxicological Summary sheets can viewed below or can also be viewed online by clicking on the following link: Health Risk Limits SONAR Appendix E.
https://www.health.state.mn.us/communities/environment/risk/docs/rules/hrlsonar23appef.pdf

Toxicological Summary for: Acetone

CAS**: 67-64-1**

Synonyms: 2-propanone, propan-2-one, β-ketopropane, dimethyl ketone, dimethylformaldehyde, DMK

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 5,000 µg/L

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

$$= \frac{\text{(3.1 mg/kg-d) x (0.5)}^* \text{ x (1000 µg/mg)}}{\text{(0. 290 L/kg-d)}^{**}}$$

$$= 5,344 \text{ rounded to } \textbf{5,000 µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.

[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 312/100 = 3.1 mg/kg-d (F344N rats)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	1485 mg/kg-d (NOAEL, (NTP, 1991) (Dietz, 1991))
Dose Adjustment Factor (DAF):	0.21 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 1485 mg/kg-d x 0.21 = 312 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	10 for intraspecies variability, and 10 for database uncertainty (lack of adequate developmental studies, including multigeneration studies, and neurotoxicity studies). No interspecies UF for toxicodynamics differences was applied as acetone plays a role in normal human metabolism and it is not anticipated that humans will be more sensitive to acetone than laboratory animals.
Critical effect(s):	Increased kidney weight (consistent with nephropathy seen in rats during the subchronic duration)
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 5,000 μg/L

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

$$= \frac{\text{(2.1 mg/kg-d) x (0.2)}^* \text{ x (1000 μg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 5,675 rounded to 6,000 μg/L

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 207/100 = 2.1 mg/kg-d (F344N rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	900 mg/kg-d (NOAEL (NTP, 1991) (Dietz, 1991))
Dose Adjustment Factor (DAF):	0.23 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 900 mg/kg-d x 0.23 = 207 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	10 for intraspecies variability, and 10 for database uncertainty (lack of adequate developmental studies, including multigenerational studies, neurotoxicity studies, and hematological studies). No interspecies UF of toxicodynamics differences was applied as acetone plays a role in normal human metabolism and it is not anticipated that humans will be more sensitive than laboratory animals.
Critical effect(s):	Nephropathy, increased relative kidney weight, changes in blood parameters (increased leukocytes, increased mean corpuscular hemoglobin, increased mean cell volume, decreased erythrocyte count, and decreased reticulocyte counts)
Co-critical effect(s):	Increased relative kidney weight, increased relative liver weight, increased incidence of hepatocellular hypertrophy, tubular degeneration in the kidneys
Additivity endpoint(s):	Hematological (blood) effects; Hepatic (liver) system; Renal (kidney) system

The Subchronic nHBV must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 5000 μg/L. Additivity endpoints: Renal (kidney) system

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = 3,000 µg/L

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

$$= \frac{(0.69 \text{ mg/kg-d}) \text{ x } (0.2)^* \text{ x } (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 3,066 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 207/300= 0.69 mg/kg-d (F344N rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	900 mg/kg-d (NOAEL, (NTP, 1991) (Dietz, 1991), subchronic exposure)
Dose Adjustment Factor (DAF):	0.23 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 900 mg/kg-d x 0.23 = 207 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	10 for intraspecies variability, and 10 for database uncertainty (lack of adequate developmental studies, including multigenerational studies, neurotoxicity studies, and hematological studies), and 3 for subchronic to chronic extrapolation. No interspecies UF of toxicodynamics differences was applied as acetone plays a role in normal human metabolism and it is not anticipated that humans will be more sensitive than laboratory animals.
Critical effect(s):	Nephropathy, increased relative kidney weight, changes in blood parameters (increased leukocytes, increased mean corpuscular hemoglobin, increased mean cell volume, decreased erythrocyte count, and decreased reticulocyte counts)
Co-critical effect(s):	Increased relative kidney weight, increased relative liver weight, increased incidence of hepatocellular hypertrophy, tubular degeneration in the kidneys
Additivity endpoint(s):	Hematological (blood) effects; Hepatic (liver) system; Renal (kidney) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not classified
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (moderate)

Summary of Guidance Value History:

In 1993/1994, MDH derived a chronic noncancer Health Risk Limit (HRL) of 700 µg/L. In 2011, MDH derived short-term, subchronic, and chronic noncancer Health Based Values (HBV) of 9,000, 8,000, and 4,000 µg/L, respectively. These HBVs were adopted as HRLs in 2011. In 2017, MDH re-evaluated the noncancer HRLs, resulting in new noncancer short-term, subchronic, and chronic HBVs of 5,000, 5,000, and 3,000 µg/L, respectively. The short-term, subchronic, and chronic values are lower as a result of 1) using MDH's most recent risk assessment methodology, including Human Equivalence Doses (HED), and 2) rounding to one significant digit. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	Yes	Yes	Yes	Yes
Effects observed?	-	No[1]	Yes[2]	Yes[3]	Yes[4]

Comments on extent of testing or effects:

[1] No immunotoxicity effects were observed in drinking water studies of mice at doses more than 200 fold higher than the chronic reference dose. Changes in thymus weight were observed in rats at doses nearly 300 fold higher than the short-term reference dose, but were not accompanied by other immunotoxicity effects.

[2] Offspring exposed to acetone through inhalation during gestation experienced decreased fetal weight and increased incidence of fetal malformations. During another inhalation study in mice, no developmental effects were seen in the offspring. A database uncertainty factor was incorporated into the derivation of short-term, subchronic, and chronic reference doses due to

lack of adequate multigenerational and developmental studies assessing developmental effects after oral exposure.

[3] Male rats exposed to acetone through drinking water for 13 weeks experienced an increase in relative testes weight, decreased caudal and epididymis weights, depressed sperm motility, and increased incidence of abnormal sperm at doses greater than 1000 fold higher than the chronic reference dose. No reproductive effects were seen when male rats were exposed to acetone in drinking water for six weeks prior to mating. A database uncertainty factor was incorporated into the derivation of short-term, subchronic, and chronic reference doses due to lack of an adequate multigenerational study assessing reproductive effects after oral exposure.

[4] A couple of neurotoxicity studies were conducted for oral exposure to acetone with only one reporting slightly altered vision in rats at a dose greater than 200 fold higher than the chronic reference dose. Excessive salivation was also observed in rats exposed to acetone in drinking water at a dose greater than 800 fold higher than the chronic reference dose, but it is unclear whether this is a neurological response or due to gavage administration. Narcotic-like effects have been reported after humans have inhaled or ingested acetone which include lethargy, minimal responsiveness, and comatose condition. A database uncertainty factor was incorporated into the derivation of short-term, subchronic, and chronic reference doses due to lack of adequate data addressing neurotoxic effects after oral exposure. Neurotoxicity observed in animals following inhalation of acetone include: inhibition of avoidance behavior, effects on fixed ratio and fixed interval response rates, and central nervous system depression measured by tests of unconditioned performance and reflexes.

Resources Consulted During Review:
Agency for Toxic Substances and Disease Registry (ATSDR) (1994). "Toxicological profile for acetone." from https://www.atsdr.cdc.gov/toxprofiles/tp21.pdf

Agency for Toxic Substances and Disease Registry (ATSDR) (2011). "Addendum to the Toxicological Profile   for Acetone." From https://www.atsdr.cdc.gov/toxprofiles/acetone_addendum.pdf

California Environmental Protection Agency. "OEHHA Toxicity Criteria Database." from https://oehha.ca.gov/chemicals

California State Water Resources Control Board (2011). "Compilation of Water Quality Goals." from http://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/

International Toxicity Estimates for Risk (ITER). from https://toxnet.nlm.nih.gov/newtoxnet/iter.htm

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."
From   https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH) (2017). "MDH Health Risk Assessment Methods to
    Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference
    Doses. (May 2011, revised 2017)." From
    https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedref
    guide.pdf

National Toxicology Program (NTP) (1988). Inhalation Developmental Toxicity Studies: Acetone
    (CAS #67-64-1) in Mice and Rats (abstract only).

National Toxicology Program (NTP) (Dietz, D. (1991). "NTP Report on the Toxicity Studies of
    Acetone in F344/N Rats and B6C3F1 Mice (Drinking Water Studies)." from
    https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox003.pdf

Syracuse Research PhysProp Database. from http://www.syrres.com/esc/physdemo.htm

U.S. Environmental Protection Agency (US EPA). "ACToR: Aggregated Computational Toxicology
    Resource" from http://actor.epa.gov/

US Environmental Protection Agency (EPA). "Office of Drinking Water " Drinking Water
Standards. from
        http://www.epa.gov/waterscience/criteria/drinking/dwstandards.pdf

US Environmental Protection Agency (US EPA) (1997). Health Effects Assessment Summary
    Tables (HEAST)

U.S. Environmental Protection Agency (US EPA) (2011). "Recommended Use of Body Weight 3/4
as the Default Method in Derivation of the Oral Reference Dose." from
        http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3
    Update 2019. Retrieved from
    https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

U.S. Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS)
    (2003). "Toxicological review of Acetone (CAS No. 67-64-1)." from
    https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=128.

Toxicological Summary for: Aminomethylphosphonic acid

CAS: **1066-51-9**

Synonyms: AMPA, 1-Aminomethylphosphonic acid; 1-Aminomethylphosphonate

NOTE: AMPA (CAS# 1066-51-9), the glyphosate metabolite/degradate, is not to be confused with AMPA, the neurotoxic agent, which is a different chemical with CAS# 74341-63-2 with the same acronym. The neurotoxic AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) is a specific agonist for the AMPA receptor where it mimics the effects of the neurotransmitter glutamate.

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

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

Subchronic Non-Cancer Health Based Value (nHBV_{Subchronic}) = 3,000 µg/L

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

$$= \frac{(0.96 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 2,594 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5

Reference Dose:	HED/Total UF = 0.96 mg/kg-d (CD rats)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	400 mg/kg-d (administered dose NOAEL, Estes et al. 1979, Monsanto unpublished test report, as cited in WHO 1997, 2005)
Dose Adjustment Factor (DAF):	0.24 (Body weight scaling, male rats (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 400 mg/kg-d x 0.24 = 96 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 (lack of multigenerational reproductive/developmental study)
Critical effect(s):	Decreased body weight gain, bladder urothelial hyperplasia, increased serum lactate dehydrogenase
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health Based Value (nHBV_{Chronic}) = 1,000 µg/L

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

$$= \frac{(0.32 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ μg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 1{,}422 \text{ rounded to } \mathbf{1{,}000 \text{ μg/L}}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5

Reference Dose:	HED/Total UF = 0.32 mg/kg-d (CD rats)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	400 mg/kg-d (administered dose NOAEL, Estes et al. 1979, Monsanto unpublished subchronic study, as cited in WHO 1997, 2005)
Dose Adjustment Factor (DAF):	0.24 (Body weight scaling, male rats (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 400 mg/kg-d x 0.24 = 96 mg/kg
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (lack of multigenerational reproductive/development study), 3 for subchronic-to-chronic extrapolation
Critical effect(s):	Decreased body weight gain, bladder urothelial hyperplasia, increased serum lactate dehydrogenase
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not Classified
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: **No**

Summary of Guidance Value History:
There are no current MDH HBVs or HRLs for AMPA. MDH developed a non-cancer pesticide rapid assessment value of 2,000 μg/L in 2016. The 2017 nHBV$_{Subchronic}$ is higher than the 2016 Pesticide Rapid Assessment due to use of a different intake rate. The 2017 nHBV$_{Chronic}$ is lower than the 2016 Pesticide Rapid Assessment Value due to use of a different relative source contribution and addition of a database uncertainty factor in the RfD derivation. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	No	No
Effects observed?	-	-[1]	Yes[2]	-	-[3]

Comments on extent of testing or effects:

[1]AMPA has not been tested for immunotoxicity via oral ingestion. However, AMPA was negative for dermal sensitization in guinea pig tests.

[2]Decreased fetal body weight was reported in a gestational exposure study in rats at a dose which also produced overt maternal toxicity (including decreased bw gain, food consumption, soft stools, hair loss). This dose was 230 times higher than the subchronic RfD and findings were inconsistent with another developmental study that reported no maternal or fetal effects at a dose approximately 240 times higher than the subchronic RfD.

[3]AMPA has not been tested for neurotoxicity. However, there were no clinical signs of neurotoxicity in any of the short-term or subchronic tests in rats or dogs (i.e., no twitching, salivation or seizures, etc.).

Resources Consulted During Review:

California State Water Resources Control Board (2010). Monitoring Strategies for Chemicals of Emerging Concern (CECs) in Recycled Water. Recommendations of a Science Advisory Panel.

European Chemicals Agency (ECHA). (2015). "Final Addendum to the Renewal Assessment Report. Public Version. Glyphosate. Risk Assessment provided by the rapporteur Member State Germany and co-rapporteur Member State Slovakia. October 2015."   Retrieved 9/2/2016

European Food Safety Authority (EFSA). (2015). "Conclusion on the Peer Review of the Pesticide Risk Assessment of the Active Substance Glyphosate. EFSA Journal 2015; 13(11): 4302 (107 pp)." from https://www.efsa.europa.eu/en/efsajournal/pub/4302.

International Agency for Research on Cancer (IARC). (2015). "IARC Monographs, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos." from http://monographs.iarc.fr/ENG/Monographs/vol112/index.php.

Kolpin, D. W., E. M. Thurman, E. A. Lee, M. T. Meyer, E. T. Furlong and S. T. Glassmeyer (2006). Urban contributions of glyphosate and its degradate AMPA to streams in the United States. *Sci Total Environ* 354(2-3): 191-197.

McGuire, M. K., M. A. McGuire, W. J. Price, B. Shafii, J. M. Carrothers, K. A. Lackey, et al. (2016). Glyphosate and aminomethylphosphonic acid are not detectable in human milk. *Am J Clin Nutr* 103(5): 1285-1290.

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.", from https://www.leg.mn.gov/archive/sonar/SONAR-03733.pdf#page=2.

Minnesota Department of Health (MDH). (2017). "MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017)." from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

Minnesota Department of Health (MDH). (2016). "Pesticide Rapid Assessment Results Table."   Retrieved 9/1/2016, from
https://www.health.state.mn.us/communities/environment/risk/guidance/dwec/rapidpest.html.

Roustan, A., M. Aye, M. De Meo and C. Di Giorgio (2014). Genotoxicity of mixtures of glyphosate and atrazine and their environmental transformation products before and after photoactivation. *Chemosphere* 108: 93-100.

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. Environmental Protection Agency - Office of Research and Development. (1988). "Recommendations for and Documentation of Biological Values for Use in Risk Assessment." from
http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855.

U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). "Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose." from
https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose.

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

U.S. Environmental Protection Agency (EPA). (1996). "Glyphosate; AMPA Toxicology Studies; ID#: 285984; Miscellaneous Toxicology Data; Metabolite of Glyphosate; P.C. Code: 103601. Memo dated Feb. 1, 1996."

U.S. Environmental Protection Agency (EPA). (2004). "Glyphosate; Notice of Filing a Pesticide Petition to Establish a Tolerance for a Certain Pesticide in or on Food. Federal Register. Volume 69 No. 159, August 18, 2004, p. 51304." from https://www.regulations.gov/document?D=EPA-HQ-OPP-2004-0160-0001.

U.S. National Library of Medicine. (2010). "TOXNET Chemical Carcinogenesis Research Information System (CCRIS). 1-Aminomethylphosphonic acid."   Retrieved 9/1/16, from https://toxnet.nlm.nih.gov/cgi-bin/sis/search2.

World Health Organization (WHO). (1997). "Pesticide Residues in Food - 1997. Aminomethylphosphonic Acid (AMPA). Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. Lyon, France. September 22 to October 1, 1997." from http://www.inchem.org/documents/jmpr/jmpmono/v097pr04.htm.

World Health Organization (WHO). (2005). "Glyphosate and AMPA in Drinking Water. Background document for the development of WHO Guidelines for Drinking-water Quality. WHO/SDE/WSH/03.04/97. (updated June 2005)."   Retrieved 9/2/2016, from http://www.who.int/water_sanitation_health/dwq/chemicals/glyphosateampa290605.pdf

World Health Organization (WHO). (2006). "Pesticide Residues in Food - 2004: Evaluations 2004, Part II - Toxicological. Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. Chapter on Glyphosate, pp. 95-169." from http://webcache.googleusercontent.com/search?q=cache:LBCdm7K4LUMJ:apps.who.int/pesticide-residues-jmpr-database/Document/164+&cd=1&hl=en&ct=clnk&gl=us.

World Health Organization (WHO). (2008). "Guidelines for Drinking Water Quality - Volume 1: Recommendations. Third edition, incorporating first and second addenda." from http://www.who.int/water_sanitation_health/dwq/fulltext.pdf

World Health Organization (WHO). (2016). "Pesticide Residues in Food 2016. Special Session of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR). FAO Plant Production and Protection Paper 227. ISSN 2070-2515. ISBN 978-92-5-109246-0." from http://www.fao.org/3/a-i5693e.pdf

Toxicological Summary for: Benzo[a]pyrene

CAS: **50-32-8**
Synonyms: BaP, Benzo[pqr]tetraphene, 3,4-Benz[a]pyrene, Benzo(d,e,f)chrysene

Acute Non-Cancer Health Based Value (nHBV$_{Acute}$) = Not Derived

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 0.5 µg/L

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

$$= \frac{(0.00031 \text{ mg/kg-d}) \times (0.5)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

= 0.53 rounded to **0.5 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	Administered Dose/Total UF = 0.0917/300 = 0.00031 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	0.0917 mg/kg-d (BMDL$_{1SD}$, Chen, 2012)
Dose Adjustment Factor (DAF):	Not calculated due to temporal differences in human and rodent brain developmental stages
Human Equivalent Dose (HED):	Not applicable
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	10 for interspecies differences, 10 for intraspecies variability, and 3 for database uncertainty due to lack of adequate developmental and multigenerational studies that include exposure throughout gestation and early life.
Critical effect(s):	Functional test of neurological changes in neonatal rats (elevated maze)
Co-critical effect(s):	Functional test of neurological changes in neonatal rats (open field and water maze testing)
Additivity endpoint(s):	Developmental, Nervous system

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 0.5 µg/L

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

$$= \frac{(0.00031 \text{ mg/kg-d})^{\#} \text{ x } (0.2)^{*} \text{ x } (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 0.83 \text{ rounded to } 0.8 \text{ µg/L}$$

[#]No Subchronic RfD was calculated due to study limitations. Therefore, the developmental-based Short-term RfD was applied to the subchronic duration.
[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

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 0.5 µg/L. Additivity endpoints: Developmental and Nervous system

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = nHBV$_{Short-term}$ = 0.5 µg/L

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

$$= \frac{(0.00031 \text{ mg/kg-d}) \text{ x } (0.2)^{*} \text{ x } (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 1.37 \text{ rounded to } 1 \text{ µg/L}$$

[#]No Chronic RfD was calculated due to study limitations. Therefore, the developmental-based Short-term RfD was applied to the chronic duration.
[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

The Chronic nHBV must be protective of the short-term exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 0.5 µg/L. Additivity endpoints: Developmental and Nervous system

Cancer Health Based Value (cHBV) = 0.1 µg/L

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

$$= \frac{(1E-5) \text{ x } (1000 \text{ µg/mg})}{[(1 \text{ x } 10^{*} \text{ x } 0.155 \text{ L/kg-d}^{**} \text{x } 2) + (1 \text{ x } 3^{*} \text{ x } 0.040 \text{ L/kg-d}^{**} \text{x } 14) + (1 \text{ x } 1^{*} \text{ x } 0.042 \text{ L/kg-d}^{**} \text{x } 54)] / 70}$$

$$= 0.099 \text{ rounded to } \mathbf{0.1 \text{ µg/L}}$$

Cancer classification:	Carcinogenic to humans (US EPA, 2017a)
Slope factor (SF):	1 (mg/kg-d)$^{-1}$ (Forestomach and oral cavity tumors in female mice, Beland and Culp, 1998 aci US EPA, 2017a)
Source of cancer slope factor (SF):	US EPA, 2017a
Tumor site(s):	Digestive tract, liver, skin, lung

Volatile: Yes (low)

Summary of Guidance Value History:

A cancer HBV of 0.05 µg/L was derived in 1995. Acute, Short-term, Subchronic, and Chronic nHBVs of 2, 0.3, 0.3, and 0.3 µg/L were derived in 2012, along with a cancer HBV of 0.06 µg/L. In 2018, MDH derived nHBVs of 0.5 µg/L for Short-term, Subchronic, and Chronic durations and a cHBV of 0.1 µg/L. The 2018 values changed as a result of: 1) using MDH's most recent risk assessment methodology; 2) incorporating more recent toxicological information; and 3) rounding to one significant digit. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the final 2018 HBVs.

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?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Endocrine effects were assessed following laboratory exposures to BaP. Changes in testosterone, estradiol, and estrous cycles were noted at doses far in excess (greater than 1,800 times) of the Short-term RfD.

[2] Immune system effects were seen at high doses in comparison to the short-term RfD. Changes in immune cell populations and decreased thymic weights were noted in multiple studies at doses greater than 5,000 times higher than the Short-term RfD.

[3] A developmental neurobehavioral effect forms the basis of the Short-term RfD. Altered blood pressure and heart rate following in utero exposure were reported at doses 400-800 times higher than the Short-term RfD. Other observed developmental toxicities include decreased weight gain in early life, stillbirth, and birth defects. These effects occurred at the lowest dose tested, however, these doses are greater than 30,000 times higher than the Short-term RfD. A database uncertainty factor of 3

was applied in deriving the Short-term RfD in order to address outstanding concerns regarding developmental effects.

[4] Most reproductive effects were noted at doses much higher than the Short-term RfD. Histopathological changes in the cervix and sperm alterations of mice were observed at the lowest doses tested in two studies (300-400 times higher than the Short-term RfD). In other studies, reduced fertility, decreased ovary weights, and decreased follicle number were reported at doses over 1,800 times higher than the Short-term RfD. A database uncertainty factor of 3 was applied in deriving the Short-term RfD in order to address concerns regarding reproductive effects that would be tested in a standard multigenerational study.

[5] Neurodevelopmental effects form the basis of the Short-term RfD. Neurotoxicity was also observed after high dose acute exposure. Three acute oral studies observed suppressed motor activity and other changes at doses nearly 2,000 times higher than the Short-term RfD. A study in adult animals reported alterations in mobility during tail suspension testing at a dose 10 times higher than the Short-term RfD, however this effect's significance was unclear and did not display a dose response. Other studies examining neurotoxicity in adult laboratory animals noted effects at doses greater than 1,000 times higher than the Short-term RfD.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). (1995). Toxicological Profile for Polycyclic Aromatic Hydrocarbons. Retrieved from https://www.atsdr.cdc.gov/toxprofiles/tp69.pdf

Aylward, L. L., Hays, S. M., Kirman, C. R., Marchitti, S. A., Kenneke, J. F., English, C., . . . Becker, R. A. (2014). Relationships of chemical concentrations in maternal and cord blood: a review of available data. *J Toxicol Environ Health B Crit Rev, 17*(3), 175-203. doi:10.1080/10937404.2014.884956

Bouayed, J., Bohn, T., Tybl, E., Kiemer, A. K., & Soulimani, R. (2012). Benzo[alpha]pyrene-induced anti-depressive-like behaviour in adult female mice: role of monoaminergic systems. *Basic Clin Pharmacol Toxicol, 110*(6), 544-550. doi:10.1111/j.1742-7843.2011.00853.x

Bouayed, J., Desor, F., Rammal, H., Kiemer, A. K., Tybl, E., Schroeder, H., . . . Soulimani, R. (2009a). Effects of lactational exposure to benzo[alpha]pyrene (B[alpha]P) on postnatal neurodevelopment, neuronal receptor gene expression and behaviour in mice. *Toxicology, 259*(3), 97-106. doi:S0300-483X(09)00123-1 [pii] 10.1016/j.tox.2009.02.010

Bouayed, J., Desor, F., & Soulimani, R. (2009b). Subacute oral exposure to benzo[alpha]pyrene (B[alpha]P) increases aggressiveness and affects consummatory aspects of sexual behaviour in male mice. *J Hazard Mater, 169*(1-3), 581-585. doi:S0304-3894(09)00537-8 [pii] 10.1016/j.jhazmat.2009.03.131

California Environmental Protection Agency Office of Environmental Health Hazard Assessment. (2010). *Public Health Goal for Benzo(a)pyrene in Drinking Water*. Retrieved from https://oehha.ca.gov/media/downloads/water/chemicals/phg/091610benzopyrene.pdf.

Chen, C., Tang, Y., Jiang, X., Qi, Y., Cheng, S., Qiu, C., . . . Tu, B. (2012). Early postnatal benzo(a)pyrene exposure in Sprague-Dawley rats causes persistent neurobehavioral impairments that emerge postnatally and continue into adolescence and adulthood. *Toxicol Sci, 125*(1), 248-261. doi:10.1093/toxsci/kfr265

Culp, S. J., Gaylor, D. W., Sheldon, W. G., Goldstein, L. S., & Beland, F. A. (1998). A comparison of the tumors induced by coal tar and benzo[a]pyrene in a 2-year bioassay. *Carcinogenesis, 19*(1), 117-124.

De Jong, W. H., Kroese, E. D., Vos, J. G., & Van Loveren, H. (1999). Detection of immunotoxicity of benzo[a]pyrene in a subacute toxicity study after oral exposure in rats. *Toxicol Sci, 50*(2), 214-220.

Gao, M., Li, Y., Sun, Y., Shah, W., Yang, S., Wang, Y., & Long, J. (2011). Benzo[a]pyrene exposure increases toxic biomarkers and morphological disorders in mouse cervix. *Basic Clin Pharmacol Toxicol, 109*(5), 398-406. doi:10.1111/j.1742-7843.2011.00755.x

Health Canada. (2016). *Guideline Technical Document - Benzo[a]pyrene*. Retrieved from https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-benzo-pyrene.html.

Ichihara, S., Yamada, Y., Gonzalez, F. J., Nakajima, T., Murohara, T., & Ichihara, G. (2009). Inhibition of ischemia-induced angiogenesis by benzo[a]pyrene in a manner dependent on the aryl hydrocarbon receptor. *Biochem Biophys Res Commun, 381*(1), 44-49. doi:S0006-291X(09)00247-2 [pii] 10.1016/j.bbrc.2009.01.187

International Agency for Research on Cancer (IARC). (2010). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 92: Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures. Retrieved from http://monographs.iarc.fr/ENG/Monographs/vol92/index.php

Knuckles, M. E., Inyang, F., & Ramesh, A. (2001). Acute and subchronic oral toxicities of benzo[a]pyrene in F-344 rats. *Toxicol Sci, 61*(2), 382-388.

Kristensen, P., Eilertsen, E., Einarsdottir, E., Haugen, A., Skaug, V., & Ovrebo, S. (1995). Fertility in mice after prenatal exposure to benzo[a]pyrene and inorganic lead. *Environ Health Perspect, 103*(6), 588-590.

Kroese, E. D., Muller, J. J. A., Mohn, G. R., Dortant, P. M., & Wester, P. W. (2001). *Tumorigenic effects in Wistar rats orally administered benzo[a]pyrene for two years (gavage studies). Implications for*

human cancer risks associated with oral exposure to polycyclic aromatic hydrocarbons. (658603 010). Retrieved from

Legraverend, C., Guenthner, T. M., & Nebert, D. W. (1984). Importance of the route of administration for genetic differences in benzo[a]pyrene-induced in utero toxicity and teratogenicity. *Teratology, 29*(1), 35-47. doi:10.1002/tera.1420290106

MacKenzie, K. M., & Angevine, D. M. (1981). Infertility in mice exposed in utero to benzo(a)pyrene. *Biol Reprod, 24*(1), 183-191.

McCallister, M. M., Li, Z., Zhang, T., Ramesh, A., Clark, R. S., Maguire, M., . . . Hood, D. B. (2016). Revealing Behavioral Learning Deficit Phenotypes Subsequent to In Utero Exposure to Benzo(a)pyrene. *Toxicol Sci, 149*(1), 42-54. doi:10.1093/toxsci/kfv212

McCallister, M. M., Maguire, M., Ramesh, A., Aimin, Q., Liu, S., Khoshbouei, H., . . . Hood, D. B. (2008). Prenatal exposure to benzo(a)pyrene impairs later-life cortical neuronal function. *Neurotoxicology, 29*(5), 846-854. doi:S0161-813X(08)00140-X [pii] 10.1016/j.neuro.2008.07.008

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

Neal, J., & Rigdon, R. H. (1967). Gastric tumors in mice red bezno(a)pyrene: a quantitative study. *Texas Reports on Biology and Medicine, 25*(4).

Rigdon, R., & Rennels, E. (1964). Effect of feeding benzpyrene on reproduction in the rat. *Experientia*.

Rigdon, R. H., & Neal, J. (1965). Effects of Feeding Benzo(a)Pyrene on Fertility, Embryos, and Young Mice. *J Natl Cancer Inst, 34*, 297-305.

Robinson, J. R., Felton, J. S., Levitt, R. C., Thorgeirsson, S. S., & Nebert, D. W. (1975). Relationship between "aromatic hydrocarbon responsiveness" and the survival times in mice treated with various drugs and environmental compounds. *Molecular pharmacology, 11*(6), 850-865.

Saunders, C. R., Das, S. K., Ramesh, A., Shockley, D. C., & Mukherjee, S. (2006). Benzo(a)pyrene-induced acute neurotoxicity in the F-344 rat: role of oxidative stress. *J Appl Toxicol, 26*(5), 427-438. doi:10.1002/jat.1157

Saunders, C. R., Ramesh, A., & Shockley, D. C. (2002). Modulation of neurotoxic behavior in F-344 rats by temporal disposition of benzo(a)pyrene. *Toxicol Lett, 129*(1-2), 33-45. doi:S0378427401004672 [pii]

Saunders, C. R., Shockley, D. C., & Knuckles, M. E. (2001). Behavioral effects induced by acute exposure to benzo(a)pyrene in F-344 rats. *Neurotox Res, 3*(6), 557-579.

Singh, S. V., Benson, P. J., Hu, X., Pal, A., Xia, H., Srivastava, S. K., . . . Awasthi, Y. C. (1998). Gender-related differences in susceptibility of A/J mouse to benzo[a]pyrene-induced pulmonary and forestomach tumorigenesis. *Cancer Lett, 128*(2), 197-204. doi:S0304-3835(98)00072-X [pii]

U. S. Environmental Protection Agency - IRIS. (2017a). *Toxicological Review of Benzo[a]pyrene [CASRN 50-32-8].* Retrieved from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0136tr.pdf.

U. S. Environmental Protection Agency - IRIS. (2017b). Toxicological Review of Benzo[a]pyrene [CASRN 50-32-8], Supplemental Information.

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Weyand, E. H., Chen, Y. C., Wu, Y., Koganti, A., Dunsford, H. A., & Rodriguez, L. V. (1995). Differences in the tumorigenic activity of a pure hydrocarbon and a complex mixture following ingestion: benzo[a]pyrene vs manufactured gas plant residue. *Chem Res Toxicol, 8*(7), 949-954.

World Health Organization (WHO). (2003). *Polynuclear aromatic hydrocarbons in Drinking-water - Background document for WHO Guidelines for Drinking-water Quality.* Retrieved from http://www.who.int/water_sanitation_health/dwq/chemicals/polyaromahydrocarbons.pdf.

Xu, C., Chen, J. A., Qiu, Z., Zhao, Q., Luo, J., Yang, L., . . . Shu, W. (2010). Ovotoxicity and PPAR-mediated aromatase downregulation in female Sprague-Dawley rats following combined oral exposure to benzo[a]pyrene and di-(2-ethylhexyl) phthalate. *Toxicol Lett, 199*(3), 323-332. doi:10.1016/j.toxlet.2010.09.015

Toxicological Summary for: Benzophenone

CAS**: 119-61-9**

Synonyms: Diphenylmethanone; Methanone, diphenyl-, diphenyl ketone, benzoyl benzene, alpha-oxo-diphenyl methane, alpha oxoditane, phenyl ketone

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

Short-term Non-Cancer Health-Based Value (nHBV$_{Short-term}$) = 900 µg/L

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

$$= \frac{(0.52 \text{ mg/kg-d}) \times (0.5)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 896 \text{ rounded to } \mathbf{900 \text{ µg/L}}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 15.5/30 = 0.52 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	67.4 mg/kg-d (administered dose NOAEL, Hoshino et al. 2005)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 67.4 mg/kg-d x 0.23 = 15.5 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased pup body weight
Co-critical effect(s):	Decreased pup body weight
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health-Based Value (nHBV$_{Subchronic}$) = 100 µg/L

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

$$= \frac{(0.053 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 143 rounded to **100 µg/L**

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 1.6/30 = 0.053 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	6.4 mg/kg-d (administered dose NOAEL, Hoshino et al., 2005)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 6.4 mg/kg-d x 0.25 = 1.6 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Increased relative liver weight, relative kidney weight, proximal tubule regeneration, proximal tubule dilatation
Co-critical effect(s):	Increased serum bile salts, relative liver weight, hepatocyte vacuolization, relative kidney weight, renal tubule protein casts
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health-Based Value (nHBV$_{Chronic}$) = nHBV$_{Subchronic}$ = 100 µg/L

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

$$= \frac{(0.053 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 235 rounded to 200 µg/L

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 1.58/30 = 0.053 mg/kg-d (Fischer 344 rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	5.86 mg/kg-d (administered dose BMDL calculated by MDH from (National Toxicology Program, 2006))
Dose Adjustment Factor (DAF):	0.27, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 5.86 mg/kg-d x 0.27 = 1.58 mg/kg-d

Total uncertainty factor (UF):	30	
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability	
Critical effect(s):	Increased renal tubule hyperplasia	
Co-critical effect(s):	Increased renal pelvis transitional hyperplasia, severity of nephropathy, and bile duct hyperplasia	
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system	

The Chronic nHBV must be protective of the subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Subchronic nHBV of 100 µg/L. Additivity endpoints: Hepatic (liver) system, Renal (kidney) system

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	2B – Possibly carcinogenic to humans (IARC 2013)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	In male mice: hepatocellular adenoma, combined hepatocellular adenoma, carcinoma and hepatoblastoma. In female mice: histiocytic sarcoma. In male rats: renal tubule adenoma.

Statement for non-linear carcinogens:
Benzophenone was reported to be neither mutagenic nor genotoxic in various *in vivo* and *in vitro* experiments, and is likely to be a nonlinear carcinogen. The chronic RfD is considered to be protective against cancer.

Volatile: Yes (low)

Summary of Guidance Value History:

In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in changes to the subchronic and chronic duration water guidance values from 200 µg/L to 100 µg/L.

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?	Yes	No	Yes	Yes	No

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

Comments on extent of testing or effects:

[1] One study identified estrogenic activity of orally-administered benzophenone based on increased uterine weight in ovariectomized rats at doses 200-fold higher than the Short-Term RfD. *In vivo* studies based on other routes of exposure did not show estrogenic effects. Based on *in vitro* studies, it appears that benzophenone and its main metabolite benzhydrol do not possess estrogenic activity, whereas a minor metabolite 4-hydroxybenzophenone is weakly estrogenic.

[2] There were no specific immunotoxicity studies available. Subchronic and chronic studies in rodents did not note any abnormalities in immune cell blood parameters or immune organ histopathology after oral benzophenone exposure at levels up to 300-fold higher than the Short-Term RfD.

[3] A two-generation reproductive/developmental study in rats noted a decrease in pup body weight close to weaning; this effect served as the basis of the Short-Term RfD. Other studies in rats and rabbits found that developmental toxicity only occurred at doses higher than those causing maternal toxicity.

[4] A two-generation reproductive/developmental study in rats did not note any reproductive abnormalities in the following tested parameters: reproductive serum hormones (testosterone, FSH, LH), estrous cycles, sperm morphology and motility and spermatid head count, mating behavior, conception, gestation, parturition, lactation, and weaning at doses up to 100-fold higher than the Short-Term RfD. Additionally, organ weights and histopathology of the testes, epididymes, prostate, seminal vesical, ovary, and uterus were unchanged.

[5] No neurotoxicity studies were found. A two-generation reproductive/developmental study in rats found no changes in reflex or pain response in pups at doses up to 100-fold higher than the Short-Term RfD.

Resources Consulted During Review:

Adams, T. B., McGowen, M. M., Williams, M. C., Cohen, S. M., Feron, V. J., Goodman, J. I., . . . Waddell, W. J. (2007). The FEMA GRAS assessment of aromatic substituted secondary alcohols, ketones, and related esters used as flavor ingredients. *Food Chem Toxicol, 45*(2), 171-201. doi:10.1016/j.fct.2006.07.029

Burdock, G. A., Pence, D. H., & Ford, R. A. (1991). Safety evaluation of benzophenone. *Food Chem Toxicol, 29*(11), 741-750.

Danish Environmental Protection Agency. (2018). Substance Evaluation Conclusion as required by REACH Article 48 and Evaluation Report for Benzophenone.

European Food Safety Authority. (2009). Toxicological evaluation of benzophenone. *EFSA Journal, 7*(6), 1104. doi:10.2903/j.efsa.2009.1104

European Food Safety Authority. (2017). Safety of benzophenone to be used as flavouring. *EFSA Journal, 15*(11), e05013. doi:10.2903/j.efsa.2017.5013

Food and Drug Administration. (2018). Food Additive Regulations; Synthetic Flavoring Agents and Adjuvants.

Frederiksen, H., Nielsen, O., Skakkebaek, N. E., Juul, A., & Andersson, A.-M. (2017). UV filters analyzed by isotope diluted TurboFlow-LC-MS/MS in urine from Danish children and adolescents. *International journal of hygiene and environmental health, 220*(2 Pt A), 244-253. doi:10.1016/j.ijheh.2016.08.005

Health Canada. (2017). Draft Screening Assessment, Methanone, diphenyl- (benzophenone).

Hoshino, N., Tani, E., Wako, Y., & Takahashi, K. (2005). A two-generation reproductive toxicity study of benzophenone in rats. *J Toxicol Sci, 30 Spec No.*, 5-20.

IARC. (2013). Benzophenone Monograph. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 101*, 285 - 304.

Jeon, H. K., Sarma, S. N., Kim, Y. J., & Ryu, J. C. (2008). Toxicokinetics and metabolisms of benzophenone-type UV filters in rats. *Toxicology, 248*(2-3), 89-95. doi:10.1016/j.tox.2008.02.009

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

Minnesota Pollution Control Agency. (2019). Personal Communication.

Nakagawa, Y., Suzuki, T., & Tayama, S. (2000). Metabolism and toxicity of benzophenone in isolated rat hepatocytes and estrogenic activity of its metabolites in MCF-7 cells. *Toxicology, 156*(1), 27-36.

Nakagawa, Y., & Tayama, K. (2002). Benzophenone-induced estrogenic potency in ovariectomized rats. *Arch Toxicol, 76*(12), 727-731. doi:10.1007/s00204-002-0401-3

National Toxicology Program. (1991). Executive Summary of Safety and Toxicity Information: Benzophenone.

National Toxicology Program. (2000). NTP Technical Report on the Toxicity Studies of Benzophenone Administered in Feed to F344/N Rats and B6C3F1 Mice.

National Toxicology Program. (2002). Developmental Toxicity Evaluation for Benzophenone Administered by Gavage to Sprague Dawley (CD) Rats on Gestational Days 6 Through 19.

National Toxicology Program. (2004). Developmental Toxicity Evaluation for Benzophenone Administered by Gavage to New Zealand White Rabbits on Gestational Days 6 Through 29.

National Toxicology Program. (2006). NTP Technical Report on the Toxicology and Carcinogenesis Studies of Benzophenone in F344/N Rats and B6C3F1 Mice.

National Toxicology Program. (2016). Toxicokinetic Evaluation (S0592) of Benzophenone (119-61-9) in F344 Rats and B6C3F1 Mice Exposed via Dosed Feed, Gavage or Intravenous Injection.

NSF International. (2013). Benzophenone Oral Risk Assessment Document.

Rhodes, M. C., Bucher, J. R., Peckham, J. C., Kissling, G. E., Hejtmancik, M. R., & Chhabra, R. S. (2007). Carcinogenesis studies of benzophenone in rats and mice. *Food Chem Toxicol, 45*(5), 843-851. doi:10.1016/j.fct.2006.11.003

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Watanabe, Y., Kojima, H., Takeuchi, S., Uramaru, N., Sanoh, S., Sugihara, K., . . . Ohta, S. (2015). Metabolism of UV-filter benzophenone-3 by rat and human liver microsomes and its effect on endocrine-disrupting activity. *Toxicol Appl Pharmacol, 282*(2), 119-128. doi:10.1016/j.taap.2014.12.002

Toxicological Summary for: 1H-Benzotriazole

CAS**: 95-14-7**

Synonyms: 1,2,3-Benzotriazole, Benzotriazole, 1H-Benzo[d][1,2,3]triazole, 1H-1,2,3-benzotriazole

Note: 1H-benzotriazole is the surrogate for water guidance values for 5-methyl-1H-benzotriazole and Tolyltriazole (https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/5mebtttr.pdf)

Acute Non-Cancer Health-Based Value (nHBV$_{Acute}$) Not Derived (Insufficient Data)

Short-term Non-Cancer Health-Based Value (nHBV$_{Short-term}$) = 20 µg/L

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

$$= \frac{(0.023 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 15.8 \text{ rounded to } \textbf{20 µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.

[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 6.9/300 = 0.023 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	30 mg/kg-d (administered dose NOAEL, JBRC, 2007)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 30 mg/kg-d x 0.23 = 6.9 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty due to the lack of reproductive/developmental studies of sufficient exposure duration
Critical effect(s):	Reduced offspring body weight
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health-Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 20 µg/L

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

$$= \frac{(0.017 \text{ mg/kg-d) x } (0.2)^* \text{ x } (1000 \text{ µg/mg)}}{(0.074 \text{ L/kg-d})^{**}}$$

= 45.9 rounded to 50 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 5.15/300 = 0.017 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	22.4 mg/kg-d (administered dose BMDL$_{10\%}$, JBRC, 2007)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 22.4 mg/kg-d x 0.23 = 5.15 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty due to the lack of adequate subchronic toxicity studies and lack of reproductive/developmental studies of sufficient exposure duration
Critical effect(s):	Proximal tubule regeneration in kidney of female rats
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

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 20 µg/L. Additivity endpoints: Developmental

Chronic Non-Cancer Health-Based Value (nHBV$_{Chronic}$) = nHBV$_{Short-term}$ = 20 µg/L

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

$$= \frac{(0.017 \text{ mg/kg-d})^{***} \text{ x } (0.2)^* \text{ x } (1000 \text{ µg/mg)}}{(0.045 \text{ L/kg-d})^{**}}$$

= 75.5 rounded to 80 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.

***The candidate Chronic RfD is significantly higher than the Subchronic RfD (0.017 mg/kg-d). Although, both identify kidney as the sensitive effect, the chronic study does not include information in the lower part of the dose-response range. Given the significant limitations of the chronic database, MDH has selected the Subchronic RfD as the final Chronic RfD.

The Chronic nHBV must be protective of the short-term exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 20 µg/L. Additivity endpoints: Developmental

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	Not Classified
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (low)

Summary of Guidance Value History:
No previous guidance has been developed for 1H-Benzotriazole. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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?	--	--	Yes[1]	Yes[2]	--

Comments on extent of testing or effects:
[1] The short-term reference dose is based on developmental toxicity in offspring (decreased body weight). A lack reproductive/developmental studies of sufficient duration form a major part of the basis for the selection of a 10-fold database uncertainty factor.

[2] Changes in reproductive organs were noted in a two-year study in males (prostate inflammation) and females (uterus/endometrium inflammation and cystic hyperplasia) at doses over 8,000 times higher than the short-term and subchronic reference doses. A lack of reproductive/developmental studies of sufficient duration form a major part of the basis for the selection of a 10-fold database uncertainty factor.

Resources Consulted During Review:

Asimakopoulos, A. G., Wang, L., Thomaidis, N. S., & Kannan, K. (2013). Benzotriazoles and benzothiazoles in human urine from several countries: a perspective on occurrence, biotransformation, and human exposure. *Environment International, 59*, 274-281. doi:10.1016/j.envint.2013.06.007

Baduel, C., Lai, F. Y., van Nuijs, A. L. N., & Covaci, A. (2019). Suspect and Nontargeted Strategies to Investigate in Vitro Human Biotransformation Products of Emerging Environmental Contaminants: The Benzotriazoles. *Environmental Science & Technology*. doi:10.1021/acs.est.9b02429

Beltoft, V., Nielsen, E., & Ladefoged, O. (2013). *Benzotriazole and Tolyltriazole. Evaluation of health hazards and proposal of health based water quality criteria for soil and drinking water*. Retrieved from https://www2.mst.dk/Udgiv/publications/2013/12/978-87-93026-81-0.pdf

ChemIDplus. Retrieved from https://chem.nlm.nih.gov/chemidplus/rn/136-85-6

European Chemicals Agency (ECHA). Benzotriazole (CAS No. 95-14-7; EC No. 202-394-1). Retrieved from https://echa.europa.eu/registration-dossier/-/registered-dossier/14234/7/7/2

European Chemicals Agency (ECHA). Methyl-1H-benzotriazole (CAS No. 29385-43-1; EC No. 249-596-6). Retrieved from https://echa.europa.eu/da/registration-dossier/-/registered-dossier/14272/7/2/2

European Chemicals Agency (ECHA). (2017). *Read-Across Assessment Framework (RAAF)*. Retrieved from https://echa.europa.eu/documents/10162/13628/raaf_en.pdf

Fairbairn, D. J., Elliott, S. M., Kiesling, R. L., Schoenfuss, H. L., Ferrey, M. L., & Westerhoff, B. M. (2018). Contaminants of emerging concern in urban stormwater: Spatiotemporal patterns and removal by iron-enhanced sand filters (IESFs). *Water Research, 145*, 332-345. doi:10.1016/j.watres.2018.08.020

Ferrey, M., Streets, S., & Lueck, A. (2013). *Pharmaceuticals and Personal Care Products in Minnesota's Rivers and Streams: 2010*.

Harris, C. A., Routledge, E. J., Schaffner, C., Brian, J. V., Giger, W., & Sumpter, J. P. (2007). Benzotriazole is antiestrogenic in vitro but not in vivo. *Environmental Toxicology and Chemistry, 26*(11), 2367-2372. doi:10.1897/06-587R.1

Janna, H., Scrimshaw, M. D., Williams, R. J., Churchley, J., & Sumpter, J. P. (2011). From dishwasher to tap? Xenobiotic substances benzotriazole and tolyltriazole in the environment. *Environmental Science & Technology, 45*(9), 3858-3864. doi:10.1021/es103267g

Japan Bioassay Research Center. (2007). *Combined Repeated Dose and Reproductive/Developmental Toxicity Screening Test of 1,2,3-Benzotriazole (CAS No. 95-14-7) by Oral Administration in Rats*. Retrieved from https://www.nite.go.jp/chem/jcheck//tempfile_list.action?tpk=12276&ppk=3121&kinou=100&type=ja

Li, X., Wang, L., Asimakopoulos, A. G., Sun, H., Zhao, Z., Zhang, J., . . . Wang, Q. (2018). Benzotriazoles and benzothiazoles in paired maternal urine and amniotic fluid samples from Tianjin, China. *Chemosphere, 199*, 524-530. doi:10.1016/j.chemosphere.2018.02.076

Liang, X., Li, J., Martyniuk, C. J., Wang, J., Mao, Y., Lu, H., & Zha, J. (2017). Benzotriazole ultraviolet stabilizers alter the expression of the thyroid hormone pathway in zebrafish (Danio rerio) embryos. *Chemosphere, 182*, 22-30. doi:10.1016/j.chemosphere.2017.05.015

Liang, X., Wang, M., Chen, X., Zha, J., Chen, H., Zhu, L., & Wang, Z. (2014). Endocrine disrupting effects of benzotriazole in rare minnow (Gobiocypris rarus) in a sex-dependent manner. *Chemosphere, 112*, 154-162. doi:10.1016/j.chemosphere.2014.03.106

Liang, X., Zha, J., Martyniuk, C. J., Wang, Z., & Zhao, J. (2017). Histopathological and proteomic responses in male Chinese rare minnow (Gobiocypris rarus) indicate hepatotoxicity following benzotriazole exposure. *Environmental Pollution, 229*, 459-469. doi:10.1016/j.envpol.2017.06.013

Luongo, G., Avagyan, R., Hongyu, R., & Ostman, C. (2016). The washout effect during laundry on benzothiazole, benzotriazole, quinoline, and their derivatives in clothing textiles. *Environmental Science and Pollution Research International, 23*(3), 2537-2548. doi:10.1007/s11356-015-5405-7

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Cancer Institute. (1978). *Bioassay of 1H-Benzotriazole For Possible Carcinogenicity (CAS No. 95-14-7)*. Retrieved from https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr088.pdf

Shi, Z. Q., Liu, Y. S., Xiong, Q., Cai, W. W., & Ying, G. G. (2019). Occurrence, toxicity and transformation of six typical benzotriazoles in the environment: A review. *Science of the Total Environment, 661*, 407-421. doi:10.1016/j.scitotenv.2019.01.138

Stouten, H., Rutten, A., van de Gevel, I., & De Vrijer, F. (2000). *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and The Dutch Expert Committee on Occupational Standards: 1,2,3-Benzotriazole*. Retrieved from http://www.inchem.org/documents/kemi/kemi/ah2000_24.pdf

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Wang, L., Asimakopoulos, A. G., Moon, H. B., Nakata, H., & Kannan, K. (2013). Benzotriazole, benzothiazole, and benzophenone compounds in indoor dust from the United States and East Asian countries. *Environmental Science & Technology, 47*(9), 4752-4759. doi:10.1021/es305000d

Weiss, S., Jakobs, J., & Reemtsma, T. (2006). Discharge of three benzotriazole corrosion inhibitors with municipal wastewater and improvements by membrane bioreactor treatment and ozonation. *Environmental Science & Technology, 40*(23), 7193-7199. doi:10.1021/es061434i

Xue, J., Yanjian W., & Kurunthachalam, K. (2017). Occurrence of benzotriazoles (BTRs) in indoor air from Albany, New York, USA, and its implications for inhalation exposure. *Toxicological & Environmental Chemistry, 99*(3), 402-414. doi:10.1080/02772248.2016.119620

Zhang, Z., Ren, N., Li, Y. F., Kunisue, T., Gao, D., & Kannan, K. (2011). Determination of benzotriazole and benzophenone UV filters in sediment and sewage sludge. *Environmental Science & Technology, 45*(9), 3909-3916. doi:10.1021/es2004057

Toxicological Summary for: 1,1'-Biphenyl

CAS: **92-52-4; DTXSID4020161**
Synonyms: Biphenyl; Phenylbenzene; Diphenyl

Acute Non-Cancer Health-Based Value (nHBV$_{Acute}$) = 400 µg/L

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

$$= \frac{(0.58 \text{ mg/kg-d}) \text{ x } (0.2)^* \text{ x } (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= \textbf{400 µg/L}$$

*Relative Source Contribution: Because inhalation is the predominant route of exposure, and infant exposure does not appear to be significantly less than exposures to older children or adults, an RSC value of 0.2 was used for all exposure durations. MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 57.5/100 = 0.58 mg/kg-d (F344 rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	250 mg/kg-d (administered dose NOAEL, Kluwe et al 1982)
Dose Adjustment Factor (DAF):	0.23 subchronic male F344 rats, body weight scaling default (U.S. EPA 2011a and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 250 mg/kg-d x 0.23 = 57.5 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 limitations, including lack of neurotoxicity testing and inadequate developmental/reproductive testing
Critical effect(s):	Increased urine volume (polyuria) accompanied by increased excretion of urinary protein, glucose, and several renal enzymes
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

Short-term Non-Cancer Health-Based Value (nHBV$_{Short-term}$) = 100 µg/L

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

$$= \frac{(0.18 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 124 \text{ rounded to } \textbf{100 µg/L}$$

*Relative Source Contribution: Because inhalation is the predominant route of exposure, and infant exposure does not appear to be significantly less than exposures to older children or adults, an RSC value of 0.2 was used for all exposure durations. MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 17.6/100 = 0.18 mg/kg-d (female F344 rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	83.7 mg/kg-d (administered dose NOAEL, Booth et al 1961. LOAEL based on Booth et al 1961 and Kluwe et al 1982.)
Dose Adjustment Factor (DAF):	0.21 female subchronic F344 rat based on body weight scaling, default (U.S. EPA 2011a and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 83.7 mg/kg-d x 0.21 = 17.6 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 limitations, including lack of neurotoxicity testing and inadequate developmental/reproductive testing
Critical effect(s):	Increased urine volume (polyuria), precipitable urinary sediment, and increased urinary glucose, protein, alkaline phosphatase (AP) and glutamic oxaloacetic transaminase (GOT) excretion
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

Subchronic Non-Cancer Health-Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 100 µg/L

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

$$= \frac{(0.18 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 486 \text{ rounded to } 500 \text{ µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 17.6/100 = 0.18 mg/kg-d (female F344 rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	83.7 mg/kg-d (administered dose NOAEL, Booth et al 1961)
Dose Adjustment Factor (DAF):	0.21 female subchronic F344 rats body weight scaling, default (U.S. EPA 2011a and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 83.7 mg/kg-d x 0.21 = 17.6 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 limitations, including lack of neurotoxicity testing and inadequate developmental/reproductive testing
Critical effect(s):	Increased urine volume and precipitable sediment accompanied by limited renal histological changes
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

The Subchronic nHBV must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 100 µg/L. Additivity endpoints: Renal (kidney) system.

Chronic Non-Cancer Health-Based Value (nHBV$_{Chronic}$) = nHBV$_{Short-term}$ = 100 µg/L

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

$$= \frac{(0.073 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 324 \text{ rounded to } 300 \text{ µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 7.31/100 = 0.073 mg/kg-d (female F344 rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	30.45 mg/kg-d (administered dose BMDL$_{10\%}$, Umeda et al 2002)
Dose Adjustment Factor (DAF):	0.24 female chronic F344 rats body weight scaling, default (U.S. EPA 2011a and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 30.45 mg/kg-d x 0.24 = 7.31 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 limitations,

including lack of neurotoxicity testing and inadequate developmental/reproductive testing

Critical effect(s):	Renal transitional cell simple hyperplasia
Co-critical effect(s):	Increased hemosiderin deposits in the kidney and mineralization of outer renal medulla and pelvis
Additivity endpoint(s):	Renal (kidney) system

The Chronic nHBV must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 100 µg/L. Additivity endpoints: Renal (kidney) system.

Cancer Health-Based Value (cHBV) = 10 µg/L

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

$$= \frac{(1E\text{-}5) \times (1000\ \mu g/mg)}{[(0.008 \times 10^* \times 0.155\ L/kg\text{-}d^{**} \times 2) + (0.008 \times 3^* \times 0.040\ L/kg\text{-}d^{**} \times 14) + (0.008 \times 1^* \times 0.042\ L/kg\text{-}d^{**} \times 54)] / 70}$$

= 12.4 rounded to **10 µg/L**

[*]ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
[**]Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Cancer classification:	Suggestive evidence of carcinogenic potential
Slope factor (SF):	0.008 per mg/kg-d (female BDF1 mice, Umeda et al 2005)
Source of cancer slope factor (SF):	U.S. EPA 2013
Tumor site(s):	Liver adenomas and carcinomas

Volatile: No (moderate)

Summary of Guidance Value History:
MDH promulgated a chronic nHRL of 300 µg/L in 1993. In 2020 MDH conducted a full review and derived nHBVs of 400 µg/L for acute duration and 100 µg/L for short-term, subchronic and chronic durations as well as a cHBV of 10 µg/L for cancer. The 2020 chronic and cancer HBVs are lower than the 1993 HRL value due to the use of MDH's multiduration methodology, more recent toxicological data, and updated water intake rates (U.S. EPA 2019).

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]	Yes[3]	-[4]

Comments on extent of testing or effects:

[1] Endocrine effects have not been specifically tested in animals. *In vitro* estrogenic assays indicate that biphenyl does not exhibit estrogenic activity, however, hydroxylated metabolites of biphenyl do exhibit estrogenic activity. This activity was mainly observed when cultures contained cells from induced rat livers as little effect was observed when cells from untreated rats were used.

[2] Decreased fetal or pup body weights, delayed ossification, and increased dead or resorbed fetuses have been reported at HED doses ~600-fold higher than the short-term and subchronic RfDs. The developmental studies are old and do not include the more extensive evaluation of current study protocols. A database uncertainty factor of 3 was incorporated into the RfD derivation, in part, to address the need for more comprehensive developmental and reproductive toxicity testing.

[3] Decreased fertility in laboratory animals has been reported at HED doses ~1000-fold higher than the short-term and subchronic RfDs. The reproductive studies are old and do not include the more extensive evaluation of current study protocols. A database uncertainty factor of 3 was incorporated into the RfD derivation, in part, to address the need for more comprehensive developmental and reproductive toxicity testing.

[4] Occupational studies in humans have reported neurological effects when exposed to air levels in excess of occupational exposure limits. No animal neurotoxicity testing has been conducted. A database uncertainty factor of 3 was incorporated into the RfD derivation, in part, to address this data gap.

Resources Consulted During Review:

Ambrose AM, Booth, A., DeEds, F., & AH Cox, J. (1960). A toxicological study of biphenyl, a citrus fungistat. *Journal of Food Science, 25*, 328-336. https://doi.org/10.1111/j.1365-2621.1960.tb00338.x

Booth, A., Ambrose, A., DeEds, F., & Cox Jr, A. (1961). The Reversible Nephrotoxic Effects of Biphenyl. *Toxicology and Applied Pharmacology, 3*, 560-567.

California State Water Resources Control Board. Search Water Quality Goals Online. Retrieved from https://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/search.html

California Water Resources Control Board. (2008). Water Quality Limits for Constituents and Parameters. Retrieved from https://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/search.html

Environment Canada. (2014). *Screening Assessment. 1,1'-Biphenyl (Chemical Abstracts Service Registry Number 92-52-4).* Retrieved from http://publications.gc.ca/collections/collection_2014/ec/En14-197-2014-eng.pdf.

European Food Safety Authority (EFSA). (2010). *Modification of the existing MRLs for biphenyl in various commodities.* .

Khera KS, Whalen, C., Angers, G., & Trivett, G. (1979). Assessment of the teratogenic potential of piperonyl butoxide, biphenyl, and phosalone in the rat. *Toxicology and Applied Pharmacology, 47*, 353-358. https://doi.org/10.1016/0041-008X(79)90330-2

Kim, H., Shin, S., Ham, M., Lim, C., & Byeon, S. (2015). Exposure Monitoring and Risk Assessment of Biphenyl in the Workplace. *Int. J. Environ. Res. Public Health, 12*, 5116-5128. doi:10.3390/ijerph120505116

Kluwe, W. (1982). Dvelopment of resistance to nephrotoxic insult: changes in urine composition and kidney morphology on repeated exposures to mercuric chloride or biphenyl. *Journal of Toxicology and Environmental Health, 9*, 619-635.

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." from https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

New Jersey Department of Environmental Protection. (2015). Standards for Drinking Water, Ground Water, Soil and Surface Water. Retrieved from https://www.nj.gov/dep/standards/Standards.htm

Ohnishi M, H. Y., S Yamamoto, T Matsuchima, T Ishii. (2000). Sex dependence of the components and structure of urinary calculi induced by biphenyl administration in rats. *Chemical Research in Toxicology, 13*, 727-735. http://dx.doi.org/710.1021/tx0000163.

Shiraiwa, K., Takita, M., Tsutsumi, M., Kinugasa, T., Denda, A., Takahashi, S., & Konishi, Y. (1989). Diphenyl Induces Urolithiasis But Does Not Possess The Ability To Promote Carcinogenesis by N-Ethyl-N-Hydroxyethylnitrosame In Kidneys of Rats. *J Toxicol Pathol, 2*, 41-48.

Søndergaard, D., & Blom, L. (1979). Polycystic changes in rat kidney induced by biphenyl fed in different diets. *Archives of Toxicology, 2*, 499-502.

U.S. Environmental Protection Agency (EPA). Regional Screening Levels (RSLs) - Generic Tables. Retrieved from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency (EPA). (2000). *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000)*. Retrieved from https://www.epa.gov/sites/production/files/2018-10/documents/methodology-wqc-protection-hh-2000.pdf.

U.S. Environmental Protection Agency (EPA). (2011a). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2011b). *Provisional Peer-Reviewed Toxicity Values for 1,1-Biphenyl (CASRN 92-52-4). EPA/690/R-11/011F.* Retrieved from https://hhpprtv.ornl.gov/issue_papers/Biphenyl11.pdf.

U.S. Environmental Protection Agency (EPA). (2013). *Toxicological Review of Biphenyl (CAS No. 92-52-4).*. Retrieved from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0013tr.pdf.

U.S. Environmental Protection Agency (EPA). (2019). *Exposure Factors Handbook Chapter 3 Update 2019*. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3.

Umeda Y, Aiso, S., Arito, H., Nagano, K., & Matsushima, T. (2004). Short communication: Induction of peroxisome proliferation in the liver of biphenyl-fed female mice. *Journal of Occupational Health, 46*, 486-488.

Umeda Y, Aiso, S., Yamazaki, K., Ohnishi, M., Arito, H., Nagano, K., . . . Matsushima, T. (2005). Carcinogenicity of biphenyl in mice by two years feeding. . *Journal of Veterinary Medicine and Science, 67*, 417-424.

Umeda, Y., Arito, H., Kano, H., Ohnishi, M., Matsumoto, M., Nagano, K., . . . Matsushima, T. (2002). Two-year study of carcinogenicity and chronic toxicity of biphenyl in rats. . *Journal of Occupational Health 44*, 176-183.

Winter, C. (2015). Chronic dietary exposure to pesticide residues in the United States. . *International Journal of Food Contamination, 2*(1), 11.

Toxicological Summary for: Bromodichloromethane

CAS: **75-27-4**

Synonyms: Dichlorobromomethane, Monobromodichloromethane, BDCM

Acute Non-Cancer Health Based Value (nHBV$_{Acute}$) = 400 µg/L

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

$$= \frac{(0.073 \text{ mg/kg-d) x } (0.2)^{*} \text{ x } (1000 \text{ µg/mg)}}{(0.038 \text{ L/kg-d})^{**}}$$

= 384 rounded to **400 µg/L**

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.

[**]Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5. The RfD is based on full litter resorptions, which occurs in utero; therefore, the intake rate for a pregnant woman is used rather than the default infant intake rate as described in the 2008 SONAR (p. 46).

Reference Dose/Concentration:	HED/Total UF = 2.18/30 = 0.073 mg/kg-d (F344 rat)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	10.4 mg/kg-d (administered dose BMDL$_{05}$, Narotsky 1997 with support from Bielmeier 2001 as an acute effect)
Dose Adjustment Factor (DAF):	0.21, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 10.4 mg/kg-d x 0.21 = 2.18 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Full litter resorptions, associated with changes in female hormones that maintain pregnancy
Co-critical effect(s):	None
Additivity endpoint(s):	Female Reproductive system (E)

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 30 µg/L

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

$$= \frac{(0.039 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 26.8 \text{ rounded to } \textbf{30 µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 3.94/100 = 0.039 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	30.3 mg/kg-d (administered dose $BMDL_{10}$, Munson 1982)
Dose Adjustment Factor (DAF):	0.13, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 30.3 mg/kg-d x 0.13 = 3.94 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	e.g. 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (due to outstanding concerns related to BDCM-induced hormonal changes in females and immunotoxicity changes in a 2-generation study that is not confounded by vehicle, BDCM volatilization, water palatability, or animal dehydration issues)
Critical effect(s):	Decreased spleen weight
Co-critical effect(s):	Full litter resorptions[***]
Additivity endpoint(s):	Immune system, Spleen

[***]Since an infant water ingestion rate exposure forms the basis of the Short-term HBV calculation, and full litter resorptions is relevant only to pregnant women and is based on a pregnant woman water ingestion rate exposure, an additivity endpoint for full litter resorptions is not necessary.

Subchronic Non-Cancer Health Based Value (nHBV_Subchronic) = nHBV_Short-term = 30 µg/L

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

$$= \frac{(0.039 \text{ mg/kg-d})^{\#} \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 105 \text{ rounded to } 100 \text{ µg/L}$$

[#]No Subchronic RfD was calculated due to study limitations. Therefore, the Short-term RfD was applied to the subchronic duration.

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

The Subchronic nHBV must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 30 µg/L. Additivity endpoints: Immune system, Spleen

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = 30 µg/L

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

$$= \frac{(0.0075 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 33 rounded to **30 µg/L**

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 0.225/30 = 0.0075 mg/kg-d (Wistar rat)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	0.776 mg/kg-d (administered dose BMDL$_{10}$, Aida 1992)
Dose Adjustment Factor (DAF):	0.29, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 0.776 mg/kg-d x 0.29 = 0.225 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Fatty degeneration of the liver
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health Based Value (cHBV) = 3 µg/L

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

$$= \frac{(1E\text{-}5) \times (1000 \text{ µg/mg})}{[(0.035 \times 10^* \times 0.155 \text{ L/kg-d}^{**} \times 2) + (0.035 \times 3^* \times 0.040 \text{ L/kg-d}^{**} \times 14) + (0.035 \times 1^* \times 0.042 \text{ L/kg-d}^{**} \times 54)] / 70}$$

= 2.8 rounded to **3 µg/L**

[*]ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
[**]Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Cancer classification: Likely to be carcinogenic to humans

<div align="right">

Slope factor (SF):   0.035 per mg/kg-d, renal tumors in male B6C3F1 mice
(NTP 1987)

Source of cancer slope factor (SF):   (US EPA 1998) as cited in US EPA 2005

Tumor site(s):   Kidney, Large intestine, Liver, Lymphatic system

</div>

Volatile: Yes (high)

Summary of Guidance Value History: In 1993, MDH promulgated a cancer HRL of 6 µg/L. The new 2018 HBV for cancer (3 µg/L) is lower because of 1) the use of a more recent slope factor; 2) the use of MDH's most recent risk assessment methodology; and 3) rounding to one significant digit. In 2018 MDH also derived noncancer HBVs of 300 µg/L for Acute and 30 µg/L for Short-term, Subchronic, and Chronic durations. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in an increase of the Acute duration HBV from 300 µg/L to 400 µg/L.

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?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1]A hormone profile was conducted on pregnant rats exposed to BDCM during pregnancy that resulted in full litter resorptions (acute critical effect). Maternal hormone changes occurred at levels 200-300 times higher than the acute RfD and 400-500 times higher than the short-term RfD.

[2]The short-term RfD is based on reduced spleen weights in mice exposed to BDCM. Altered immune cell levels and function occurred at doses 300-400 times higher than the RfD. Other studies in rodents demonstrated changes in thymus weights at levels 100 times higher than the short-term RfD and lymphoid atrophy of the thymus, spleen, and lymph nodes at levels 1,000 times higher than the short-term RfD.

[3]The acute-duration RfD is based on maternally-mediated full litter resorptions in rats, which was noted in a reproductive and developmental study. At doses 300 times higher than the short-duration RfD, fetal skeletal anomalies were also reported in rats. However, there were no fetal or pup developmental effects noted in rabbits at doses between 50 to 900 times higher than the short-term RfD.

[4]The acute RfD is based on maternally-mediated full litter resorptions in rats, and this effect is also identified as a co-critical effect for the short-term duration, occurring at a dose approximately 200 times higher than the Short-term RfD. Ovarian abscesses were reported in mice at doses

200 times higher than the short-term RfD, and sperm velocity in rats was observed to decrease at BDCM doses 300 times higher than the short-term RfD, although with no supporting histology.

[5]Neurotoxic effects appear to be minimal after BDCM exposure. At levels 400 times higher than the short-term RfD, rats in one study had slightly altered behavior. At BDCM doses 3,000 times higher than the short-term RfD, another study reported hyperactivity in rats.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). (2018). Toxicological Profile for Bromodichloromethane - Draft for Public Comment. Retrieved from https://www.atsdr.cdc.gov/toxprofiles/tp129.pdf

Aida, Y., Takada, K., Uchida, O., Yasuhara, K., Kurokawa, Y., & Tobe, M. (1992). Toxicities of microencapsulated tribromomethane, dibromochloromethane and bromodichloromethane administered in the diet to Wistar rats for one month. *J Toxicol Sci, 17*(3), 119-133.

Aida, Y., Yasuhara, K., Takada, K., Kurokawa, Y., & Tobe, M. (1992). Chronic toxicity of microencapsulated bromodichloromethane administered in the diet to Wistar rats. *J Toxicol Sci, 17*(2), 51-68.

Australian Natural Resource Management Ministerial Council; Environmental Protection and Heritage Council; and National Health and Medical Research Council. (2008). Australian Guidelines for Water Recycling. Augmentation of Drinking Water Supplies. Retrieved from https://www.waterquality.gov.au/sites/default/files/documents/water-recycling-guidelines-augmentation-drinking-22.pdf

Bielmeier, S. R., Best, D. S., Guidici, D. L., & Narotsky, M. G. (2001). Pregnancy loss in the rat caused by bromodichloromethane. *Toxicol Sci, 59*(2), 309-315.

Bowman, F. J., Borzelleca, J. F., & Munson, A. E. (1978). The toxicity of some halomethanes in mice. *Toxicol Appl Pharmacol, 44*(1), 213-215.

California Environmental Protection Agency - OEHHA Cancer Potency Values. (2005). OEHHA Toxicity Criteria Database. Retrieved from https://oehha.ca.gov/chemicals/bromodichloromethane

Cantor, K. P., Villanueva, C. M., Silverman, D. T., Figueroa, J. D., Real, F. X., Garcia-Closas, M., . . . Kogevinas, M. (2010). Polymorphisms in GSTT1, GSTZ1, and CYP2E1, disinfection by-products, and risk of bladder cancer in Spain. *Environ Health Perspect, 118*(11), 1545-1550.

Chen, J., Thirkill, T. L., Lohstroh, P. N., Bielmeier, S. R., Narotsky, M. G., Best, D. S., . . . Douglas, G. C. (2004). Bromodichloromethane inhibits human placental trophoblast differentiation. *Toxicol Sci, 78*(1), 166-174.

Christian, M. S., York, R. G., Hoberman, A. M., Diener, R. M., & Fisher, L. C. (2001). Oral (drinking water) developmental toxicity studies of bromodichloromethane (BDCM) in rats and rabbits. *Int J Toxicol, 20*(4), 225-237.

Christian, M. S., York, R. G., Hoberman, A. M., Diener, R. M., Fisher, L. C., & Gates, G. A. (2001). Biodisposition of dibromoacetic acid (DBA) and bromodichloromethane (BDCM) administered to rats and rabbits in drinking water during range-finding reproduction and developmental toxicity studies. *Int J Toxicol, 20*(4), 239-253.

Christian, M. S., York, R. G., Hoberman, A. M., Fisher, L. C., & Brown, W. R. (2002). Oral (drinking water) two-generation reproductive toxicity study of bromodichloromethane (BDCM) in rats. *Int J Toxicol, 21*(2), 115-146.

Chu, I., Secours, V., Marino, I., & Villeneuve, D. C. (1980). The acute toxicity of four trihalomethanes in male and female rats. *Toxicol Appl Pharmacol, 52*(2), 351-353.

Chu, I., Villeneuve, D. C., Secours, V. E., Becking, G. C., & Valli, V. E. (1982). Trihalomethanes: II. Reversibility of toxicological changes produced by chloroform, bromodichloromethane, chlorodibromomethane and bromoform in rats. *J Environ Sci Health B, 17*(3), 225-240.

Condie, L. W., Smallwood, C. L., & Laurie, R. D. (1983). Comparative renal and hepatotoxicity of halomethanes: bromodichloromethane, bromoform, chloroform, dibromochloromethane and methylene chloride. *Drug Chem Toxicol, 6*(6), 563-578.

DeAngelo, A. B., Geter, D. R., Rosenberg, D. W., Crary, C. K., & George, M. H. (2002). The induction of aberrant crypt foci (ACF) in the colons of rats by trihalomethanes administered in the drinking water. *Cancer Lett, 187*(1-2), 25-31.

Faustino-Rocha, A. I., Rodrigues, D., da Costa, R. G., Diniz, C., Aragao, S., Talhada, D., . . . Oliveira, P. A. (2016). Trihalomethanes in liver pathology: Mitochondrial dysfunction and oxidative stress in the mouse. *Environ Toxicol, 31*(8), 1009-1016.

French, A. S., Copeland, C. B., Andrews, D., Wiliams, W. C., Riddle, M. M., & Luebke, R. W. (1999). Evaluation of the potential immunotoxicity of bromodichloromethane in rats and mice. *J Toxicol Environ Health A, 56*(5), 297-310.

George, M. H., Olson, G. R., Doerfler, D., Moore, T., Kilburn, S., & DeAngelo, A. B. (2002). Carcinogenicity of bromodichloromethane administered in drinking water to Male F344/N Rats and B6C3F1 mice. *Int J Toxicol, 21*(3), 219-230.

Health Canada. (2014). Guidelines for Canadian Drinking Water Quality. Retrieved from https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality/guidelines-canadian-drinking-water-quality-summary-table.html

Keegan, T. E., Simmons, J. E., & Pegram, R. A. (1998). NOAEL and LOAEL determinations of acute hepatotoxicity for chloroform and bromodichloromethane delivered in an aqueous vehicle to F344 rats. *J Toxicol Environ Health A, 55*(1), 65-75.

Kenyon, E. M., Eklund, C., Leavens, T., & Pegram, R. A. (2016). Development and application of a human PBPK model for bromodichloromethane to investigate the impacts of multi-route exposure. *J Appl Toxicol, 36*(9), 1095-1111.

Klinefelter, G. R., Suarez, J. D., Roberts, N. L., & DeAngelo, A. B. (1995). Preliminary screening for the potential of drinking water disinfection byproducts to alter male reproduction. *Reprod Toxicol, 9*(6), 571-578.

Leavens, T. L., Blount, B. C., DeMarini, D. M., Madden, M. C., Valentine, J. L., Case, M. W., . . . Pegram, R. A. (2007). Disposition of bromodichloromethane in humans following oral and dermal exposure. *Toxicol Sci, 99*(2), 432-445.

Lilly, P. D., Andersen, M. E., Ross, T. M., & Pegram, R. A. (1998). A physiologically based pharmacokinetic description of the oral uptake, tissue dosimetry, and rates of metabolism of bromodichloromethane in the male rat. *Toxicol Appl Pharmacol, 150*(2), 205-217.

Lilly, P. D., Ross, T. M., & Pegram, R. A. (1997). Trihalomethane comparative toxicity: acute renal and hepatic toxicity of chloroform and bromodichloromethane following aqueous gavage. *Fundam Appl Toxicol, 40*(1), 101-110.

Lilly, P. D., Simmons, J. E., & Pegram, R. A. (1994). Dose-dependent vehicle differences in the acute toxicity of bromodichloromethane. *Fundam Appl Toxicol, 23*(1), 132-140.

Lilly, P. D., Simmons, J. E., & Pegram, R. A. (1996). Effect of subchronic corn oil gavage on the acute toxicity of orally administered bromodichloromethane. *Toxicol Lett, 87*(2-3), 93-102.

Melnick, R. L., Kohn, M. C., Dunnick, J. K., & Leininger, J. R. (1998). Regenerative hyperplasia is not required for liver tumor induction in female B6C3F1 mice exposed to trihalomethanes. *Toxicol Appl Pharmacol, 148*(1), 137-147.

Mink, F. L., Brown, T. J., & Rickabaugh, J. (1986). Absorption, distribution, and excretion of 14C-trihalomethanes in mice and rats. *Bull Environ Contam Toxicol, 37*(5), 752-758.

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

Moser, V. C., Phillips, P. M., McDaniel, K. L., & Sills, R. C. (2007). Neurotoxicological evaluation of two disinfection by-products, bromodichloromethane and dibromoacetonitrile, in rats. *Toxicology, 230*(2-3), 137-144.

Munson, A. E., Sain, L. E., Sanders, V. M., Kauffmann, B. M., White, K. L., Jr., Page, D. G., . . . Borzelleca, J. F. (1982). Toxicology of organic drinking water contaminants: trichloromethane, bromodichloromethane, dibromochloromethane and tribromomethane. *Environ Health Perspect, 46*, 117-126.

Narotsky, M. G., Pegram, R. A., & Kavlock, R. J. (1997). Effect of dosing vehicle on the developmental toxicity of bromodichloromethane and carbon tetrachloride in rats. *Fundam Appl Toxicol, 40*(1), 30-36.

National Toxicology Program. (1987). NTP Toxicology and Carcinogenesis Studies of Bromodichloromethane (CAS No. 75-27-4) in F344/N Rats and B6C3F1 Mice (Gavage Studies). *Natl Toxicol Program Tech Rep Ser, 321*, 1-182.

National Toxicology Program. (2006). *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Bromodichloromethane in Male F344/N Rats and Female B6C3F$_1$ Mice (Drinking Water Studies).* Retrieved from Research Triangle Park, NC: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr532.pdf

National Toxicology Program. (2007). *Toxicology Studies of Bromodichloromethane in Genetically Modified (FVB Tg.AC Hemizygous) Mice and Carcinogenicity Studies of Bromodichloromethane in Genetically Modified [B6.129-Trp53^{tm1Brd} (N5) Haploinsufficient] Mice*. Retrieved from Research Triangle Park, NC: https://ntp.niehs.nih.gov/ntp/htdocs/gmm_rpts/gmm5.pdf

Ruddick, J. A., Villeneuve, D. C., Chu, I., & Valli, V. E. (1983). A teratological assessment of four trihalomethanes in the rat. *J Environ Sci Health B, 18*(3), 333-349.

Thornton-Manning, J. R., Seely, J. C., & Pegram, R. A. (1994). Toxicity of bromodichloromethane in female rats and mice after repeated oral dosing. *Toxicology, 94*(1-3), 3-18.

Tumasonis, C. F., McMartin, D. N., & Bush, B. (1985). Lifetime toxicity of chloroform and bromodichloromethane when administered over a lifetime in rats. *Ecotoxicol Environ Saf, 9*(2), 233-240.

U.S. Environmental Protection Agency - IRIS. (1987). *Bromodichloromethane; CASRN 75-27-4*. Washington, D.C. Retrieved from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0213_summary.pdf.

U.S. Environmental Protection Agency - Office of Water. (2005). *Drinking Water Criteria Document for Brominated Trihalomethanes*. U.S. Environmental Protection Agency Retrieved from https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1006GVD.TXT.

U.S. Environmental Protection Agency - Office of Water. (2018). Drinking Water Standards and Health Advisories. Retrieved from https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Waller, K., Swan, S. H., DeLorenze, G., & Hopkins, B. (1998). Trihalomethanes in drinking water and spontaneous abortion. *Epidemiology, 9*(2), 134-140.

Water, U. S. E. P. A.-O. o. (2015). *Update of Human Health Ambient Water Quality Criteria: Dichlorobromomethane 75-27-4*. Washington, D.C. Retrieved from https://www.regulations.gov/document?D=EPA-HQ-OW-2014-0135-0195.

World Health Organization (WHO). (2011). Guidelines for Drinking Water Quality - Fourth Edition. Retrieved from http://apps.who.int/iris/bitstream/10665/44584/1/9789241548151_eng.pdf

Zeng, Q., Li, M., Xie, S. H., Gu, L. J., Yue, J., Cao, W. C., . . . Lu, W. Q. (2013). Baseline blood trihalomethanes, semen parameters and serum total testosterone: a cross-sectional study in China. *Environ Int, 54*, 134-140.

Web Publication Date: August 2020

Toxicological Summary for: 1,4-Dichlorobenzene

CAS: **106-46-7**

Synonyms: p-Dichlorobenzene, paradichlorobenzene, para-Dichlorobenzene

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

Short-term Non-Cancer Health-Based Value (nHBV$_{Short-term}$) = 50 µg/L

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

$$= \frac{(0.069 \text{ mg/kg-d) x } (0.2)^* \text{ x } (1000 \text{ µg/mg)}}{(0.290 \text{ L/kg-d})^{**}}$$

= 47.5 rounded to **50 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 6.9/100 = 0.069 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	30 mg/kg-d (administered dose NOAEL, Bornatowicz 1994 cited in US EPA 2006.)
Dose Adjustment Factor (DAF):	0.23 Body weight scaling, default for female Sprague-Dawley rat, subchronic (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 30 mg/kg-d x 0.23 = 6.9 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 for lack of neurotoxicity studies and limitations in study reporting.
Critical effect(s):	Reduced pup body weight, increased pup mortality, increased incidence postnatal dry and scaly skin, increased postnatal tail constriction, and a reduction in the number of pups with a positive reaction in the neurobehavioral draw-up test.
Co-critical effect(s):	Increased liver weight and hepatocyte proliferation
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Nervous system

Subchronic Non-Cancer Health-Based Value (nHBV$_{\text{Subchronic}}$) = nHBV$_{\text{Short-term}}$ = 50 µg/L

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

$$= \frac{(0.042 \text{ mg/kg-d}) \text{ x } (0.2)^* \text{ x } (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 113 rounded to 100 µg/L

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 4.21/100 = 0.042 mg/kg-d (Beagle)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	7.14 mg/kg-d (administered time-weighted-average dose NOAEL, Naylor 1996, cited in EPA, 1996.)
Dose Adjustment Factor (DAF):	0.59 Body weight scaling, default for female beagle in 1-yr toxicity study (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 7.14 mg/kg-d x 0.59 = 4.21 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 for lack of neurotoxicity studies and limitations in study reporting.
Critical effect(s):	Increased liver weight, hepatocellular hypertrophy, hepatocyte pigment deposition, hepatic portal inflammation, increased serum alkaline phosphatase, and decreased serum albumin; increased kidney weight and incidence of collecting duct epithelial vacuolation; increased blood platelet count; and increased thyroid weight
Co-critical effect(s):	Reduced pup body weight, increased pup mortality, increased incidence postnatal dry and scaly skin, increased postnatal tail constriction, and a reduction in the number of pups with a positive reaction in the neurobehavioral draw-up test; increased hepatocyte proliferation, increased bile duct/ductile hyperplasia, increased serum alanine aminotransaminase, and increased gamma-glutamyl transferase; increased incidence of renal discoloration; increased incidence of anemia and hyperplastic changes in hematopoietic tissues; and increased adrenal gland weight

Additivity endpoint(s): Adrenal, Developmental, Hematological (blood) system, Hepatic (liver) system, Nervous system, Renal (kidney) system, Thyroid

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 50 μg/L. Additivity endpoints: Developmental, Hepatic (liver) system, Nervous system

Chronic Non-Cancer Health-Based Value (nHBV$_{Chronic}$) = nHBV$_{Short-term}$ = 50 μg/L

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

$$= \frac{\text{(0.032 mg/kg-d) x (0.2)}^* \text{ x (1000 μg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

$$= 142 \text{ rounded to } 100 \text{ μg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration: HED/Total UF = 32.1/1000 = 0.032 mg/kg-d (B6C3F$_1$ mouse)
Source of toxicity value: Determined by MDH in 2019
Point of Departure (POD): 214 mg/kg-d (administered time-weighted-average dose LOAEL, NTP 1987)
Dose Adjustment Factor (DAF): 0.15 Body weight scaling, default for male and female B6C3F$_1$ mouse, chronic (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED): POD x DAF = 214 mg/kg-d x 0.15 = 32.1 mg/kg-d
Total uncertainty factor (UF): 1000
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for extrapolation from a LOAEL, and 3 for database uncertainty for lack of neurotoxicity studies and limitations in study reporting.

Critical effect(s): Hepatocellular degeneration; lymphoid hyperplasia; nephropathy and renal tubular regeneration; and adrenal gland hyperplasia
Co-critical effect(s): Reduced pup body weight, increased pup mortality, increased incidence postnatal dry and scaly skin, increased postnatal tail constriction, and a reduction in the number of pups with a positive reaction in the neurobehavioral draw-up test; increased liver weight, hepatocyte proliferation, hepatocyte hypertrophy, hepatocellular pigment deposition, hepatic portal inflammation, bile

| | duct/ductile hyperplasia, increased serum alanine aminotransaminase, increased gamma-glutamyl transferase, increased serum alkaline phosphatase, and decreased serum albumin; increased kidney weight, changes in renal proximal tubule cell proliferation, increased incidence collecting duct epithelial vacuolation, and renal discoloration; anemia, increased blood platelet count, and hyperplastic changes in hematopoietic tissues; increased adrenal weight; and increased thyroid weight |
| Additivity endpoint(s): | Adrenal, Developmental, Hematological (blood) system, Hepatic (liver) system, Immune system, Nervous system, Renal (kidney system), Thyroid |

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 50 µg/L. Additivity endpoints: Developmental, Hepatic (liver) system, Nervous system

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	"Not likely to be carcinogenic to humans based on evidence that a non-mutagenic mode-of-action involving mitogenesis was established for *p*-dichlorobenzene-induced liver tumors in mice, and that the carcinogenic effects are not likely below a defined dose that does not perturb normal liver homeostasis (*e.g.* increased liver cell proliferation)". (US EPA 2018) Group 2B, possibly carcinogenic to humans (IARC 1999 cited in IARC 2019) Reasonably anticipated to be a human carcinogen (ATSDR 2006; NTP 2016)
Slope factor (SF):	Not applicable
Source of cancer slope factor (SF):	Not applicable
Tumor site(s):	Liver

Statement for non-linear carcinogens:
Based on the available information, MDH has determined that 1,4-dichlorobenzene is a nonlinear carcinogen. The MDH Short-term, Subchronic, and Chronic nHBVs of 50 µg/L are based on preventing hepatocellular proliferation, the key event in 1,4-dichlorobenzene carcinogenicity.

Volatile: Yes (high)

Summary of Guidance Value History:
A cancer HRL of 10 µg/L was promulgated in 1994. A revised non-cancer HBV of 50 µg/L was derived in 2019. This value is higher than the 1994 cancer HRL and is protective of cancer effects as the result of: 1) the use of MDH's most recent risk assessment methodology; 2) better understanding of the mode-

of-action for 1,4-dichlorobenzene toxicity (hepatocellular proliferation); and 3) an updated cancer classification from EPA (not likely to be carcinogenic to humans at doses that do not perturb normal liver homeostasis). In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Increased thyroid and adrenal gland weights were observed in exposed laboratory animals and were identified as critical and co-critical effects for the subchronic duration. The dose levels at which these effects were observed were 300 to 1,000-fold higher than the derived reference doses (RfDs). Adrenal gland hyperplasia was an effect of the chronic critical study and occurred at levels 500 to 1,000 times higher than the derived RfDs. Thyroid hyperplasia occurred at levels 900 to 2,000 times higher than the derived RfDs. 1,4-Dichlorobenzene is currently on the EPA Endocrine Disruptor Screening Program's List 2 for endocrine activity testing.

[2] Although one short-term immunotoxicity study in male mice did not detect any immunological effects at doses greater than 2,000 to 4,000 times higher than the derived RfDs, other toxicity studies did note secondary immunological effects during longer exposures at lower doses. The chronic duration RfD is partly based on a secondary immune effect (lymphoid hyperplasia). This effect, along with hypoplasia of the bone marrow, reduced spleen weights, and lymphoid depletion of the spleen and thymus were observed at doses 250 to 2,000-fold higher than the derived RfDs.

[3] Developmental effects (reduced body weight at birth, increased mortality, dry and scaly skin, tail constriction, and a reduction in positive reactions in a neurodevelopmental test) in rat pups forms the basis of the short-term RfD. Additional developmental effects were also observed as dose levels increased, with increased incidence of delayed eye opening and ear erection, skeletal variations, and cyanosis occurring at doses greater than 900-fold higher than the short-term RfD. Reduced fetal weight was also reported at doses greater than 3,000 times higher than the short-term RfD.

[4] In developmental and 2-generational studies no reproductive effects were reported at doses greater than 900 fold higher than the short-term RfD. In subchronic and chronic studies, uterine hyperplasia and changes in female reproductive organ weights were reported at dose levels 700 to 2,000 times higher than the derived RfDs.

[5] The short-term RfD is based in part on a neurodevelopmental effect (positive reaction to the "draw-up" test) in rat pups. The decision to apply a database uncertainty factor of "3" in part is due to the lack of any other neurotoxicity tests in the 1,4-dichlorobenzene database.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry. (2006). *Toxicological Profile for Dichlorobenzenes*. Retrieved from https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=704&tid=126.

Agency for Toxic Substances and Disease Registry. (2018). Minimal Risk Levels (MRLs) for Hazardous Substances. Retrieved from https://www.atsdr.cdc.gov/mrls/mrllist.asp

Buckman, F. (2013). Paradichlorobenzene (toxin)-induced leucoencephalopathy. *BMJ Case Rep, 2013*.

Butterworth, B. E., Aylward, L. L., & Hays, S. M. (2007). A mechanism-based cancer risk assessment for 1,4-dichlorobenzene. *Regul Toxicol Pharmacol, 49*(2), 138-148.

California State Water Resources Control Board. (2017). Compilation of Water Quality Goals. Retrieved from http://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/

Carlson, G. P., & Tardiff, R. G. (1976). Effect of chlorinated benzenes on the metabolism of foreign organic compounds. *Toxicol Appl Pharmacol, 36*(2), 383-394.

Eldridge, S. R., Goldsworthy, T. L., Popp, J. A., & Butterworth, B. E. (1992). Mitogenic stimulation of hepatocellular proliferation in rodents following 1,4-dichlorobenzene administration. *Carcinogenesis, 13*(3), 409-415.

European Commission Joint Research Centre. (2004). *European Union Risk Assessment Report 1,4-dichlorobenzene*. France Retrieved from https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/european-union-risk-assessment-report-14-dichlorobenzene-cas-no-106-46-7-einecs-no-203-400-5

Giavini, E., Broccia, M. L., Prati, M., & Vismara, C. (1986). Teratologic evaluation of p-dichlorobenzene in the rat. *Bull Environ Contam Toxicol, 37*(2), 164-168.

Health Canada. (2014). Guidelines for Canadian Drinking Water Quality: Technical Document - Dichlorobenzenes. Retrieved from https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-dichlorobenzenes.html

Hollingsworth, R. L., Hoyle, H. R., Oyen, F., Rowe, V. K., & Spencer, H. C. (1956). Toxicity of paradichlorobenzene; determinations on experimental animals and human subjects. *AMA Arch Ind Health, 14*(2), 138-147.

International Agency for Research on Cancer. (2019). IARC Monographs on the Identification of Carcinogenic Hazards to Humans. Retrieved from https://monographs.iarc.fr/agents-classified-by-the-iarc/

Lake, B. G., Cunninghame, M. E., & Price, R. J. (1997). Comparison of the hepatic and renal effects of 1,4-dichlorobenzene in the rat and mouse. *Fundam Appl Toxicol, 39*(1), 67-75.

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Health and Medical Research Council (Australia). (2018). Australian Drinking Water Guidelines (2011) - Updated in 2018. Retrieved from https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines#block-views-block-file-attachments-content-block-1

National Institutes of Health. (Accessed April 2019). Toxnet: International Toxicity Estimates for Risk (ITER) Database. Retrieved from https://toxnet.nlm.nih.gov/newtoxnet/iter.htm

National Toxicology Program. (1987). *Toxicology and Carcinogenesis Studies of 1,4-Dichlorobenzene (CAS No. 106-46-7) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies).* (319). U.S. Department of Health and Human Services. Retrieved from https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr319.pdf

National Toxicology Program. (2016). *Report on Carcinogens, Fourteenth Edition*. Retrieved from https://ntp.niehs.nih.gov/ntp/roc/content/listed_substances_508.pdf

Suhua, W., Rongzhu, L., Changqing, Y., Guangwei, X., Fangan, H., Junjie, J., . . . Aschner, M. (2010). Lipid peroxidation and changes of trace elements in mice treated with paradichlorobenzene. *Biol Trace Elem Res, 136*(3), 320-336.

U.S. Environmental Protection Agency. (1996). *p-Dichlorobenzene - Chronic Oral Toxicity in Dogs (Naylor Data Evaluation Report)*. Retrieved from https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/061501/061501-009.pdf

U.S. Environmental Protection Agency. (2006). *Toxicological Review of Dichlorobenzenes - In Support of Summary Information on the Integrated Risk Information System (IRIS)*. Retrieved from https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=155906.

U.S. Environmental Protection Agency. (2018). *para-Dichlorobenzene: Human Health Risk Assessment in Support of Registration Review*. Retrieved from https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0117-0013

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2018). Office of Water. 2018 Edition of the Drinking Water Standards and Health Advisories. Retrieved from https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Valentovic, M. A., Ball, J. G., Anestis, D., & Madan, E. (1993). Acute hepatic and renal toxicity of dichlorobenzene isomers in Fischer 344 rats. *J Appl Toxicol, 13*(1), 1-7.

World Health Organization (WHO). (2011). Guidelines for Drinking Water Quality - Volume 1: Recommendations. Fourth edition, incorporating first, second, and third addenda. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/44584/9789241548151_eng.pdf;jsessionid=E976BBE12F8BAFAB85ABB52688615C06?sequence=1

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Toxicological Summary for: trans-1,2-Dichloroethene

CAS: 156-60-5

Synonyms: 1,2-Dichloroethylene (trans); 1,2-trans-dichloroethylene; (E)-1,2-dichloroethene; (E)-1,2-Dichloroethylene; trans-1,2-Dichloroethene; trans-1,2-dichloroethylene; trans-1,2-dichloroethylene ; trans-1,2-DCE; trans-acetylene dichloride; trans-dichloroethylene

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

Short-term Non-Cancer Health-Based Value (nHBV$_{Short-term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health-Based Value/Risk Assessment Advice (nHBV$_{Subchronic}$) = 50 µg/L

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

$$= \frac{(0.020 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 54 rounded to **50 µg/L**

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 2.03/100 = 0.020 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	14.5 mg/kg-d (BMDL$_{ADM-1SD}$ based on 2018 OEHHA modeling of immunotoxicity data from Shopp et al 1985)
Dose Adjustment Factor (DAF):	0.14, Body weight scaling, default (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 14.5 mg/kg-d x 0.14 = 2.03 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 due to lack of a multigenerational study and supplementing database with inhalation studies
Critical effect(s):	Decreased ability to produce antibodies against sheep RBCs in male spleen cells

Co-critical effect(s): Decreased thymus weight, clinical chemistry effects
Additivity endpoint(s): Immune system

Chronic Non-Cancer Health-Based Value (nHBV$_{Chronic}$) = 9 µg/L

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

$$= \frac{(0.0020 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 8.8 rounded to **9 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 2.03/1000 = 0.0020 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	14.5 mg/kg-d (BMDL$_{ADM-1SD}$ based on 2018 OEHHA modeling of immunotoxicity data from Shopp et al 1985, subchronic exposure)
Dose Adjustment Factor (DAF):	0.14, Body weight scaling, default (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 14.5 mg/kg-d x 0.14 = 2.03 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for subchronic-to-chronic extrapolation due to clear and significant immunotoxicity in the subchronic study, and 3 for database uncertainty due to lack of a multigenerational study and supplementing database with inhalation studies
Critical effect(s):	Decreased ability to produce antibodies against sheep RBCs in male spleen cells
Co-critical effect(s):	Decreased thymus weight, clinical chemistry effects
Additivity endpoint(s):	Immune system

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	*"Inadequate information to assess the carcinogenic potential"* of trans-1,2-DCE
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	EPA IRIS 2010
Tumor site(s):	Not Applicable

Volatile: Yes (High)

Summary of Guidance Value History:

A chronic HRL of 100 µg/L was promulgated in 1993. In 2011, subchronic and chronic Health-Based Values (HBVs) of 600 and 100 µg/L, respectively, were derived. In 2012, MDH re-evaluated the HBVs to incorporate HED methodology, resulting in subchronic and chronic HBVs of 200 and 40 µg/L, respectively. The 2012 HBVs were adopted as HRLs in 2013 and the 1993 HRL was repealed. In 2020, MDH re-evaluated the 2013 HRLs and derived subchronic and chronic HBVs of 60 and 9 µg/L, respectively. The re-evaluation resulted in values that were 3 to 4-fold lower as the result of using the most recent risk assessment methodology (specifically, improvements in benchmark dose modeling for POD calculation). In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in a decrease in the Subchronic HBV from 60 µg/L to 50 µg/L.

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	Yes	Yes	No	No
Effects observed?	No	Yes[1]	Yes[2]	No[3]	Secondary observations[4]

Comments on extent of testing or effects:

[1]Shopp et al. (1985) measured depression in humoral immune status following 90 days of exposure via drinking water. These effects form the basis of the subchronic and chronic HBVs.
[2]A single inhalation developmental study exists. Decreased fetal body weight was observed at doses estimated to be over 400-fold higher than the minimal short-term critical Human Equivalent Dose. A database uncertainty factor has been applied, in part, due to the lack of oral developmental/reproductive studies.
[3]Examination of the reproductive organs of animals in the 90-day study did not report any histological changes. A database uncertainty factor has been applied, in part, due to the absence of a multigenerational study.
[4]Neurological effects have not been adequately studied. Acute exposures (e.g., a single high dose) have reported effects.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). Minimal Risk Levels. URL: https://www.atsdr.cdc.gov/mrls/index.html

Agency for Toxic Substances and Disease Registry (ATSDR). 1996. Toxicological Profile for 1,2 Dichloroethane.

Barnes DW, VM Sanders, KL White, GM Shopp, AL Munson. 1985. Toxicology of Trans-1,2-Dichloroethylene in the Mouse. Drug and Chem Tox 8(5)373-392.

California Environmental Protection Agency, OEHHA Toxicity Criteria Database. URL: http://www.oehha.ca.gov/risk/ChemicalDB/index.asp

California Environmental Protection Agency, OEHHA Public Health Goals for Chemicals in Drinking Water: *Cis-* and *Trans*-1,2-Dicholorethylene (2018). URL: http://www.oehha.ca.gov/water/phg/allphgs.html

Freundt KJ, GP Liebaldt and E Lieberwirth. 1977. Toxicity Studies on Trans-1,2-Dichloroethylene. Toxicology 7:141-153.

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). 2011. MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses. Available: https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Toxicology Program (NTP) 2002. NTP Technical Report on the Toxicity Studies of trans-1,2-Dichloroethylene Administered in Microcapsules in Feed to F344/N Rats and B6C3F$_1$ Mice.

Shopp GM, VM Sanders, KL White, and AE Munson. 1985. Humoral and Cell-Mediated Immune Status of Mice Exposed to trans-1,2-Dichloroethylene. Drug Chem. Tox., 8(5):393-407.

Syracuse Research PhysProp Database. URL: http://www.syrres.com/esc/physdemo.htm

U.S. Environmental Protection Agency (EPA) - Health Effects Assessment Summary Tables (HEAST). July 1997.

U.S. Environmental Protection Agency (EPA), Integrated Risk Information System. Trans-1,2-Dichloroethylene. URL: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=314

U.S. Environmental Protection Agency (EPA), Office of Drinking Water. Drinking Water Standards and Health Advisories (August, 2006). URL: http://www.epa.gov/waterscience/criteria/drinking/dwstandards.pdf

U.S. Environmental Protection Agency - Office of Research and Development. (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. from http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf

U.S. Environmental Protection Agency (EPA) - Toxicological Review of cis-1,2-dichloroethylene and trans-1,2-dichloroethylene. 2010. URL: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0418tr.pdf

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Web Publication Date: August 2020

Toxicological Summary for: 1,1-Dichloroethylene

CAS: **75-35-4**

Synonyms: Vinylidene chloride, 1,1-Dichloroethene

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = 200 µg/L

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

$$= \frac{(0.069 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 186 \text{ rounded to } \textbf{200 µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 2.07/30 = 0.069 mg/kg-d (Sprague Dawley Rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	9 mg/kg-d (NOAEL, Nitschke et al. 1983 supported by Quast et al. 1977)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 9 mg/kg-d x 0.23 = 2.07 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Fatty changes in the liver
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = 200 µg/L

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

$$= \frac{\text{(0.040 mg/kg-d) x (0.2)}^* \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

$$= 177 \text{ rounded to } \textbf{200 µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 1.20/30 = 0.040 mg/kg-d (Sprague Dawley Rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	4.6 mg/kg-d (BMDL$_{10}$, Quast et al. 1983 as calculated by USEPA, 2002)
Dose Adjustment Factor (DAF):	0.26, Body weight scaling, default (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 4.6 mg/kg-d x 0.26 = 1.20 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Fatty changes in the liver
Co-critical effect(s):	Fatty changes in the liver
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Data are inadequate for an assessment of human carcinogenic potential (oral route); Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential (inhalation route) (USEPA, 2002)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (high)

Summary of Guidance Value History:
 A non-cancer Health Risk Limit (HRL) of 6 µg/L was promulgated in 1993/1994. Subchronic and chronic health-based values (HBV) of 200 µg/L were derived in 2009 and were promulgated as Health Risk Limits (HRL) in 2011. In 2019, MDH re-evaluated the noncancer HRLs using the most recent risk assessment methodology, resulting in no changes to the subchronic and chronic guidance values. In

2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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?	-	-	Yes[1]	Yes[2]	-[3]

Comments on extent of testing or effects:
[1]Two developmental studies with oral exposure have been conducted in laboratory animals. No developmental effects were observed at doses up to 100 times higher than the subchronic reference dose. Developmental effects were tested and observed in inhalation studies, however, maternal toxicity was evident at levels that resulted in developmental toxicity.

[2]One multi-generation reproductive study with oral exposure has been conducted in laboratory animals. No reproductive effects were observed at doses up to 100 times higher than the subchronic reference dose. No reproductive effects were observed in developmental inhalation studies in laboratory animals.

[3]Neurotoxicity of 1,1-dichloroethylene has not been studied. However, neurotoxicity endpoints were included in a developmental inhalation study in laboratory animals. No evidence of developmental neurotoxicity was observed up to the highest dose tested.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). (1994). *Toxicological Profile for 1,1-Dichloroethene*. Retrieved from https://www.atsdr.cdc.gov/toxprofiles/tp39.pdf

Agency for Toxic Substances and Disease Registry (ATSDR). (2009). *Addendum to the Toxicological Profile for 1,1-Dichloroethene*. Retrieved from https://www.atsdr.cdc.gov/toxprofiles/1_1_dichloroethene_addendum.pdf

Agency for Toxic Substances and Disease Registry (ATSDR) - MRLs. (2019). Minimal Risk Levels for Hazardous Substances (MRLs). Retrieved from https://www.atsdr.cdc.gov/mrls/mrllist.asp

California Environmental Protection Agency. (2019). OEHHA Toxicity Criteria Database. Retrieved from https://data.ca.gov/dataset/toxicity-criteria-database

California Environmental Protection Agency (OEHHA). (1999). *Public Health Goal for 1,1-Dichloroethylene in Drinking Water*. Retrieved from https://oehha.ca.gov/media/downloads/water/chemicals/phg/11dcef.pdf

Canada, H. (1994). *Guidelines for Canadian Drinking Water Quality: Guideline Technical Document for 1,1-Dichloroethylene*. Retrieved from https://www.canada.ca/content/dam/canada/health-canada/migration/healthy-canadians/publications/healthy-living-vie-saine/water-dichloroethylene-eau/alt/water-dichloroethylene-eau-eng.pdf

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Toxicology Program (NTP). (2015). *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Vinylidene Chloride in F344/N Rats and B6C3F1/N Mice.*

Nitschke, K., Smith, FA., Quast, JF., Norris, JM., Schwetz, BA. (1983). A three-generation rat reproductive toxicity study of vinylidene chloride in the drinking water. *Fund Appl Tox, 3*, 75-79.

Quast, J., Humiston, CG., Schwetz, RW., Balmer, MF., Rampy, LW., Norris, JM., Gehring, PJ. (1977). Results of 90-day toxicity study in rats given vinylidene chloride in their drinking water or exposed to VDC vapor by inhalation. (abstract for 16th Annual Meeting of the Society of Toxicology). *Toxicol Appl Pharmacol, 4*(187).

Quast, J., Humiston, CG., Wade, CE., Hallard, J., Beyer, JE., Schwetz, RW., Norris, JM. (1983). A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidene chloride. *Fund Appl Tox, 3*, 55-62.

Syracuse Research PhysProp Database. Retrieved from http://www.syrres.com/what-we-do/databaseforms.aspx?id=386

U.S. Environmental Protection Agency (EPA). ChemView Pollution, Prevention, Toxics Page - VCCEP Chemicals. Voluntary Children's Chemical Evaluation Program (VCCEP). Retrieved from https://chemview.epa.gov/chemview

U.S. Environmental Protection Agency (EPA). Regional Screening Levels (RSLs) - Generic Tables. Retrieved from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables-november-2017

U.S. Environmental Protection Agency (EPA). (2002). *Integrated Risk Information System (IRIS) Toxicological Review of 1,1-Dichloroethylene*. Retrieved from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0039tr.pdf

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2018). *2018 Edition of the Drinking Water Standards and Health Advisories Tables*. Retrieved from https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

World Health Organization (WHO). (2003). *Concise International Chemical Assessment Document 51 for 1,1-Dichloroethene*. Retrieved from https://www.who.int/ipcs/publications/cicad/en/cicad51.pdf?ua=1

World Health Organization (WHO). (2005). *1,1-Dichloroethene in Drinking Water: Background document for development of WHO Guidelines for Drinking-water Quality* Retrieved from https://www.who.int/water_sanitation_health/dwq/chemicals/11dichloroethenefinal.pdf

Web Publication Date: September 2021

Toxicological Summary for: 1,2-Dichloropropane

CAS**: 78-87-5**

Synonyms: Propylene dichloride

Individuals with inherited glucose-6-phosphate dehydrogenase (G6PDH) deficiency may be more susceptible to the negative health effects associated with 1,2-dichloropropane toxicity, particularly hemolytic anemia (ATSDR 2019). According to the g6pd Deficiency Foundation, the overall frequency of G6PDH deficiency is 4-7% in the US, almost exclusively in males, with higher rates (~12%) in African American males. Due to lack of data, a quantitative estimate of sensitivity associated with G6PDH deficiency could not be conducted. However, MDH has applied a 10-fold uncertainty factor to account for human variability in the response to 1,2-dichloropropane toxicity. People who have questions about G6PDH deficiency should contact their physician.

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

Short-term Non-Cancer Health-Based Value (nHBV$_{Short-term}$) = 20 µg/L

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

$$= \frac{(0.029 \text{ mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{(0.290 \text{ L/kg-d)}^{**}}$$

$$= \mathbf{20 \text{ µg/L}}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.

[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 2.94/100 = 0.029 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	12.8 mg/kg-d (administered dose BMDL$_{05}$, developmental toxicity study by Kirk 1995)
Dose Adjustment Factor (DAF):	0.23, body weight scaling, default (US EPA 2011 and MDH 2017)

Human Equivalent Dose (HED):	POD x DAF = 12.8 mg/kg-d x 0.23 = 2.94 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 due to the absence of an adequate 2-generational study and a developmental neurotoxicity study in offspring
Critical effect(s):	Delayed ossification of the fetal skull
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health-Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 20 µg/L

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

$$= \frac{(0.029 \text{ mg/kg-d})^{***} \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 78 \text{ rounded to } 80 \text{ µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.
[***] The calculated subchronic RfD (0.059 mg/kg-d) is higher than the Short-term RfD (0.029 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.

The Subchronic HBV must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic HBV is set equal to the Short-term nHBV of 20 µg/L. Additivity endpoint: Developmental

Chronic Non-Cancer Health-Based Value (nHBV$_{Chronic}$) = nHBV$_{Short-term}$ = 20 µg/L

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

$$= \frac{(0.018 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 80 \text{ µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 17.8/1000 = 0.018 mg/kg-d (Sprague-Dawley rat)

1,2-Dichloropropane -2

Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	71 mg/kg-d (administered dose LOAEL; Bruckner 1989, subchronic exposure)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 71 mg/kg-d x 0.25= 17.8 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for database uncertainty due to the absence of an adequate 2-generational study and a developmental neurotoxicity study in offspring, 3 for using a LOAEL in place of a NOAEL, and 3 for using a subchronic study for a chronic duration
Critical effect(s):	Hemolytic anemia (increased bilirubin and increased hemosiderosis and hyperplasia of erythropoietic elements of the spleen)
Co-critical effect(s):	Increased absolute and relative liver weights, fatty change of the liver, hepatocytomegaly, increased cholesterol and glycerin, and liver necrosis; mammary gland hyperplasia; transient neurotoxicity in pregnant dams, and delayed ossification of the fetal skull.
Additivity endpoint(s):	Developmental, Female Reproductive system, Hematological (blood) system, Hepatic (liver) system, and Nervous system

The Chronic nHBV must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 20 µg/L. Additivity endpoint: Developmental

Cancer Health-Based Value (cHBV) = 3 µg/L

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

$$= \frac{1E\text{-}5) \times (1000\ \mu g/mg)}{[(0.037 \times 10^{*} \times 0.155\ L/kg\text{-}d^{**} \times 2) + (0.037 \times 3^{*} \times 0.040\ L/kg\text{-}d^{**} \times 14) + (0.037 \times 1^{*} \times 0.042\ L/kg\text{-}d^{**} \times 54)] / 70}$$

= 2.68 rounded to **3 µg/L**

[*]ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
[**]Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Cancer classification:	Carcinogenic to humans (WHO 2017)

Slope factor (SF): 0.037 $(mg/kg-d)^{-1}$ based on liver tumors in male mice (NTP 1986)

Source of cancer slope factor (SF): (EPA 2016)

Tumor site(s): Liver

Volatile: Yes (high)

Summary of Guidance Value History:

In 1994, MDH developed a cancer HRL (cHRL) of 5 µg/L. The 2021 cHBV (3 µg/L) is based on the same NTP 1986 study (liver tumors in male mice), however, MDH used an updated EPA slope factor (EPA 2016) and incorporated age dependent adjustment factors (ADAFs) to determine the 2021 cHBV. Updated EPA water intake rates also contributed to a lower MDH 2021 cHBV.

Noncancer guidance values previously did not exist, therefore, the short-term, subchronic, and chronic noncancer HBVs derived in 2021 represent new values.

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	Yes
Effects observed?	-[1]	-	Yes[2]	Yes[3]	Yes[4]

Comments on extent of testing or effects:

[1] Thyroid follicular cell adenoma or carcinoma occurred in female mice (NTP 1986) at a dose 900 times higher than the short-term RfD.

[2] The short-term duration RfD is based on delayed skull ossification in fetal rats. This effect was also observed in rabbits at a dose approximately 2.4-fold higher than the dose in rats. A database UF of 3 was applied due to the lack of a developmental neurotoxicity study in offspring.

[3] Reproductive effects include complete litter resorptions in rabbits at a level 4,000 times higher than the short-term duration RfD. Testicular degeneration and declines in sperm number in rats occurred at levels 3,000 to 5,000 times the short-term RfD. Mammary gland hyperplasia occurred in rats at a dose 700 times higher than the short-term RfD. A database UF of 3 was added in part due to the absence of an adequate 2-generational study. A 2-generation study exists in rats, however, 1,2-dichloropropane was added to the drinking water and due to palatability issues as the dose increased, dams drank significantly less water. This obscured the results of the study, as effects could be attributed, in part, to dehydration from lower water ingestion.

[4] Transient central nervous system (CNS) depression was a common occurrence in test animals after exposure to 1,2-dichloropropane and occurred at levels starting at 100 times higher than the short-term RfD. Only one study was specifically designed to test neurotoxicity in adult animals and aside from transient CNS depression, found no other effects. However, neurodevelopmental data are lacking, especially for offspring of exposed parental animals, and therefore a database UF of 3 was applied to account for the uncertainty around developmental neurotoxicity.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). (2019). *Toxicological Profile for 1,2-Dichloropropane. Draft for Public Comment.* Retrieved from https://www.atsdr.cdc.gov/toxprofiles/tp134.pdf

Berdasco, N.M., Johnson, K.A., & Hanley, T.R., Jr. (1988). *Propylene Dichloride: Oral Teratology Probe Study in New Zealand White Rabbits*. The Dow Chemical Company.

Bruckner, J.V., MacKenzie, W.F., Ramanathan, R., Muralidhara, S., Kim, H.J., & Dallas, C.E. (1989). Oral toxicity of 1,2-dichloropropane: acute, short-term, and long-term studies in rats. *Fundam Appl Toxicol, 12*(4), 713-730.

California EPA - OEHHA. (1999). *Public Health Goal for 1,2-Dichloropropane in Drinking Water*. Retrieved from https://oehha.ca.gov/media/downloads/water/public-health-goal/12dcpf.pdf

California EPA - OEHHA. (2004). *No Significant Risk Level (NSRL) for the Proposition 65 Carcinogen 1,2-Dichloropropane*. https://oehha.ca.gov/proposition-65/chemicals/12-dichloropropane

California State Water Resources Control Board. Compilation of Water Quality Goals. Retrieved from http://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/

g6pd Deficiency Foundation. (Accessed 2021). https://g6pddf.org/

Gi, M., Fujioka, M., Yamano, S., Shimomura, E., Ishii, N., Kakehashi, A., . . . Wanibuchi, H. (2015). Determination of Hepatotoxicity and Its Underlying Metabolic Basis of 1,2-Dichloropropane in Male Syrian Hamsters and B6C3F1 Mice. *Toxicol Sci, 145*(1), 196-208.

Gi, M., Fujioka, M., Yamano, S., Shimomura, E., Kanki, M., Kawachi, S., . . . Wanibuchi, H. (2015). Modifying effects of 1,2-dichloropropane on N-nitrosobis(2-oxopropyl)amine-induced cholangiocarcinogenesis in male Syrian hamsters. *J Toxicol Sci, 40*(5), 647-656.

Imberti, R., Mapelli, A., Colombo, P., Richelmi, P., Berte, F., & Bellomo, G. (1990). 1,2-Dichloropropane (DCP) toxicity is correlated with DCP-induced glutathione (GSH) depletion and is modulated by factors affecting intracellular GSH. *Arch Toxicol, 64*, 459-465.

Kennedy, G.L., & Graepel, J. (1991). Acute Toxicity in the Rat Following Either Oral or Inhalation Exposure. *Toxicol Letters, 56*(n3), 317-326.

Kirk, H.D., Berdasco, N.M., Breslin, W.J., & Hanley, T.R., Jr. (1995). Developmental toxicity of 1,2-dichloropropane (PDC) in rats and rabbits following oral gavage. *Fundam Appl Toxicol, 28*(1), 18-26.

Kirk, H.D., Hanley Jr,T.R., Bond, D.M., Firchau, C.N., Peck, C.N., Stebbins, K.E., and Johnson, K.A.,. (1990). *Propylene Dichloride: Two-Generation Reproduction Study in Sprague-Dawley Rats. Submitted to the EPA, TSCA Program by Dow Chemical Company.*

Kirk, H.D., Hanley, T.R., Jr., & Johnson, K.A. (1988). *Propylene Dichloride: A 13-Day Repeated Oral Gavage Study in New Zealand White Rabbits*. Dow Chemical Company.

Kirk, H.D., Hanley, T.R., Jr., Johnson, K.A., & Dietz, F.K. (1989). *Propylene Dichloride: Oral Teratology Probe Study in Sprague-Dawley Rats*. The Dow Chemical Company.

Loeuillard, E., Fischbach, S.R., Gores, G.J., & Rizvi, S. (2019). Animal models of cholangiocarcinoma. *Biochim Biophys Acta Mol Basis Dis, 1865*(5), 982-992.

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Toxicology Program (NTP). (1986). *Toxicology and Carcinogenesis Studies of 1,2-Dichloropropane in F344/N Rats and B6C3F1 Mice (Gavage Studies). Technical Report Series. No. 263.* Research Triangle Park, NC.

New Jersey Department of Environmental Protection. (2015). Standards for Drinking Water, Ground Water, Soil and Surface Water. Retrieved from https://www.nj.gov/dep/standards/Standards.htm

Organization for Economic Co-operation and Development (OECD). (2006). 1,2-Dichloropropane CAS No: 78-87-5 Screening Information Dataset (SIDS) Initial Assessment Report In. Berne, Switzerland.

U.S. Environmental Protection Agency (EPA). (1985). *Research and Development Drinking Water Criteria Document for 1,2-Dichloropropane*.

U.S. EPA. (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. EPA. (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. EPA. (2016). *Provisional Peer-Reviewed Toxicity Values for 1,2-Dichloropropane (CASRN 78-87-5)*. Cincinnati, OH.

U.S. EPA. (2018). 2018 Edition of the Drinking Water Standards and Health Advisories. Retrieved from https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf

U.S. EPA. (2019). *Exposure Factors Handbook Chapter 3 Update 2019*. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3.

U.S. EPA. (2020). *Final Scope of the Risk Evaluation for 1,2-Dichloropropane*.

U.S. EPA. (Accessed 2021). EPA Chemistry Dashboard. Retrieved from https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID0020448#toxicity-values

U.S. EPA. (Accessed 2021). Regional Screening Levels (RSLs) - Generic Tables. Retrieved from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables

World Health Organization (WHO). (2011). Guidelines for drinking-water quality, fourth edition. Retrieved from https://www.who.int/publications/i/item/9789241549950

World Health Organization (WHO). (2017). *IARC Monographs: Some Chemicals Used as Solvents and In Polymer Manufacture* Lyon, France Retrieved from https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Chemicals-Used-As-Solvents-And-In-Polymer-Manufacture-2016.

Toxicological Summary for: 17α-Ethinylestradiol

CAS: 57-63-6

Synonyms: Ethinyl estradiol; Ethinylestradiol; 17-α ethinyl estradiol; 17-α EE; EE2; 17-ethinylestradiol; ethynylestradiol; 17α-ethynyl-1,3,5(10)-estratriene-3,17β-diol;19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol (IUPAC)

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 0.0005 µg/L

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

$$= \frac{(1.7 \times 10^{-7} \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 0.000468 \text{ rounded to } \mathbf{0.0005 \text{ µg/L}}$$

* Relative Source Contribution: MDH 2008, Section IV.E.1. MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate Relative Source Contributions (RSCs) (MDH 2008, Appendix K). Typically an RSC of 0.5 is utilized for nonvolatile contaminants for the acute and short-term durations and an RSC of 0.2 is used for subchronic and chronic durations. Given the limited potential for exposure from other sources, an RSC of 0.8 was selected rather than applying the default RSC value. For individuals who take 17α-ethinylestradiol by prescription, the additional exposure from drinking water will be negligible.

** Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	(POD x DAF)/Total UF = 1.7 x 10⁻⁷ mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	0.00050 mg/kg-d (LOAEL, Delclos et al. 2014)
Human Equivalent Dose (MDH, 2011):	Not applied (doses directly given to neonatal animals were not adjusted due to interspecies and life-stage differences in toxicokinetics)
Total uncertainty factor:	3000
Uncertainty factor allocation:	10 for interspecies differences, 10 for intraspecies variability, and 10 for LOAEL-to-NOAEL, 3 for database uncertainty regarding potential latent effects
Critical effect(s):	Male mammary gland hyperplasia, decreased ovary weight, increased uterine weight, delayed vaginal opening
Co-critical effect(s):	In humans: reduced fertility (prevention of ovulation), increased sex hormone binding globulin, decreased corticosteroid-binding globulin, decreased follicle-stimulating hormone, decreased luteinizing hormone, breast development (gynecomastia) in infants

	In laboratory animals: Decreased body weight gain in adults, post-implantation loss, increased resorptions, decreased number of live pups/litter, decreased fetal/neonatal survival, reduced pup body weight and body weight gain, histopathology in female sex organs (uterus, ovaries and clitoral gland), latent uterine atypical focal hyperplasia, increased malformations in female external genitalia, increased number of female nipples, changes in sexually dimorphic behaviors, decreased fertility, early female pubertal onset, effects on estrous cyclicity, ovarian dysfunction, increased gestation length, changes in male reproductive organ weights and histopathology effects in various male reproductive organs, increased male mammary gland terminal end buds and density, decreased testosterone, decreased epididymal sperm counts, increased pituitary gland weight
Additivity endpoint(s):	Developmental (E), Female reproductive system (E), Male reproductive system (E)

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = 0.0002 µg/L

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

$$= \frac{(1.4 \times 10^{-8} \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 0.000151 \text{ rounded to } \mathbf{0.0002 \text{ µg/L}}$$

*Rationale for selecting RSC of 0.8 – same explanation as that provided for the short-term duration (see above)
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	(POD x DAF)/Total UF = 1.4 x 10^{-8} mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	4.2 x 10^{-5} mg/kg-d (BMDL$_{10}$, NTP 2010a)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 4.2 x 10^{-5} mg/kg-d x 0.01 = 4.2 x 10^{-7} mg/kg-d (DAF chemical-specific basis)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Mammary gland hyperplasia in adult males
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = 0.0002 µg/L

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

$$= \frac{(1.4 \times 10^{-8} \text{ mg/kg-d**}) \times (0.8^*) \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{***}}$$

= 0.000248, rounded to **0.0002 µg/L**

Additivity endpoint(s): Developmental

*Rationale for selecting RSC of 0.8 – same explanation as that provided for the short-term duration (see above)
**See the subchronic information above for details about the reference dose
*** Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Cancer Health Based Value (cHBV) = Not Derived

After carefully reviewing the available data MDH concluded that the non-cancer HBVs are sufficiently protective for potential cancer effects.

Cancer classification:	IARC Group 1, Carcinogenic to humans
Slope factor:	Not available
Source of slope factor:	Not Applicable
Tumor site(s):	Endometrium, ovary, mammary

Volatile: No

Summary of Guidance Value History:
The HBVs for 17α-ethinylestradiol are new. No previous values exist. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in the Chronic duration HBV no longer being set to the Subchronic duration HBV. However, the Chronic duration HBV remains the same value.

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?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:
[1]Ethinylestradiol is used as a human contraceptive for its ability to disrupt the human endocrine system at human contraceptive doses over 260 times higher than the short-term RfD and over 9,000 times higher than the sub/chronic RfD. Endocrine-mediated effects on a variety of male and female endocrine-responsive tissues form the basis for all of the RfDs. In humans, hormonal effects including increased sex hormone binding globulin and angiotensinogen with decreased corticosteroid binding globulin and follicle-stimulating hormone were reported at doses more than 300 times higher than all of the RfDs. In laboratory animal studies, steroid hormonal effects including reduced testosterone, luteinizing hormone, follicle-stimulating hormone, prolactin, progesterone and increased serum estradiol have been reported at doses more than 100 times higher than all of the RfDs. Thyroid hormones were affected in adult rats at doses more than 350 times higher than the subchronic RfD.

No effects on thyroid hormones were found in neonatal animals. Increased pituitary gland weight was reported at doses more than 2,800 times higher than the subchronic RfD.

[2]Ethinylestradiol produced decreased bone marrow DNA synthesis and blood cell progenitor cells in rats, indicating a potential impact on the immune system at doses over 2,000 times higher than all of the RfDs. Other immune system effects occurring at doses more than 1,000 times higher than the subchronic RfD included increased natural killer cell activity, increased spleen cell proliferation related to cell-mediated immunity, decreased spleen cell numbers (B, T, and NK cells), and increased relative spleen weight. Significant, but inconsistent increases in thymus weight were reported in adult rat offspring at doses over 140 times higher than the subchronic RfD.

[3]The short-term RfD is based, in part, on male and female developmental effects reported in laboratory animal studies. The sub/chronic RfDs are based on male mammary gland hyperplasia, considered an aberrant developmental effect for males. Epidemiological studies have found no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy and also do not suggest any overt birth defects effects when taken inadvertently during early pregnancy. However, potential for subtle, long-term effects from gestational exposure in humans has not been fully evaluated. In a clinical study of children whose mothers used oral contraceptives during lactation (starting at age 2 months), no effects on intellectual or behavioral development were found when children were followed up to age 8 years. A few adverse effects in nursing infants whose mothers were taking ethinylestradiol have been reported, including jaundice and breast enlargement. These effects in nursing infants occurred at maternal doses more than 2,000 times higher than the short-term RfD and more than 30,000 times higher than the subchronic RfD.

[4]Ethinylestradiol is a human contraceptive drug that is used deliberately for its ability to disrupt human reproduction by inhibiting ovulation. Oral contraceptives given during nursing may also interfere with lactation by decreasing the quantity and quality of breast milk. The lowest human contraceptive dose is 260 times higher than the short-term RfD and over 9,000 times higher than the sub/chronic RfDs. The short-term RfD is based, in part, on female reproductive system effects in laboratory animals.

[5]Neurobehavioral developmental effects related to feminization or masculinization of behaviors were reported in rats exposed to doses more than 100 times higher than the short-term RfD and 30,000 higher than the subchronic RfD. Effects included changes in saccharin and sodium preferences and decreased female rearing behavior. Increased activity and startle responses were reported in rat offspring. In a clinical study of children whose mothers used oral contraceptives during lactation (starting at age 2 months), no effects on intellectual or behavioral development were found when children were followed up to age 8 years.

Resources Consulted During Review:

Actavis Pharma Inc. (2014). FDA-Approved Drug Label for Norinyl 1+50 - norethindrone and mestranol.

Australian Natural Resource Management Ministerial Council; Environmental Protection and Heritage Council; and National Health and Medical Research Council. (2008). Australian Guidelines for Water Recycling. Augmentation of Drinking Water Supplies. from https://www.waterquality.gov.au/sites/default/files/documents/water-recycling-guidelines-augmentation-drinking-22.pdf

Borgert, C. J., LaKind, J. S., & Witorsch, R. J. (2003). A critical review of methods for comparing estrogenic activity of endogenous and exogenous chemicals in human milk and infant formula. *Environ Health Perspect* 111(8): 1020-1036.

Brody, S. A., Turkes, A., & Goldzieher, J. W. (1989). Pharmacokinetics of three bioequivalent norethindrone/mestranol-50 micrograms and three norethindrone/ethinyl estradiol-35 micrograms OC formulations: are "low-dose" pills really lower? *Contraception* 40(3): 269-284.

Canadian Drug Products Monograph. (2011). *Product Monograph. FEMHRT and FEMHRT LO. Estrogen-progestin combination. Warner Chilcott Canada Co.,.* Toronto, Ontario.

Cao, J., Rebuli, M. E., Rogers, J., Todd, K. L., Leyrer, S. M., Ferguson, S. A., & Patisaul, H. B. (2013). Prenatal bisphenol A exposure alters sex-specific estrogen receptor expression in the neonatal rat hypothalamus and amygdala. *Toxicol Sci* 133(1): 157-173.

Capel-Edwards, K., D.E. Hall, A.G. Sansom, (1971). Hematological changes observed in female beagle dogs given ethynylestradiol. *Toxicology and Applied Pharmacology* 20: 319-326.

Curtis, E. M. (1964). Oral-Contraceptive Feminization of a Normal Male Infant: Report of a Case. *Obstet Gynecol* 23: 295-296.

Delclos, K. B., Camacho, L., Lewis, S. M., Vanlandingham, M. M., Latendresse, J. R., Olson, G. R., . . . Thorn, B. T. (2014). Toxicity evaluation of bisphenol A administered by gavage to Sprague Dawley rats from gestation day 6 through postnatal day 90. *Toxicol Sci* 139(1): 174-197.

Delclos, K. B., Weis, C. C., Bucci, T. J., Olson, G., Mellick, P., Sadovova, N., . . . Newbold, R. R. (2009). Overlapping but distinct effects of genistein and ethinyl estradiol (EE(2)) in female Sprague-Dawley rats in multigenerational reproductive and chronic toxicity studies. *Reprod Toxicol* 27(2): 117-132.

Ferguson, S. A., Delclos, K. B., Newbold, R. R., & Flynn, K. M. (2003). Dietary ethinyl estradiol exposure during development causes increased voluntary sodium intake and mild maternal and offspring toxicity in rats. *Neurotoxicol Teratol* 25(4): 491-501.

Ferguson, S. A., Law, C. D., & Abshire, J. S. (2012). Developmental treatment with bisphenol A causes few alterations on measures of postweaning activity and learning. *Neurotoxicol Teratol* 34(6): 598-606.

Ferguson, S. A., Law, C. D., Jr., & Abshire, J. S. (2011). Developmental treatment with bisphenol A or ethinyl estradiol causes few alterations on early preweaning measures. *Toxicol Sci* 124(1): 149-160.

Ferguson, S. A., Law, C. D., & Kissling, G. E. (2014). Developmental treatment with ethinyl estradiol, but not bisphenol A, causes alterations in sexually dimorphic behaviors in male and female Sprague Dawley rats. *Toxicol Sci* 140(2): 374-392.

Guo, T. L., Germolec, D. R., Musgrove, D. L., Delclos, K. B., Newbold, R. R., Weis, C., & White, K. L., Jr. (2005). Myelotoxicity in genistein-, nonylphenol-, methoxychlor-, vinclozolin- or ethinyl estradiol-exposed F1 generations of Sprague-Dawley rats following developmental and adult exposures. *Toxicology* 211(3): 207-219.

He, Z., Paule, M. G., & Ferguson, S. A. (2012). Low oral doses of bisphenol A increase volume of the sexually dimorphic nucleus of the preoptic area in male, but not female, rats at postnatal day 21. *Neurotoxicol Teratol* 34(3): 331-337.

Hines, R. N. (2007). Ontogeny of human hepatic cytochromes P450. *J Biochem Mol Toxicol* 21(4): 169-175.

Hines, R. N. (2008). The ontogeny of drug metabolism enzymes and implications for adverse drug events. *Pharmacol Ther* 118(2): 250-267.

Hotchkiss, C. E., Weis, C., Blaydes, B., Newbold, R., & Delclos, K. B. (2008). Multigenerational exposure to ethinyl estradiol affects bone geometry, but not bone mineral density in rats. *Bone* 43(1): 110-118.

Howdeshell, K. L., Furr, J., Lambright, C. R., Wilson, V. S., Ryan, B. C., & Gray, L. E., Jr. (2008). Gestational and lactational exposure to ethinyl estradiol, but not bisphenol A, decreases androgen-dependent

reproductive organ weights and epididymal sperm abundance in the male long evans hooded rat. *Toxicol Sci* 102(2): 371-382.

HSDB. (2011). Hazardous Substances Database. U.S. National Library of Medicine, TOXNET. Mestranol. Retrieved February 2016, from http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~Ys45bR:1

HSDB. (2012). Hazardous Substances Database. U.S. National Library of Medicine, TOXNET. Ethinylestradiol. Retrieved December, 2014, from http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~ecUdyv:1

International Agency for Research on Cancer (IARC). (1979). IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Sex Hormones (II). Ethinyloestradiol. (Vol. Vol. 21). Lyon, France.

International Agency for Research on Cancer (IARC) (1999). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Postmenopausal Estrogen Therapy. Lyon, France, IARC. Vol. 72.

International Agency for Research on Cancer (IARC). (2007). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Combined Estrogen–Progestogen Contraceptives and Combined Estrogen–Progestogen Menopausal Therapy (Vol. Vol. 91). Lyon, France: IARC.

International Agency for Research on Cancer (IARC). (2011a). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Part A: Pharmaceuticals. Estrogen-Only Menopausal Therapy (Vol. Vol. 100). Lyon, France: IARC.

International Agency for Research on Cancer (IARC) (2011b). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Part A: Combined Estrogen-Progestogen Contraceptives. Lyon, France, IARC. Vol. 100.

JECFA. (2000). Toxicological Evaluation of Certain Veterinary Drug Residues in Food: WHO Food Additives Series 43: Production Aids: Estradiol-17beta, Progesterone, and Testosterone. In Prepared by the fifty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (Ed.).

Kendig, E. L., Buesing, D. R., Christie, S. M., Cookman, C. J., Gear, R. B., Hugo, E. R., . . . Belcher, S. M. (2012). Estrogen-like disruptive effects of dietary exposure to bisphenol A or 17alpha-ethinyl estradiol in CD1 mice. *Int J Toxicol* 31(6): 537-550.

Koukouritaki, S. B., Manro, J. R., Marsh, S. A., Stevens, J. C., Rettie, A. E., McCarver, D. G., & Hines, R. N. (2004). Developmental expression of human hepatic CYP2C9 and CYP2C19. *J Pharmacol Exp Ther* 308(3): 965-974.

Latendresse, J. R., Bucci, T. J., Olson, G., Mellick, P., Weis, C. C., Thorn, B., . . . Delclos, K. B. (2009). Genistein and ethinyl estradiol dietary exposure in multigenerational and chronic studies induce similar proliferative lesions in mammary gland of male Sprague-Dawley rats. *Reprod Toxicol* 28(3): 342-353.

Laurenzana, E. M., Weis, C. C., Bryant, C. W., Newbold, R., & Delclos, K. B. (2002). Effect of dietary administration of genistein, nonylphenol or ethinyl estradiol on hepatic testosterone metabolism, cytochrome P-450 enzymes, and estrogen receptor alpha expression. *Food Chem Toxicol* 40(1): 53-63.

Madhavapeddi, R., & Ramachandran, P. (1985). Side effects of oral contraceptive use in lactating women--enlargement of breast in a breast-fed child. *Contraception* 32(5): 437-443.

Mandrup, K. R., Hass, U., Christiansen, S., & Boberg, J. (2012). Perinatal ethinyl oestradiol alters mammary gland development in male and female Wistar rats. *Int J Androl* 35(3): 385-396.

Mandrup, K. R., Jacobsen, P. R., Isling, L. K., Axelstad, M., Dreisig, K., Hadrup, N., . . . Boberg, J. (2013). Effects of perinatal ethinyl estradiol exposure in male and female Wistar rats. *Reprod Toxicol* 42: 180-191.

Marriq, P., & Oddo, G. (1974, Nov 30-Dec 14). [Letter: Gynecomastia in the newborn induced by maternal milk? An unusual complication of oral contraceptives]; article in French. *Nouv Presse Med.* from as cited by Drugs.com, last updated 5/5/2015; http://www.drugs.com/breastfeeding/contraceptives-oral-combined.html

Mashchak, C. A., Lobo, R. A., Dozono-Takano, R., Eggena, P., Nakamura, R. M., Brenner, P. F., & Mishell, D. R., Jr. (1982). Comparison of pharmacodynamic properties of various estrogen formulations. *Am J Obstet Gynecol* 144(5): 511-518.

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.", from https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2.

Minnesota Department of Health (MDH). (2011). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses. from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Toxicology Program (NTP). (2004). *Final Report. Pubertal Toxicity Study of Vinclozolin, Flutamide and Phenobarbital in Male Sprague Dawley Rats and Methoxychlor, Ethinyl Estradiol and Phenobarbital in Female Sprague Dawley Rats when Administered in Corn Oil by Oral Gavage*. TherImmune Research Corporation No. 7244-600.

National Toxicology Program (NTP). (2010a). *Multigenerational Reproductive Toxicology Study Of Ethinyl Estradiol (Cas No. 57-63-6) In Sprague-Dawley Rats* Retrieved from http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR547.pdf.

National Toxicology Program (NTP). (2010b). *NTP Technical Report on the Toxicology and Carcinogenesis Study of Ethinyl estradiol (CAS No. 57-63-6) in Sprague-Dawley Rats.* . Retrieved from https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr548.pdf?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=tr548. .

National Toxicology Program (NTP). (2011). *Report on Carcinogens, Twelfth Edition. Estrogens, Steroidal*. Retrieved from http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/EstrogensSteroidal.pdf.

Nilsson, S., Mellbin, T., Hofvander, Y., Sundelin, C., Valentin, J., & Nygren, K. G. (1986). Long-term follow-up of children breast-fed by mothers using oral contraceptives (reviewed abstract only). *Contraception* 34(5): 443-457.

Nilsson, S., Nygren, K. G., & Johansson, E. D. (1978). Ethinyl estradiol in human milk and plasma after oral administration. *Contraception* 17(2): 131-139.

Norgaard, M., Wogelius, P., Pedersen, L., Rothman, K. J., & Sorensen, H. T. (2009). Maternal use of oral contraceptives during early pregnancy and risk of hypospadias in male offspring (reviewed abstract only). *Urology* 74(3): 583-587.

OEHHA. (1992). *Expedited Cancer Potency Values and Proposed Regulatory Levels for Concern for Certain Proposition 65 Carcinogens*.

OEHHA. (2001). No Significant Risk Level (NSRL) for the Proposition 65 Carcinogen Di(2-ethylhexyl)phthalate. from http://www.oehha.ca.gov/prop65/law/pdf_zip/dehpnsrl.pdf

Pillon, D., Cadiou, V., Angulo, L., & Duittoz, A. H. (2012). Maternal exposure to 17-alpha-ethinylestradiol alters embryonic development of GnRH-1 neurons in mouse. *Brain Res* 1433: 29-37.

Rebuli, M. E., Cao, J., Sluzas, E., Delclos, K. B., Camacho, L., Lewis, S. M., . . . Patisaul, H. B. (2014). Investigation of the effects of subchronic low dose oral exposure to bisphenol A (BPA) and ethinyl estradiol (EE) on estrogen receptor expression in the juvenile and adult female rat hypothalamus. *Toxicol Sci* 140(1): 190-203.

Ryan, B. C., Hotchkiss, A. K., Crofton, K. M., & Gray, L. E., Jr. (2010). In utero and lactational exposure to bisphenol A, in contrast to ethinyl estradiol, does not alter sexually dimorphic behavior, puberty, fertility, and anatomy of female LE rats. *Toxicol Sci* 114(1): 133-148.

Sandoz Inc. (2014). *FDA-Approved Drug Label for Altavera - levonorgestrel and ethinyl estradiol*.

Sawaki, M., Noda, S., Muroi, T., Mitoma, H., Takakura, S., Sakamoto, S., & Yamasaki, K. (2003). In utero through lactational exposure to ethinyl estradiol induces cleft phallus and delayed ovarian dysfunction in the offspring. *Toxicol Sci* 75(2): 402-411.

Schardein, J. L. (1980). Studies of the components of an oral contraceptive agent in albino rats. I. Estrogenic component. *J Toxicol Environ Health* 6(4): 885-894.

Schmider, J., Greenblatt, D. J., von Moltke, L. L., Karsov, D., Vena, R., Friedman, H. L., & Shader, R. I. (1997). Biotransformation of mestranol to ethinyl estradiol in vitro: the role of cytochrome P-450 2C9 and metabolic inhibitors. *J Clin Pharmacol* 37(3): 193-200.

Siddique, Y. H., Beg, T., & Afzal, M. (2005). Genotoxic potential of ethinylestradiol in cultured mammalian cells. *Chem Biol Interact* 151(2): 133-141.

Snyder, S., RA Trenholm, EM Snyder, GM Bruce, RC Pleus, and JDC Hemming,. (2008). Toxicological Relevance of EDCs and Pharmaceuticals in Drinking Water. In AWWA Research Foundation (Ed.).

Tavassoli, F. A., Casey, H. W., & Norris, H. J. (1988). The morphologic effects of synthetic reproductive steroids on the mammary gland of rhesus monkeys. Mestranol, ethynerone, mestranol-ethynerone, chloroethynyl norgestrel-mestranol, and anagestone acetate-mestranol combinations. *Am J Pathol* 131(2): 213-234.

Tennant, B. C., Balazs, T., Baldwin, B. H., Hornbuckle, W. E., Castleman, W. L., Boelsterli, U., & Kallfelz, F. A. (1981). Assessment of hepatic function in rabbits with steroid-induced cholestatic liver injury. *Fundam Appl Toxicol* 1(4): 329-333.

Twaddle, N. C., Churchwell, M. I., Newbold, R. R., Delclos, K. B., & Doerge, D. R. (2003). Determination using liquid-chromatography-electrospray tandem mass spectroscopy of ethinylestradiol serum pharmacokinetics in adult Sprague-Dawley rats. *J Chromatogr B Analyt Technol Biomed Life Sci* 793(2): 309-315.

U. S. Environmental Protection Agency - Office of Water. (2009). Contaminant Information Sheets for the PCCL Chemicals Considered for CCL3. from http://www2.epa.gov/sites/production/files/2014-05/documents/final-pccl-3-contaminant-information-sheets.pdf

U.S. Environmental Protection Agency - Office of Research and Development. (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. from http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

U.S. Food and Drug Administration (FDA). (2015). Drugs@FDA: FDA Approved Drug Products database; search for Estinyl, Lynoral, Feminone historical dosage information.   Retrieved June 26, 2015, from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Vosges, M., Braguer, J. C., & Combarnous, Y. (2008). Long-term exposure of male rats to low-dose ethinylestradiol (EE2) in drinking water: effects on ponderal growth and on litter size of their progeny. *Reprod Toxicol* 25(2): 161-168.

Warner Chilcott (US), L. (2012). Lo Loestrin Fe, approved drug label. from http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c33072cf-625d-4b4a-981e-ec049c5d78aa

Wogelius, P., Horvath-Puho, E., Pedersen, L., Norgaard, M., Czeizel, A. E., & Sorensen, H. T. (2006). Maternal use of oral contraceptives and risk of hypospadias - a population-based case-control study (reviewed abstract only). *Eur J Epidemiol* 21(10): 777-781.

Yadav, M., & Volkar, J. (2013). Female Contraception. Mechanism of Action of Hormonal Contraceptives. Cleveland Clinic Center for Continuing Education. Disease Management. Retrieved 3/17/2016, from http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/womens-health/female-contraception/

Yanagimachi, R., & Sato, A. (1968). Effects of a single oral administration of ethinyl estradiol on early pregnancy in the mouse. *Fertil Steril* 19(5): 787-801.

Yasuda, Y., Kihara, T., & Nishimura, H. (1981). Effect of ethinyl estradiol on development of mouse fetuses. *Teratology* 23(2): 233-239.

DEPARTMENT OF HEALTH

Web Publication Date: August 2020

Toxicological Summary for: Ethylbenzene

CAS**: 100-41-4**

Synonyms: Phenylethane, ethylbenzol, EB, 1-Ethylbenzene

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 40 µg/L

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

$$= \frac{(0.06 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 41 \text{ rounded to } \mathbf{40 \text{ µg/L}}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.

[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 18/300 = 0.06 mg/kg-d (Wistar rat)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	75 mg/kg-d (administered dose NOAEL, Mellert 2007)
Dose Adjustment Factor (DAF):	0.24, Body weight scaling, default (USEPA 2011) (MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 75 mg/kg-d x 0.24 = 18 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (lack of studies via oral exposure including a lack of developmental and reproductive studies and toxicity data in multiple species)
Critical effect(s):	Changes in liver and kidney weight in males with corresponding histological changes; and blood chemistry changes at higher doses
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 40 µg/L

(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)
(Subchronic Intake Rate, L/kg-d)

= (0.036 mg/kg-d) x (0.2)[*] x (1000 µg/mg)
(0.074 L/kg-d)[**]

= 97 rounded to 100 µg/L

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 10.68/300 = 0.036 mg/kg-d (Wistar rat)
Source of toxicity value:	ATSDR 2010
Point of Departure (POD):	6.61 µmol/L (Liver serum concentration BMDL$_{10}$, ATSDR 2010 analysis of Mellert 2007)
Dose Adjustment Factor (DAF):	Chemical-Specific PBPK model (ATSDR 2010)
Human Equivalent Dose (HED):	10.68 mg/kg-d HED from PBPK modelling conducted by ATSDR 2010
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (lack of studies via oral exposure including a lack of developmental and reproductive studies and toxicity data in multiple species)
Critical effect(s):	Centrilobular hepatocyte hypertrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

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 40 µg/L. Additivity endpoints: Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = nHBV$_{Short-term}$ = 40 µg/L

(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)
(Chronic Intake Rate, L/kg-d)

= (0.011 mg/kg-d) x (0.2)[*] x (1000 µg/mg)
(0.045 L/kg-d)[**]

= 48 rounded to 50 µg/L

Reference Dose/Concentration:	HED/Total UF = 10.68/1000 = 0.011 mg/kg-d (Wistar rat)
Source of toxicity value:	ATSDR 2010
Point of Departure (POD):	6.61 μmol/L (BMDL$_{10}$ based on concentration of ethylbenzene in the liver, ATSDR 2010 analysis of Mellert 2007) (subchronic exposure)
Dose Adjustment Factor (DAF):	Chemical-Specific PBPK model (ATSDR 2010)
Human Equivalent Dose (HED):	10.68 mg/kg-d HED from PBPK modelling conducted by ATSDR 2010
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for database uncertainty (lack of studies via oral exposure including a lack of developmental and reproductive studies and toxicity data in multiple species), and 3 for extrapolation to a chronic duration from a subchronic duration study
Critical effect(s):	Centrilobular hepatocyte hypertrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

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 40 μg/L. Additivity endpoints: Hepatic (liver) system, Renal (kidney) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	2B - possibly carcinogenic to humans (IARC 2000); D - not classifiable as to human carcinogenicity (USEPA 1991)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	liver and kidney

Volatile: Yes (high)

Summary of Guidance Value History:

A noncancer chronic Health Risk Limit (HRL) of 700 μg/L was promulgated in 1993. In 2011, MDH derived short-term, subchronic, and chronic HRLs of 50 μg/L. In 2015, MDH evaluated the potential of incorporating an oral slope factor into the assessment. There was no new

information to support derivation of a cancer water guidance value. In 2018, MDH re-evaluated the existing HRLs, resulting in slightly lower Health Based Values (HBV). The 2018 HBVs are lower than the previous HRLs as a result of 1) use of MDH's most recent risk assessment methodology and 2) rounding to one significant digit. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	No	Yes	Yes
Effects observed?	_[1]	_[2]	_[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Endocrine activity of ethylbenzene has not been tested. However, an acute oral study noted decreases in peripheral hormone levels and possible effects on the estrus cycle in rats at doses 2000 or more times higher than the short-term reference dose. Rats and mice exposed to ethylbenzene in an inhalation exposure study showed an increased incidence of follicular cell hyperplasia in the thyroid gland and hyperplasia in the pituitary gland over the two-year study period.

[2] Immunotoxicity of ethylbenzene has only been studied by inhalation in laboratory animals. Some studies noted changes in immune cell numbers and increased spleen weights, but these results were not consistently seen across all studies. One general toxicity oral study noted decreased thymus weights in rats exposed at doses over 900 times higher than the short-term reference dose.

[3] Developmental effects have not been studied in laboratory animals exposed through the oral route. Effects observed in rat inhalation exposure studies include reduced fetal weight and skeletal and urogenital anomalies observed in the presence of maternal toxicity.

[4] Very limited information is available on reproductive effects following oral exposures. Decreases in hormone levels affecting the estrus cycle and uterine effects were indicated in a single acute reproductive study in laboratory animals with oral exposure at doses 2000 or more times higher than the short-term reference dose. Adverse reproductive effects were not observed in laboratory animals studies with inhalation exposure.

[5] Significant ototoxic effects have been reported, including loss of the outer hair cells in a part of the ear. This effect was observed in male rats at a single oral dose over 3000 times higher than the short-term reference dose. Ototoxicity has also been seen following inhalation exposure to ethylbenzene.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). (2010). *Toxicological Profile for Ethylbenzene*. Retrieved from https://www.atsdr.cdc.gov/toxprofiles/tp110.pdf.

Agency for Toxic Substances and Disease Registry (ATSDR). (2018). Minimal Risk Levels (MRLs) for Hazardous Substances. Retrieved from https://www.atsdr.cdc.gov/mrls/mrllist.asp

California Water Resources Control Board. (2017). Compilation of Water Quality Goals Retrieved from https://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/

Faber, W., Roberts, LSG., Stump, DG. (2006). Two-generation reproduction study of ethylbenzene by inhalation in Crt-CD rats. *Birth Defects Res B Dev Reprod Toxicol, 77*(1), 10-21.

Gangnaire, F., Langlais, C., Grossman, S. (2007). Ototoxicity in rats exposed to ethylbenzene and to two technical xylene vapours for 13 weeks. *Arch Toxicol, 81*(2), 127-143.

Government of Canada. (2016). Screening Assessment Report - Ethylbenzene Retrieved from https://www.canada.ca/en/health-canada/services/chemical-substances/other-chemical-substances-interest/ethylbenzene.html

Hard, G. (2002). Significance of the renal effects of ethylbenzene in rodents for assessing human carcinogenic risk. *Toxicol Sci, 69*, 30-41.

Hardin, B., Bond, GP., Sikov, MR. (1981). Testing of selected workplace chemicals for teratogenic potential. *Scand J Work Environ Health, 7*, 66-75.

Health Canada. (2014). Guidelines for Drinking Water Quality - Guideline Technical Document for Toluene, Ethylbenzene, and Xylenes. Retrieved from https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-toluene-ethylbenzene-xylenes.html?page=6&wbdisable=true

International Agency for Research on Cancer (IARC). Complete List of Agents evaluated and their classification. Retrieved from http://monographs.iarc.fr/ENG/Classification/index.php

Li, A., Maurissen, JP., Barnett, JF., Foss, J., Freshwater, L., Garman, RH., Peachee, VL., Hong, SJ., Stump, DG., Bus, JS. (2010). Oral gavage subchronic neurotoxicity and inhalation subchronic immunotoxicity studies of ethylbenzene in the rat. *Neurotoxicology, 31*, 247-258.

Maltoni, C., Conti, B., Cotti, G. (1985). Experimental studies on benzene carcinogenicity at the Bologna Institute of Oncology: Current results and ongoing research. *Am J Ind Med, 7*, 415-446.

Maltoni, C., Ciliberti, A., Pinto, C. (1997). Results of long-term experimental carcinogenicity studies of the effects of gasoline, correlated fuels, and major gasoline aromatics on rats. . *Ann NY Acad Sci, 837*, 15-52.

Mellert, W., Deckhardt, K., Kaufmann, W. (2007). Ethylbenzene: 4 and 13 week rat oral toxicity. *Arch Toxicol, 81*, 361-370.

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Institute for Occupational Safety and Health (NIOSH). (1981). *Teratologic assessment of ethylbenzene and 2-ethoxyethanol. PB83208074*.

National Toxicology Program (NTP). (1999). *NTP Technical report on the toxicology and carcinogenesis studies of ethylbenzene in F344/N rats and B6C3F1 mice (inhalation studies). NTP TR 466.*

Office of Environmental Health Hazard Assessment (OEHHA). (2018). Chemicals Database Retrieved from https://oehha.ca.gov/chemicals

Saillenfait, A., Gallissot, F., Morel, G. (2003). Developmental toxicities of ethylbenzene, ortho-, meta-, para-xylene and technical xylenes in rats following inhalation exposure. *Food Chem Toxicol, 41*, 415-429.

Saillenfait, A., Gallissot, F., Sabate, JP. (2006). Developmental toxicity of combined ethylbenzene and methylethylketone administered by inhalation to rats. *Food Chem Toxicol, 44*(8), 1287-1298.

Ungvary, G., Tatrai, E. (1985). On the embryotoxic effects of benzene and its alkyl derivatives in mice, rats, and rabbits. *Arch Toxicol Suppl, 8*, 425-430.

United States Environmental Protection Agency (USEPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

United States Environmental Protection Agency (USEPA). (1991). Integrated Risk Information System (IRIS) Chemical Assessment Summary for Ethylbenzene. Retrieved from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0051_summary.pdf

United States Environmental Protection Agency (USEPA). (2008). *Child-Specific Exposure Factors Handbook.* Retrieved from https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=199243.

United States Environmental Protection Agency (USEPA). (2009). Provisional Peer-Reviewed Toxicity Values for Ethylbenze. Retrieved from https://cfpub.epa.gov/ncea/pprtv/documents/Ethylbenzene.pdf

United States Environmental Protection Agency (USEPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

United States Environmental Protection Agency (USEPA). (2014). Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. Risk Assessment Forum. Office of Research and Development. EPA/100/R-14/002F.

United States Environmental Protection Agency (USEPA). (2014). *IRIS Toxicological Review of Ethylbenzene (Scoring and Problem Formulation Materials)*. (EPA/625/R-14/198).

United States Environmental Protection Agency (USEPA). (2018). 2018 Edition of the Drinking Water Standards and Health Advisories Tables. Retrieved from https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Voluntary Children's Chemical Evaluation Program (VCCEP). (2010). https://chemview.epa.gov/chemview

Wolf, M., Rowe, VK., McCollister, DD. (1956). Toxicological studies of certain alkylated benzenes and benzene: Experiments on laboratory animals. *AMA Arch Ind Health, 14*, 387-398.

World Health Organization (WHO). (2005). Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for the Use of Data in Dose/Concentration-Response Assessment. International Programme on Chemical Safety, IPCS Harmonization Project Document No. 2. WHO/IPCS/01.4, 1-96, Geneva, Switzerland.

World Health Organization (WHO). (2008). Guidelines for Drinking-water Quality Third Edition Volume 1 Recommendations. Retrieved from http://www.who.int/water_sanitation_health/dwq/fulltext.pdf

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Toxicological Summary for: Ethylene Glycol

CAS: **107-21-1**

Synonyms: Ethane-1,2-diol, Monoethylene glycol (MEG), 1,2-Ethanediol, Glycol

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 2000 µg/L

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

$$= \frac{(0.33 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.038 \text{ L/kg-d})^{**}}$$

$$= 1{,}736 \text{ rounded to } \textbf{2,000 µg/L}$$

[*] Relative Source Contribution: MDH 2008, Section IV.E.1.

[**] The RfD is based on malformations that occur *in utero*, therefore, the intake rate for a pregnant woman is utilized rather than the default infant intake rate as described in the MDH 2008 SONAR (page 46). Effects relevant to post-natal development occurred at higher dose levels. As the short-term duration intake is based on pregnant women, not infants, a Relative Source Contribution of 0.2 is utilized. (Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.)

Reference Dose/Concentration:	HED/Total UF = 9.83/30 = 0.33 mg/kg-d (CD-1 mice)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	75.6 mg/kg-d (BMDL$_{10}$; derived by ATSDR 2010, using data from Neeper-Bradley, 1995)
Dose Adjustment Factor (DAF):	0.13 (Body weight scaling, default) (MDH, 2017) (US EPA, 2011)
Human Equivalent Dose (HED):	POD x DAF = 75.6 mg/kg-d x 0.13 = 9.83 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Increased fetal skeletal malformations
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = 2000 µg/L

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

$$= \frac{(0.33\ mg/kg\text{-}d)^{**} \times (0.2)^* \times (1000\ µg/mg)}{(0.038\ L/kg\text{-}d)^{**}}$$

= 1,736 rounded to **2,000 µg/L**

[*] Relative Source Contribution: MDH 2008, Section IV.E.1.
[**] The calculated Subchronic RfD (0.57 mg/kg-d) is higher than the Short-term RfD (0.33 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). Therefore, the Short-term RfD is used in place of the calculated subchronic RfD and the water intake rate for a pregnant woman is used. (Intake rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5).

The calculated Subchronic nHBV, before consideration of the Short-term RfD and HBV, resulted in the same water guidance value after rounding to one significant digit. Therefore, the subchronic duration additivity endpoint of Renal (kidney) system is added to Developmental. **Additivity endpoints: Developmental, Renal (kidney) system**

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = 2000 µg/L

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

$$= \frac{(0.33\ mg/kg\text{-}d)^{**} \times (0.2)^* \times (1000\ µg/mg)}{(0.038\ L/kg\text{-}d)^{**}}$$

= 1,736 rounded to **2,000 µg/L**

[*] Relative Source Contribution: MDH 2008, Section IV.E.1
[**] The calculated Chronic RfD (0.44 mg/kg-d) is higher than the Short-term RfD (0.33 mg/kg-d), which is based on developmental effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure, including short-term effects (MDH, 2008). Therefore, the Short-term RfD is used in place of the calculated Chronic RfD and the water intake rate for a pregnant woman is used. (Intake rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5)

The calculated Chronic nHBV, before consideration of the Short-term RfD and HBV, resulted in the same water guidance value after rounding to one significant digit. Therefore, the chronic duration additivity endpoints of Male Reproductive system and Renal (kidney) system are added to Developmental. **Additivity endpoints: Developmental, Male Reproductive system, Renal (kidney) system**

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification: Not Classified
Slope factor (SF): Not Applicable
Source of cancer slope factor (SF): Not Applicable
Tumor site(s): Not Applicable

Volatile: No

Summary of Guidance Value History:

In 1993/1994, MDH promulgated a Health Risk Limit (HRL) of 10,000 µg/L. In 2011, MDH derived acute, short-term, subchronic, and chronic noncancer Health Based Values (HBV) of 4,000 µg/L, 4,000 µg/L, 2,000 µg/L, and 2,000 µg/L, respectively. These HBVs were adopted as HRLs in 2011. In 2017, MDH re-evaluated the noncancer HRLs, resulting in the removal of the acute guidance, and the derivation of new noncancer short-term, subchronic, and chronic HBVs of 2,000 µg/L. The revisions were a result of 1) using MDH's most recent risk assessment methodology including the application of Human Equivalent Doses (HED) and updated intake rates; and 2) rounding to one significant digit. In 2020, MDH incorporated updated intake rates (USEPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	Yes
Effects observed?	–[1]	–[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Studies assessing endocrine function have not been conducted, however, secondary observations from histological examinations of endocrine organs in existing studies of ethylene glycol showed no effects in rats or mice.

[2] Repeat-dose studies assessing immunotoxicity and immune function have not been conducted. However, one study reported decreased leukocyte levels in rats at a dose 400 times higher than the short-term RfD.

[3] The short-term RfD is based on skeletal malformations observed in mouse fetuses following *in utero* exposure. Numerous developmental studies have been conducted, and mice have been shown to be

Ethylene Glycol - 3

more sensitive than rats or rabbits regarding developmental effects. In addition to skeletal effects in mice, decreased fetal and pup body weights were observed at doses approximately 300 and 600 times higher than the short-term RfD.

[4] Reproductive and multi-generational studies have been conducted. Decreased reproductive success was observed at dose levels more than 600 times higher than the short-term RfD. Decreased sperm counts were observed at doses approximately 400 times higher than the short-term RfD, while sperm motility and morphology were altered at doses over 700 times higher than the short-term RfD.

[5] Following acute ingestion (poisoning incidents) of very high doses approximately 8000 times higher than the short-term RfD, ethylene glycol has a direct toxic effect on the nervous system with effects including ataxia, convulsion, and coma. In animal studies at doses 3000 times higher than the short-term RfD, calcium oxalate crystals have been observed in brain and nervous system tissue.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). (2010). Toxicological Profile for Ethylene Glycol. https://www.atsdr.cdc.gov/ToxProfiles/tp96.pdf

Armstrong, E. (2006). Homicidal ethylene glycol intoxication: a report of a case. *Am J Forensic Med Pathol, 27*(2), 151-155.

Blood, F. R. (1965). Chronic toxicity of ethylene glycol in the rat. *Food and Cosmetics Toxicology, 3*, 229-234. doi:http://dx.doi.org/10.1016/S0015-6264(65)80080-3

California Environmental Protection Agency (OEHHA). (2000). Ethylene Glycol. https://oehha.ca.gov/chemicals/ethylene-glycol

California Water Resources Control Board. http://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/

Carney, E. W., Tornesi, B., Markham, D. A., Rasoulpour, R. J., & Moore, N. (2008). Species-specificity of ethylene glycol-induced developmental toxicity: toxicokinetic and whole embryo culture studies in the rabbit. *Birth Defects Research Part B: Developmental and Reproductive Toxicology, 83*(6), 573-581. doi:10.1002/bdrb.20178

Corley, R. A., Saghir, S.A., Bartels, M.J., Hansen, S.C., Creim, J., McMartin, K.E., Snellings, W.M. (2011). "Extension of a PBPK model for ethylene glycol and glycolic acid to include the competitive formation and clearance of metabolites associated with kidney toxicity in rats and humans." Toxicology and Applied Pharmacology **250**: 229-244.

Corley, R. A., Wilson, D. M., Hard, G. C., Stebbins, K. E., Bartels, M. J., Soelberg, J. J., Snellings, W. M. (2008). Dosimetry considerations in the enhanced sensitivity of male Wistar rats to chronic ethylene glycol-induced nephrotoxicity. *Toxicology and Applied Pharmacology, 228*(2), 165-178. doi:http://dx.doi.org/10.1016/j.taap.2007.11.024

Cruzan, G., Corley, R. A., Hard, G. C., Mertens, J. J. W. M., McMartin, K. E., Snellings, W. M., . . . Deyo, J. A. (2004). Subchronic Toxicity of Ethylene Glycol in Wistar and F-344 Rats Related to Metabolism and Clearance of Metabolites. *Toxicological Sciences, 81*(2), 502-511. doi:10.1093/toxsci/kfh206

DePass, L. R., Garman, R. H., Woodside, M. D., Giddens, W. E., Maronpot, R. R., & Weil, C. S. (1986). Chronic toxicity and oncogenicity studies of ethylene glycol in rats and mice. *Fundamental and Applied Toxicology, 7*(4), 547-565. doi:http://dx.doi.org/10.1016/0272-0590(86)90105-3

Guo, C., Cenac, T. A., Li, Y., & McMartin, K. E. (2007). Calcium oxalate, and not other metabolites, is responsible for the renal toxicity of ethylene glycol. *Toxicology Letters, 173*(1), 8-16. doi:http://dx.doi.org/10.1016/j.toxlet.2007.06.010

Health Canada. 2007. Priority Substances Assessment Program and Screening Assessment Reports. https://www.ec.gc.ca/lcpe-cepa/documents/substances/eg/eg_draft-eng.pdf

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2.

Minnesota Department of Health (MDH). (2017). *MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses. (May 2011, revised 2017)*. Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf.

Morrissey, R., Lamb, J., Morris, R., Chapin, R., Gulati, D., Heindel, J.,,. (1989). Results and Evaluations of 48 Continuous Breeding Reproduction Studies Conducted in Mice. *Fundamental and Applied Toxicology, 13*, 747-777.

National Toxicology Program (NTP). (1984). *Ethylene Glycol (CAS #107-21-1): Reproduction and Fertility Assessment in CD-1 Mice When Administered in Drinking Water. NTP Report #RAC84051. (Study abstract only)*.

National Toxicology Program (NTP). (1984). *Teratologic Evaluation of Ethylene Glycol (CAS No. 107-21-1) Administered to CD-1 Mice on Gestational Days 6 Through 15. NTP Study TER84073. (Study abstract only)*.

National Toxicology Program (NTP). (1986). *Ethylene Glycol (CAS #107-21-1): Reproduction and Fertility Assessment in CD-1 Mice When Administered in Drinking Water. NTP Report #RAC84096. (Study abstract only)*.

National Toxicology Program (NTP). (1988). *Developmental Toxicity of Ethylene Glycol (CAS #107-21-1) in CD Rats. NTP Study TER84128. (Study abstract only)*.

National Toxicology Program (NTP). (1990). *Developmental Stages of the CD Rat Skeleton: Part II: Development after Maternal Exposure to Ethylene Glycol (CAS #107-21-1). NTP Study: TER89126. (Study abstract only).*

National Toxicology Program (NTP). (1991). *Developmental Toxicity of Ethylene Glycol (CAS No. 107-21-1) in New Zealand White Rabbits. NTP Study TER90005. (Study abstract only).*

National Toxicology Program (NTP). (1993). *TR-143. Toxicology and Carcinogenesis Studies of Ethylene Glycol (CAS No. 107-21-1) in B6C3F1 Mice (Feed Studies). (Study abstract only).*

National Toxicology Program (NTP). (2004). *NTP-CERHR Expert Panel report on the reproductive and developmental toxicity of ethylene glycol. Reproductive Toxicology 18:457-532.*

Neeper-Bradley, T. L., Tyl, R. W., Fisher, L. C., Kubena, M. F., Vrbanic, M. A., & Losco, P. E. (1995). Determination of a No-Observed-Effect Level for Developmental Toxicity of Ethylene Glycol Administered by Gavage to CD Rats and CD-1 Mice. *Fundamental and Applied Toxicology, 27*(1), 121-130. doi:http://dx.doi.org/10.1006/faat.1995.1115

Pellegrino, B. (2006). Ethylene glycol intoxication: Disparate findings of immediate versus delayed presentation. *W. V. Med. J., 102*(4), 32-34.

Reddy, N. J., Lewis, L. D., Gardner, T. B., Osterling, W., Eskey, C. J., & Nierenberg, D. W. (2007). Two Cases of Rapid Onset Parkinson's Syndrome Following Toxic Ingestion of Ethylene Glycol and Methanol. *Clinical Pharmacology & Therapeutics, 81*(1), 114-121. doi:10.1038/sj.clpt.6100013

Snellings, W. M., Corley, R.A., McMartin, K.E., Kirman, C.R., Bobst, S.M. (2013). "Oral Reference Dose for ethylene glycol based on oxalate cystal-induced renal tubule degeneration as the critical effect." Regulatory Toxicology and Pharmacology **65**(229-241).

Syracuse Research PhysProp Database. http://www.syrres.com/esc/physdemo.htm .

U.S. Environmental Protection Agency (EPA). Office of Drinking Water. http://www.epa.gov/waterscience/criteria/drinking/dwstandards.pdf

U.S. Environmental Protection Agency (EPA). (1989). Integrated Risk Assessment System (IRIS) Summary for Ethylene Glycol. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0238_summary.pdf

U.S. Environmental Protection Agency (EPA). (1997). *Health Effects Assessment Summary Tables (HEAST).*

U.S. Environmental Protection Agency (EPA). (2008). EPA Region 3, 6 and 9 harmonized human health screening values.

U.S. Environmental Protection Agency (EPA). (2011). *Recommended Use of Body Weight 3/4 as the Default Method in Derivation of the Oral Reference Dose*. http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf.

U.S. Environmental Protection Agency (EPA). (2017). EPA Regional Screening Levels. Retrieved from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables-june-2017

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3. Update 2019. Retrieved from http://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Upadhyay, S., Carstens, J., Klein, D., Faller, T. H., Halbach, S., Kirchinger, W., . . . Filser, J. G. (2008). Inhalation and epidermal exposure of volunteers to ethylene glycol: Kinetics of absorption, urinary excretion, and metabolism to glycolate and oxalate. *Toxicology Letters, 178*(2), 131-141. doi:http://dx.doi.org/10.1016/j.toxlet.2008.02.010

Wilson, D. M. (2006). SOT Abstract. *Toxicol. Sci., 90*(1-S), 95.

World Health Organization (WHO). (2002). Concise International Chemical Assessment Document 45. Ethylene Glycol: Human Health Aspects. http://www.inchem.org/documents/cicads/cicads/cicad45.htm

Toxicological Summary for: Fluorene

CAS**: 86-73-7**

Synonyms: 9H-fluorene, 2,2'-methylenebiphenyl, diphenylenemethane, O-biphenylenemethane

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = 200 µg/L

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

$$= \frac{(0.058 \text{ mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{(0.074 \text{ L/kg-d)}^{**}}$$

= 156 rounded to **200 µg/L**

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 17.5 / 300 = 0.058 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	125 mg/kg-d (administered dose NOAEL, US EPA, 1989)
Dose Adjustment Factor (DAF):	0.14 from body weight scaling, study specific (US EPA, 2011 and MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 125 mg/kg-d x 0.14 = 17.5 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty to account for the absence of adequate developmental, reproductive, and neurotoxicity studies in the database.
Critical effect(s):	Decreased red blood cells in female mice, decreased packed cell volume in female and male mice, and increased relative spleen weight in male and female mice
Co-critical effect(s):	None identified
Additivity endpoint(s):	Hematological (blood) system, Spleen

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = 80 µg/L

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

$$= \frac{(0.018 \text{ mg/kg-d}) \text{ x } (0.2)^* \text{ x } (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= \mathbf{80 \text{ µg/L}}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 17.5/1000 = 0.018 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	125 mg/kg-d (administered dose NOAEL, US EPA, 1989 subchronic exposure)
Dose Adjustment Factor (DAF):	0.14 from body weight scaling, study specific (US EPA, 2011 and MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 125 mg/kg-d x 0.14 = 17.5 mg/kg-d (study specific body weight scaling basis)
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for subchronic-to-chronic extrapolation, and 10 for database uncertainty to account for the absence of adequate developmental, reproductive, and neurotoxicity studies in the database.
Critical effect(s):	Decreased red blood cells in female mice, decreased packed cell volume in female and male mice, and increased relative spleen weight in male and female mice
Co-critical effect(s):	None identified
Additivity endpoint(s):	Hematological (blood) system, Spleen

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not Classified
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (moderate)

Summary of Guidance Value History:
A non-cancer chronic HRL of 300 µg/L was promulgated in 1993. The 2019 chronic and subchronic nHBVs are lower than the previous HRL as a result of using MDH's most recent risk assessment

methodology. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	Yes	No	No	Yes
Effects observed?	-	No[1]	-	-	No[2]

Comments on extent of testing or effects:

[1] Very little information relating to immunotoxicity is available. One limited acute oral gavage study in male mice did not find any reduction in humoral or cell mediated immunity following exposure to fluorene.

[2] Results from a limited neurobehavioral gavage study in adult male rats did not indicate any adverse effects on locomotor activity or learning ability. A slight, but significant, decrease in anxiety-related behavior was observed in rats exposed to fluorene at a dose approximately 13-fold higher than the current chronic reference dose when tested in the elevated plus maze, although there was no dose response and the biological significance of this finding is unknown. In the subchronic/chronic critical study, increased incidence of salivation and hypoactivity were noted in the fluorene-exposed rats, however, there was no statistical analysis performed on these endpoints and they are not clear indicators of neurotoxicity but may point to central nervous system effects. No other neurotoxicity studies were available. A database uncertainty factor of 10 was applied, in part, to account for possibility of neurotoxic effects.

Resources Consulted During Review:

Agency for Toxic Substances & Disease Registry (ATSDR). (1995). *Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAHs)*. Atlanta, GA: US Department of Health and Human Services, Public Health Service, Retrieved from https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=122&tid=25

Aylward, L. L., Hays, S. M., Kirman, C. R., Marchitti, S. A., Kenneke, J. F., English, C., . . . Becker, R. A. (2014). Relationships of chemical concentrations in maternal and cord blood: a review of available data. *J Toxicol Environ Health B Crit Rev, 17*(3), 175-203. doi:10.1080/10937404.2014.884956

California Environmental Protection Agency (CalEPA). (2018). State Water Resources Control Board Water Quality Goals Database. Retrieved from https://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/

Crepeaux, G., Bouillaud-Kremarik, P., Sikhayeva, N., Rychen, G., Soulimani, R., & Schroeder, H. (2012). Late effects of a perinatal exposure to a 16 PAH mixture: Increase of anxiety-related behaviours and decrease of regional brain metabolism in adult male rats. *Toxicol Lett, 211*(2), 105-113. doi:10.1016/j.toxlet.2012.03.005

Crepeaux, G., Bouillaud-Kremarik, P., Sikhayeva, N., Rychen, G., Soulimani, R., & Schroeder, H. (2013). Exclusive prenatal exposure to a 16 PAH mixture does not impact anxiety-related behaviours and regional brain metabolism in adult male rats: a role for the period of exposure in the modulation of PAH neurotoxicity. *Toxicol Lett, 221*(1), 40-46. doi:10.1016/j.toxlet.2013.05.014

Crepeaux, G., Grova, N., Bouillaud-Kremarik, P., Sikhayeva, N., Salquebre, G., Rychen, G., . . . Schroeder, H. (2014). Short-term effects of a perinatal exposure to a 16 polycyclic aromatic hydrocarbon mixture in rats: assessment of early motor and sensorial development and cerebral cytochrome oxidase activity in pups. *Neurotoxicology, 43*, 90-101. doi:10.1016/j.neuro.2014.03.012

Dewhurst, F. (1962). The hydroxylation of fluorene in the rat and the rabbit. *Br J Cancer, 16*, 371-377.

Drwal, E., Rak, A., & Gregoraszczuk, E. L. (2019). Review: Polycyclic aromatic hydrocarbons (PAHs)-Action on placental function and health risks in future life of newborns. *Toxicology, 411*, 133-142. doi:10.1016/j.tox.2018.10.003

International Agency for Research on Cancer (IARC). (1983). *Polynuclear Aromatic Compounds, Part 1, Chemical, Environmental and Experimental Data*. Lyon, France: World Health Organization (WHO), Retrieved from https://monographs.iarc.fr/wp-content/uploads/2018/06/mono32.pdf.

International Agency for Research on Cancer (IARC). (2010). *Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures*. Lyon, France: World Health Organization (WHO), Retrieved from https://monographs.iarc.fr/wp-content/uploads/2018/06/mono92-14.pdf.

International Programme on Chemical Safety (IPCS). (1998). *Environmental Health Criteria 202: Polycyclic aromatic hydrocarbons, selected non-heterocyclic*. Retrieved from Geneva, Switzerland: http://www.inchem.org/documents/ehc/ehc/ehc202.htm#SubSectionNumber:7.3.1

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2016). *Guidance for Evaluating the Cancer Potency of Polycyclic Aromatic Hydrocarbon (PAH) Mixtures in Environmental Samples*. St. Paul, MN: Minnesota Department of Health Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/pahguidance.pdf.

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

Morris, H. P., Velat, C. A., Wagner, B. P., Dahlgard, M., & Ray, F. E. (1960). Studies of carcinogenicity in the rate of derivatives of aromatic amines related to N-2-fluorenylacetamide. *J Natl Cancer Inst, 24*, 149-180.

National Institute of Public Health and the Environment (RIVM). (2001). *Re-evaluation of human-toxicological maximum permissible risk levels.* Bilthoven, The Netherlands Retrieved from https://www.rivm.nl/bibliotheek/rapporten/711701025.pdf.

Peiffer, J., Cosnier, F., Grova, N., Nunge, H., Salquebre, G., Decret, M. J., . . . Schroeder, H. (2013). Neurobehavioral toxicity of a repeated exposure (14 days) to the airborne polycyclic aromatic hydrocarbon fluorene in adult Wistar male rats. *PLoS One, 8*(8), e71413. doi:10.1371/journal.pone.0071413

Peiffer, J., Grova, N., Hidalgo, S., Salquebre, G., Rychen, G., Bisson, J. F., . . . Schroeder, H. (2016). Behavioral toxicity and physiological changes from repeated exposure to fluorene administered orally or intraperitoneally to adult male Wistar rats: A dose-response study. *Neurotoxicology, 53*, 321-333. doi:10.1016/j.neuro.2015.11.006

Silkworth, J. B., Lipinskas, T., & Stoner, C. R. (1995). Immunosuppressive potential of several polycyclic aromatic hydrocarbons (PAHs) found at a Superfund site: new model used to evaluate additive interactions between benzo[a]pyrene and TCDD. *Toxicology, 105*(2-3), 375-386.

U.S. Environmental Protection Agency (EPA). Chemistry Dashboard. Retrieved from https://comptox.epa.gov/dashboard

U.S. Environmental Protection Agency (EPA). Regional Screening Levels (RSLs) - Generic Tables. Retrieved from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency (EPA). (1990). *Chemical Assessment Summary Fluorene; CASRN 86-73-4*. Washington DC, Retrieved from https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=435.

U.S. Environmental Protection Agency (EPA). (2002). *Provisional Peer Reviewed Toxicity Values for Fluorene* Washinton, DC Retrieved from https://cfpub.epa.gov/ncea/pprtv/recordisplay.cfm?deid=338946.

U.S. Environmental Protection Agency (EPA). (2010). Development of a Relative Potency Factor (Rpf) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures (External Review Draft) Retrieved from https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=194584

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2018). *Office of Water. 2018 Edition of the Drinking Water Standards and Health Advisories*. Washington, DC Retrieved from https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf.

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

U.S. Geological Survey - Health-Based Screening Levels. Retrieved from https://cida.usgs.gov/hbsl/apex/f?p=104:1

Yan, J., Wang, L., Fu, P. P., & Yu, H. (2004). Photomutagenicity of 16 polycyclic aromatic hydrocarbons from the US EPA priority pollutant list. *Mutat Res, 557*(1), 99-108.

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Toxicological Summary for: Fomesafen

CAS: 72178-02-0

Synonyms: IUPAC 5-[2-chloro-4-(trifluoromethyl)phenoxy]-N-methanelsulfonyl-2-nitrobenzamide; 5-(-2-chloro-α-α-α-trifluoro-4-tolyloxy)-N-methylsulphonyl-2-nitro benzamide; PP021

Acute Noncancer Health-Based Value (nHBV$_{Acute}$) = Not Derived

Short-term Noncancer Health-Based Value (nHBV$_{Short-term}$) = 200 µg/L

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

$$= \frac{(0.12 \text{ mg/kg-d}) \times (0.5)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

= 206 rounded to **200 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 3.50/30 = 0.12 mg/kg-d (Alderley Park Wistar rat)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	12.5 mg/kg-d (administered dose NOAEL, 2-generation reproductive study, MRID 00144862, US EPA 1984a)
Dose Adjustment Factor (DAF):	0.28 study-specific, Body weight scaling, default (US EPA 2011c and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 12.5 mg/kg-d x 0.28 = 3.50 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased litter weight gain, decreased pup survival, and reduced number of pups born alive
Co-critical effect(s):	Decreased plasma cholesterol and triglycerides, increased liver weight and hepatocyte hypertrophy; reduced IgM antibody and lymph node enlargement
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Immune system

Subchronic Noncancer Health-Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 200 µg/L

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

$$= \frac{(0.14 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 378 rounded to 400 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 14/100 = 0.14 mg/kg-d (beagle)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	25 mg/kg-d (administered dose LOAEL, 26-week toxicity study, MRID 00103014, US EPA 1981a)
Dose Adjustment Factor (DAF):	0.56, Body weight scaling, default (US EPA 2011c and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 25 mg/kg-d x 0.56 = 14 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for using a LOAEL in place of a NOAEL because of wide dose spacing
Critical effect(s):	Blood changes (decreased hemoglobin, hematocrit, red blood cell count accompanied by an increased number of platelets); Decreased plasma cholesterol and triglycerides
Co-critical effect(s):	Reduced litter weight gain and pup survival, and a reduction in the number of pups born alive; Reduced plasma triglycerides and cholesterol, increased liver weight, hepatocyte hypertrophy, liver inflammation, and liver necrosis; Decreased IgM antibody and increased lymph node enlargement
Additivity endpoint(s):	Developmental, Hematological (blood) system, Hepatic (liver) system, Immune system

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 200 µg/L. Additivity endpoints: Developmental, Hepatic (liver) system, Immune system

Chronic Noncancer Health-Based Value (nHBV$_{Chronic}$) = 20 µg/L

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

$$= \frac{(0.005 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 22.2 \text{ rounded to } \textbf{20 µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.15/30 = 0.005 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	0.96 mg/kg-d (administered dose NOAEL, 2-year toxicity study, MRID 00131491, US EPA 1983);
Dose Adjustment Factor (DAF):	0.16 study-specific, Body weight scaling, default (US EPA 2011c and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 0.96 mg/kg-d x 0.16 = 0.15 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Increased liver weight, enlarged and discolored liver; the presence of pigmented macrophages and/or Kupffer cells in the liver (inflammation), liver masses, increased serum alkaline phosphatase activity, and increased glutamic pyruvic transaminase activity
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	Not likely to be carcinogenic to humans (US EPA 2018)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: No

Summary of Guidance Value History:
In 2018, MDH derived a Pesticide Rapid Assessment value of 3 µg/L, which used an infant water intake rate with a chronic RfD and an RSC of 0.5 (MDH Pesticide Rapid Assessment Results Table, updated 2020). The 2020 nHBV is based on MDH's duration-specific methodology, which matches the RfD and intake rate, resulting in a higher value of 20 µg/L. In 2020, MDH also incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	Yes	Yes	Yes	Yes
Effects observed?	_[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Although, there are no *in vivo* toxicity studies that tested specifically for endocrine changes after fomesafen treatment, the EPA's Endocrine Disruptor Screening Program tested fomesafen for endocrine activity *in vitro*. Fomesafen was found to have activity in a small fraction of *in vitro* tests (EPA Chemical Dashboard).

[2] The short duration co-critical effects of reduced antibody response and lymph node enlargement are based on an immunotoxicity assay in mice.

[3] The short-term duration critical study is based on developmental effects in rat pups whose mothers were exposed to fomesafen. The reference dose is based on decreased litter weight gain, decreased pup survival, and a reduction in the number of pups born alive. In another developmental study in rats, post-implantation loss and decreased litter weight occurred at a dose approximately 400 times higher than the short-term reference dose.

[4] A reduction in the number of rat pups born alive was a critical effect for the short-term duration study, and is also listed as a developmental effect. Additionally, in a separate experiment, increased post-implantation loss occurred in pregnant rats at a dose approximately 400 times higher than the short-term reference dose. Small uteri was observed in female mice at a dose 300 times higher than the short-term reference dose, and pale uteri occurred at a dose 1,000 times higher than the short-term reference dose.

[5] Neurotoxicity was evaluated in an acute toxicity study in rats. Motor activity was briefly reduced beginning at a dose 500 times higher than the short-term duration reference dose. However, a 13-week neurotoxicity study in rats found no neurotoxic effects at levels 400 times higher than the short-term reference dose.

Resources Consulted During Review:

Corton, J. C., Peters, J. M., & Klaunig, J. E. (2018). The PPARalpha-dependent rodent liver tumor response is not relevant to humans: addressing misconceptions. *Arch Toxicol, 92*(1), 83-119.

Hall, A. P., Elcombe, C. R., Foster, J. R., Harada, T., Kaufmann, W., Knippel, A., . . . York, M. J. (2012). Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes--conclusions from the 3rd International ESTP Expert Workshop. *Toxicol Pathol, 40*(7), 971-994.

Health Canada. (2018). *Fomesafen and Its Associated End-use Products - Proposed Re-evaluation Decision*. Ottawa, Ontario Retrieved from https://www.canada.ca/content/dam/hc-sc/documents/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/reevaluation-decision/2019/rvd2019-07-eng.pdf.

Holden, P. R., & Tugwood, J. D. (1999). Peroxisome proliferator-activated receptor alpha: role in rodent liver cancer and species differences. *J Mol Endocrinol, 22*(1), 1-8.

Krijt, J. S., P; Sanitrak, J; Chlumska, A; Fakan, F;. (1999). Liver preneoplastic changes in mice treated with the herbicide fomesafen. *Human & Experimental Toxicology, 18*, 338-344.

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

Minnesota Department of Health (MDH) Pesticide Rapid Assessment Results Table. (updated 2020). Rapid Assessments for Pesticides Web Page. Retrieved from: https://www.health.state.mn.us/communities/environment/risk/guidance/dwec/rapidpest.html

U.S. Environmental Protection Agency. (1980). *Preliminary Assessment of PP 021 Toxicity to Mice by Dietary Administration for 4 Weeks (MRID 40786709, Freedom of Information Act Request by MDH)*.

U.S. Environmental Protection Agency. (1981a). *PP021: 26 Week Oral Dosing Study in Dogs (MRID 00103014, Freedom of Information Act Request by MDH)*.

U.S. Environmental Protection Agency. (1981b). *PP021: 90 Day Feeding Study in Rats (MRID 00103013, Freedom of Information Act Request by MDH)*.

U.S. Environmental Protection Agency. (1981c). *PP021: Teratogenicity Study in the Rabbit (MRID 00109214, Freedom of Information Act Request by MDH)*.

U.S. Environmental Protection Agency. (1982a). *Fomesafen: Teratogenicity Study in the Rat (MRID 00103016, Freedom of Information Act Request by MDH)*.

U.S. Environmental Protection Agency. (1982b). *PP021: Teratogenicity Study in the Rat (MRID 00164903, Freedom of Information Act Request by MDH)*.

U.S. Environmental Protection Agency. (1983). *Fomesafen: 2-year Feeding Study in Mice (MRID 00131491, Freedom of Information Act Request by MDH)*.

U.S. Environmental Protection Agency. (1984a). *Fomesafen: Two Generation Reproduction Study in the Rat (MRID 00144862, Freedom of Information Act Request by MDH)*.

U.S. Environmental Protection Agency. (1984b). *Fomesafen: Two Year Feeding Study in Rats (MRID 00142125, Freedom of Information Act Request by MDH)*.

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency. (2005). *Fomesafen: Second Report of the Cancer Assessment Review Committee*. Retrieved from https://www.regulations.gov/document?D=EPA-HQ-OPP-2010-0122-0013.

U.S. Environmental Protection Agency. (2011a). *Fomesafen - A 28 Day Immunotoxicity Study of Fomesafen by Oral (Dietary) Administration in Mice using Sheep Red Blood Cells as the Antigen (MRID 48762301, Freedom of Information Act Request by MDH).*

U.S. Environmental Protection Agency (EPA). (2011b). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency. (2013). *Fomesafen Sodium: Human Health Risk Assessment for the Section 3 Registration Action on Canteloupe, Cucumber, Pea (Succulent), Pumpkin, Summer Squash, Winter Squash, Watermelon, Soybean (Succulent) and Lima Bean (Succulent).* Washington, D.C. Retrieved from https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0589-0009.

U.S. Environmental Protection Agency. (2017). Human Health Benchmarks for Pesticides. Retrieved from https://ofmpub.epa.gov/apex/pesticides/f?p=122:3:

U.S. Environmental Protection Agency. (2018a). *Fomesafen - Interim Registration Review Decision*. Retrieved from https://www.regulations.gov/document?D=EPA-HQ-OPP-2006-0239-0186.

U.S. Environmental Protection Agency. (2018b). *Fomesafen: Revised Draft Human Health Risk Assessment for Registration Review and for the Section 3 Registration Action on Tuberous and Corm Vegetables (Crop Group 1C), Legume Vegetable (Crop Group 6) and Low Growing Berry (Except Cranberry) (Crop Group 13-07G).* Retrieved from https://mn365.sharepoint.com/teams/MDH/bureaus/hpb/ehd/esa/HRA_DocumentForReview/Fomesafen%20Tox%20Worksheet.docx

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3. Update 2019. Retrieved from http://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

U.S. Environmental Protection Agency (EPA). Regional Screening Levels (RSLs) - Generic Tables. Retrieved from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables-november-2017

World Health Organization. (2015). *JMPR Pesticide residues in food: guidance document for WHO monographers and reviewers.* Geneva, Switzerland. Retrieved from: https://www.who.int/foodsafety/publications/JMPR-guidance-document/en/

Yang, Q., Nagano, T., Shah, Y., Cheung, C., Ito, S., & Gonzalez, F. J. (2008). The PPAR alpha-humanized mouse: a model to investigate species differences in liver toxicity mediated by PPAR alpha. *Toxicol Sci, 101*(1), 132-139.

Toxicological Summary for: n-Hexane

CAS: **110-54-3**

Synonyms: hexane

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

Short-term Non-Cancer Risk Assessment Advice (RAA$_{Short-term}$) = 100 µg/L

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

$$= \frac{(0.19 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

= 131 rounded to **100 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 188/1000 = 0.19 mg/kg-d (male Wistar rat)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	785 mg/kg-d (administered dose LOAEL, neurotoxicity study by Ono et al. 1981)
Dose Adjustment Factor (DAF):	0.24, body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 785 mg/kg-d x 0.24 = 188 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for toxicodynamic differences between species; 10 for intraspecies variation; 3 for use of a LOAEL; 10 for database limitations, including the lack of multigenerational and neurodevelopmental studies
Critical effect(s):	Reduced motor nerve conduction velocity
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Subchronic Non-Cancer Risk Assessment Advice (RAA$_{Subchronic}$) = RAA$_{Short-term}$ = 100 µg/L

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

$$= \frac{\text{(0.063 mg/kg-d) x (0.2)}^* \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

$$= 170 \text{ rounded to 200 µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 188/3000 = 0.063 mg/kg-d (male Wistar rat)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	785 mg/kg-d (administered dose LOAEL, neurotoxicity study by Ono et al., 1981)
Dose Adjustment Factor (DAF):	0.24 Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 785 mg/kg-d x 0.24 = 188 mg/kg-d
Total uncertainty factor (UF):	3000
Uncertainty factor allocation:	3 for toxicodynamic differences between species; 10 for intraspecies variation; 3 for use of a LOAEL; 3 for extrapolation from a short-term duration study; 10 for database limitations, including lack of multigenerational and neurodevelopmental studies
Critical effect(s):	Reduced motor nerve conduction velocity
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

The Subchronic RAA must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic RAA is set equal to the Short-term RAA of 100 µg/L. Additivity endpoints: Nervous system

Chronic Non-Cancer Risk Assessment Advice (RAA$_{Chronic}$) = 80 µg/L

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

$$= \frac{\text{(0.019 mg/kg-d) x (0.2)}^* \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

$$= 84.4 \text{ rounded to } \mathbf{80 \text{ µg/L}}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 188/10000 = 0.019 mg/kg-d (male Wistar rat)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	785 mg/kg-d (administered dose LOAEL, neurotoxicity study by Ono et al. 1981, short-term exposure)
Dose Adjustment Factor (DAF):	0.24 Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 785 mg/kg-d x 0.24 = 188 mg/kg-d
Total uncertainty factor (UF):	10000
Uncertainty factor allocation:	3 for toxicodynamic differences between species; 10 for intraspecies variation; 3 for use of a LOAEL; 10 for the use of a shorter duration study.; 10 for database limitations, including lack of multigenerational and neurodevelopmental studies
Critical effect(s):	Reduced motor nerve conduction velocity
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Cancer Risk Assessment Advice (cRAA) = Not Applicable

Cancer classification:	Not Classified—Inadequate information (EPA, 2005)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (high)

Summary of Guidance Value History:
A noncancer chronic HRL of 400 µg/L was promulgated in 1994. MDH derived short-term, subchronic and chronic noncancer RAAs in 2021 that are lower than the 1994 HRL as a result of: 1) using MDH's most recent assessment methodology; and 2) incorporation of additional toxicological information.

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	Yes	Yes	Yes	Yes
Effects observed?	-	Yes[1]	Yes[2]	Yes[3]	Yes[4]

Comments on extent of testing or effects:

1. In one rat study, animals had increased levels of white blood cells, lymphocytes, granulocytes, and eosinophils in the blood and inflammatory cells and macrophages in the lung following oral exposure to levels 380 times higher than the short-term RfD.

2. One developmental mouse study reported decreased fetal body weight at doses more than 5,400 times the short-term reference dose. Absence of multigenerational developmental and neurodevelopmental study data is addressed with the application of a database uncertainty factor.

3. Oral rat studies reported decreased prostate weight and increased seminal vesicle weight at doses more than 13,000 and 26,000 times higher than the short-term reference dose, respectively. No histopathological changes were noted; however, testicular sperm count was decreased following a single exposure to a dose over 26,000 times higher than the short-term reference dose. Additionally, in a subchronic neurotoxicity study in rats, testicular atrophy was observed following exposure to doses more than 3,700 times the short-term reference dose. The absence of a multigenerational reproductive study contributed to the application of a database uncertainty factor.

4. The reference dose for short-term, subchronic, and chronic durations is based on neurotoxicity (i.e., reduced motor nerve conduction velocity). Uncertainty regarding the effects of n-hexane on a developing organism's nervous system are addressed with the addition of a database uncertainty factor.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). (1999). *Toxicological Profile for n-Hexane.* Atlanta, Georgia. Retrieved from https://www.atsdr.cdc.gov/toxprofiles/tp113.pdf

Baelum, J., Molhave, L., Hansen, S. H., & Vaeth, M. (1998). Metabolic interaction between toluene, trichloroethylene and n-hexane in humans. *Scand J Work Environ Health, 24*(1), 30-37.

Bouakkaz, I., Khelili, K., Rebai, T., & Lock, A. (2018). Pulmonary Toxicity Induced by N-Hexane in Wistar Male Rats After Oral Subchronic Exposure. *Dose Response, 16*(4).

California Environmental Protection Agency - OEHHA Cancer Potency Values. (2005). OEHHA Toxicity Criteria Database. Retrieved from https://oehha.ca.gov/chemicals

California Environmental Protection Agency - OEHHA Proposition 65. Most Current Proposition 65 No Significant Risk Levels (NSRLs) Maximum Allowable Dose Levels (MADLs). Retrieved from http://www.oehha.ca.gov/prop65/getNSRLs.html

California Environmental Protection Agency (CalEPA). (2017). *Consideration of n-Hexane for Listing Under Proposition 65 as Known to Cause Reproductive Toxicity*. Retrieved from https://oehha.ca.gov/proposition-65/chemicals/n-hexane

California State Water Resources Control Board. Search Water Quality Goals Online. Retrieved from https://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/search.html

Danish Ministry of the Environment (Danish EPA). (2014). *Survey of n-hexane*. Copenhagen, Denmark. Retrieved from https://www2.mst.dk/Udgiv/publications/2014/12/978-87-93283-41-1.pdf

European Chemicals Agency (ECHA). (2017). *Substance Evaluation Conclusion as Required by REACH Article 48 and Evaluation Report for n-Hexane*. Retrieved from https://echa.europa.eu/documents/10162/9ec3d80b-452f-08d6-bfdc-d55d2c05118a

Health Canada. (2009). *Screening Assessment for the Challenge Hexane.* Retrieved from http://www.ec.gc.ca/ese-ees/default.asp?lang=En&xml=C1B542C5-4A04-DD1F-74D8-0E7B1459065C

Krasavage, W. J., O'Donoghue, J. L., DiVincenzo, G. D., & Terhaar, C. J. (1980). The relative neurotoxicity of methyl-n-butyl ketone, n-hexane and their metabolites. *Toxicol Appl Pharmacol, 52*(3), 433-441.

LoPachin, R. M. (2000). Redefining toxic distal axonopathies. *Toxicol Lett, 112-113*, 23-33.

Massachusetts Department of Environmental Protection (MA DEP). (2004). *Updated Petroleum Hydrocarbon Fraction Toxicity Values For The VPH/EPH/APH Methodology.* Boston, MA. Retrieved from https://www.mass.gov/doc/updated-petroleum-hydrocarbon-fraction-toxicity-values-for-the-vphephaph-methodology/download

Massachussetts Department of Environmental Protection (MA DEP). (1994). *Interim Final Petroleum Report: Development of Health-Based Alternative to the Total Petroleum Hydrocarbon (TPH) Parameter.* Boston, MA. Retrieved from https://clu-in.org/conf/tio/cra6/resources/MADEP-TPH-Toxicity-Factors-(2003).pdf

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

New Jersey Department of Environmental Protection. (2015). Standards for Drinking Water, Ground Water, Soil and Surface Water. Retrieved from https://www.nj.gov/dep/standards/Standards.htm

New Jersey Drinking Water Quality Institute. (1987). *Maxiumum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water.* Retrieved from https://www.state.nj.us/dep/watersupply/pdf/1987.pdf

Occupational Safety and Health Administration (OSHA). (2021). Hexane (n-hexane). Retrieved from https://www.osha.gov/chemicaldata/112.

Ono, Y., Takeuchi, Y., & Hisanaga, N. (1981). A comparative study on the toxicity of n-hexane and its isomers on the peripheral nerve. *Int Arch Occup Environ Health, 48*(3), 289-294.

Organisation for Economic Co-operation and Development (OECD). (2020). QSAR Toolbox Version 4.4.1.

Spencer, P. S. (2020). Neuroprotein Targets of gamma-Diketone Metabolites of Aliphatic and Aromatic Solvents That Induce Central-Peripheral Axonopathy. *Toxicol Pathol, 48*(3), 411-421.

Spencer, P. S. & Chen, X. (2021). The Role of Protein Adduction in Toxic Neuropathies of Exogenous and Endogenous Origin. *Toxics, 9*(5). doi:10.3390/toxics9050098

Texas Commission on Environmental Quality (TCEQ). (2010). *Memo: Toxicity Factor Update for Total Petroleum Hydrocarbon Surrogate Chemicals Under the Texas Risk Reduction Program and 1993 Risk Reduction Rule.*

Title 21- Food and Drugs, 21CFR173.270 (2020).

Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG). (1997). *Total Petroleum Hydrocarbon Criteria Working Group Series, Volume 4: Development of Fraction Specific Reference Doses (RfDs) and Reference Concentrations (RfCs) for Total Petroleum Hydrocarbons (TPH)*. Amherst, MA.

Twerdok, L. E. (1999). Development of toxicity criteria for petroleum hydrocarbon fractions in the Petroleum Hydrocarbon Criteria Working Group approach for risk-based management of total petroleum hydrocarbons in soil. *Drug Chem Toxicol, 22*(1), 275-291.

U.S. Environmental Protection Agency (EPA). Chemistry Dashboard. Retrieved from https://comptox.epa.gov/dashboard

U.S. Environmental Protection Agency (EPA). Regional Screening Levels (RSLs) - Generic Tables. Retrieved from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables

U.S. Environmental Protection Agency (EPA). (1987). *n-Hexane Health Advisory.* Washington, DC. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/9100I9KX.PDF?Dockey=9100I9KX.PDF

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency (EPA). (1997). Health Effects Assessment Summary Table (HEAST). Retrieved from https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=2877

U.S. Environmental Protection Agency (EPA). (2005). *Toxicological review of n-hexane.* Washington, D.C. Retrieved from https://iris.epa.gov/static/pdfs/0486tr.pdf

U.S. Environmental Protection Agency (EPA). (2009a). *Provisional Peer-Reviewed Provisional Subchronic Toxicity Values for n-Hexane*. Cincinnati, OH. Retrieved from https://cfpub.epa.gov/ncea/pprtv/documents/HexaneN.pdf

U.S. Environmental Protection Agency (EPA). (2009b). *Provisional Peer-Reviewed Toxicity Values for Commercial or Practical Grade Hexane*. Cincinnati, OH. Retrieved from https://cfpub.epa.gov/ncea/pprtv/documents/HexaneCommercial.pdf

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2018). 2018 Edition of the Drinking Water Standards and Health Advisories. Retrieved from https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf.

U.S. Environmental Protection Agency (EPA) (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Yin, H., Guo, Y., Zeng, T., Zhao, X., & Xie, K. (2013). Correlation between levels of 2, 5-hexanedione and pyrrole adducts in tissues of rats exposure to n-hexane for 5-days. *PLoS One, 8*(9), e76011.

Web Publication Date: September 2020

Toxicological Summary for: Imidacloprid

CAS: **138261-41-3**

Synonyms: N-[1-[(6-chloropyridin-3-yl)methyl]-4,5-dihydroimidazol-2-yl]nitramide; 1-((6-chloro-3-pyridinyl)methyl)-N-nitro-2-imidazolidinimine; [N-(6-chloropyridin-3-ylmethyl)-2-nitroiminoimidazolidine]; *(E)* -1-(6-Chloro-3-pyridinylmethyl)-*N*-nitroimidazolidin-2-ylideneamine; NTN; 2-Imidazolidinimine

Acute Non-Cancer Health Based Value (nHBV$_{Acute}$) = 100 µg/L

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

$$= \frac{(0.15 \text{ mg/kg-d) x (0.2)}^* \text{ x (1000 µg/mg)}}{(0.290 \text{ L/kg-d})^{**}}$$

= 103 rounded to **100 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1. MDH deviated from the default RSC of 0.5 based on assessments from California EPA (2006) and U.S. EPA (2017) indicating that infant dietary exposures and infant exposures from residential pesticide treatments, including pet treatments, are high enough to warrant allocation of only 20% of the RfD to drinking water.

**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 4.4/30 = 0.15 mg/kg-d (Beagle dogs)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	8 mg/kg-d (administered dose NOAEL, Ruf 1990 cited in California EPA 2006)
Dose Adjustment Factor (DAF):	0.55, Body weight scaling based on dog body weights at start of study (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 8 mg/kg-d x 0.55 = 4.4 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Tremors
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 2 µg/L

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

$$= \frac{(0.0036 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 2.48 \text{ rounded to } \textbf{2 µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1. MDH deviated from the default RSC of 0.5 based on assessments from California EPA (2006) and U.S. EPA (2017) indicating that infant dietary exposures and infant exposures from residential pesticide treatments, including pet treatments, are high enough to warrant allocation of only 20% of the RfD to drinking water.

[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.107/30 = 0.0036 mg/kg-d (BALB/c mice)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	0.820 mg/kg-d (administered dose BMDL$_{1SD}$, Badgujar 2013)
Dose Adjustment Factor (DAF):	0.13, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 0.820 mg/kg-d x 0.13 = 0.107 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Reduced delayed-type hypersensitivity response
Co-critical effect(s):	None
Additivity endpoint(s):	Immune system

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 2 µg/L

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

$$= \frac{(0.0036 \text{ mg/kg-d})^{***} \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 9.72 \text{ rounded to } 10 \text{ µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.

[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

[***]The calculated Subchronic RfD (0.073 mg/kg-d) is higher than the Short-term RfD (0.0036 mg/kg-d), which is based on immune 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.

The Subchronic nHBV must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 2 µg/L. Additivity endpoints: Immune system

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = nHBV$_{Short-term}$ = 2 µg/L

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

$$= \frac{(0.0036 \text{ mg/kg-d})^{***} \text{ x } (0.2)^{*} \text{ x } (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 16 \text{ rounded to } 20 \text{ µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.

[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

[***]The calculated Chronic RfD (0.019 mg/kg-d) is higher than the Short-term RfD (0.0036 mg/kg-d), which is based on immune effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure, including subchronic and short-term effects (MDH 2008, page 34). Therefore, the Short-term RfD is used in place of the calculated Chronic RfD.

The Chronic HBV must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic HBV is set equal to the Short-term HBV of 2 µg/L. Additivity endpoints: Immune system

Cancer Health Based Value (cHBV) = "Not Applicable"

Cancer classification:	Evidence of non-carcinogenicity for humans (U.S. EPA 2017a)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: No

Summary of Guidance Value History: In 2014, MDH derived a pesticide rapid assessment value for imidacloprid (90 µg/L) based on a US EPA risk assessment from 2010 (US EPA 2010) and the thyroid as a critical health endpoint. The 2019 HBVs for short-term, subchronic, and chronic durations (this assessment) are lower than the pesticide rapid assessment due to the incorporation of a toxicologically more sensitive health endpoint that occurred in a shorter-duration study than the chronic thyroid effects. The 2019 MDH risk assessment methodology includes BMD modeling for the delayed-type hypersensitivity response in mice. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in a change in the short-term duration water guidance value from 3 µg/L to 2 µg/L. As in the 2019 MDH risk assessment, the subchronic and chronic guidance values were set to equal the short-term guidance value (2 µg/L).

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?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes [3]	Yes [4]	Yes[5]

Comments on extent of testing or effects:

[1] At an imidacloprid exposure 1,000 times higher than the short-term RfD, reduced ovarian weight was associated with increased ovarian lipid peroxidation, decreased ovarian antioxidant activity, and changes in ovarian hormones and ovarian morphology in the female rat 90-days after exposure. At a dose 2,500 times higher than the short-term RfD, male rats had increased adrenal weight, increased adrenal cholesterol, and increased hypothalamic and pituitary acetylcholinesterase activity. Changes in male hormones were observed in two lower quality, single dose studies in both rat pups and adults at doses 25 – 70 times higher than the short-term RfD. Thyroid lesions were observed in male rats after 2 years of exposure at doses 300 times higher than the short-term RfD. Thyroid changes occurred in female beagles at doses 4,000 times higher than the short-term RfD.

[2] The short-term RfD is based on immunotoxicity (decreased delayed-type hypersensitivity response) in female mice in a 28-day immunotoxicity study. In the same study, a five-fold higher dose resulted in reduced T-cell stimulation and a reduction in the number of lymphocytes. In a longer-duration study, the spleen weight in mice was reduced at a dose 17,000 times higher than the short-term RfD. Immunotoxicity was also observed in other study animals. Rat pups had a reduced hemagglutination titer and phagocytic index at a dose 150 times higher, and had a delayed-type hypersensitivity response at imidacloprid levels 400 times higher than the short-term RfD. At levels 1,000 times higher than the short-term RfD, rat pups had a decreased number of white blood cells. Beagles after a one-month exposure, had atrophy of the bone marrow, involution of the thymus, and a drop in serum α-1 globulin M at a dose 7,000 times higher than the short-term RfD.

[3] Skeletal abnormalities were observed in both rat and rabbit fetuses at doses 6,000 and 9,000 times higher than the short-term RfD, respectively. Reduced body weight in rat pups occurred at doses 2,000 to 6,000 times higher than the short-term RfD. Some of these pups also had morphometric changes in the brain, learning delays, or changes in motor activity. A lower quality, single dose study using a commercial formulation in mice reported changes in neuronal branching and neuronal density in the brain at doses 25 times higher than the short-term RfD.

[4] Maternal death, abortion, total resorption, and post-implantation loss were only observed in rabbits; and at imidacloprid doses 10,000 times higher than the short-term RfD. Despite no apparent change in reproductive outcomes, female rats had reduced ovarian weight along with changes in ovarian

morphology, and increased lipid peroxidation and decreased anti-oxidant activity in the ovaries at doses 1,000 times higher than the short-term RfD. Male rats, at doses 70 to 500 times higher than the short-term RfD, had reduced seminal vesicle and testicular weight, testicular atrophy, reduced sperm concentration, reduced sperm mobility and viability, increased sperm abnormalities, and changes in male reproductive hormones. Conversely, increased testicular weight was noted in rats after one-year of exposure at imidacloprid levels 8,000 times higher than the short-term RfD, and increased ovarian weight was noted after two-years exposure at levels 10,000 times higher than the short-term RfD. Testicular degeneration was observed in the beagle at imidacloprid doses 7,500 times higher than the short-term RfD.

[5] The acute duration RfD is based on tremors in beagles after imidacloprid exposure. This occurred at imidacloprid concentrations 3,500 times higher than the short-term RfD. In the rat, tremors (at 1,000 times higher than the short-term RfD), occurred in addition to uncoordinated gait, reduced motor and locomotor activity, reduced hindlimb grip strength, and the absence of response to human touch or a tail pinch at levels 5,000 to 10,000 times higher than the short-term RfD. Rat fetuses, at maternal doses 3,000 times higher than the short-term RfD, had changes in brain thickness. Rat pups had a delay in learning and a decrease in memory consolidation at imidacloprid levels 2,000 times higher than the short-term RfD, and adults were affected at levels 100 to 500 times higher than the short-term RfD in the same study. Chemical changes in the brain were measured in female rat at levels 60 times higher than the short-term RfD. Tremors in mice occurred at levels 4,000 times higher than the short-term RfD. A lower quality, single dose study using a commercial formulation found that male mice had changes in brain thickness at levels 25 times higher than the short-term RfD.

Resources Consulted During Review:

Abdel-Rahman Mohamed, A., Mohamed, W. A. M., & Khater, S. I. (2017). Imidacloprid induces various toxicological effects related to the expression of 3beta-HSD, NR5A1, and OGG1 genes in mature and immature rats. *Environ Pollut, 221*, 15-25.

Annabi, A., Dhouib, I. B., Lamine, A. J., El Golli, N., Gharbi, N., El Fazaa, S., & Lasram, M. M. (2015). Recovery by N-acetylcysteine from subchronic exposure to Imidacloprid-induced hypothalamic-pituitary-adrenal (HPA) axis tissues injury in male rats. *Toxicol Mech Methods, 25*(7), 524-531.

Australian Pesticides and Veterinary Medicines Authority. (2018). Acceptable Daily Intakes for Agricultural and Veterinary Chemicals. Retrieved from https://apvma.gov.au/node/26596

Badgujar, P. C., Jain, S. K., Singh, A., Punia, J. S., Gupta, R. P., & Chandratre, G. A. (2013). Immunotoxic effects of imidacloprid following 28 days of oral exposure in BALB/c mice. *Environ Toxicol Pharmacol, 35*(3), 408-418.

Bagri, P., Kumar, V., & Sikka, A. K. (2015). An in vivo assay of the mutagenic potential of imidacloprid using sperm head abnormality test and dominant lethal test. *Drug Chem Toxicol, 38*(3), 342-348.

Bagri, P., Kumar, V., & Sikka, A. K. (2016). Assessment of imidacloprid-induced mutagenic effects in somatic cells of Swiss albino male mice. *Drug Chem Toxicol, 39*(4), 412-417.

Bagri, P., Kumar, V., Sikka, A.K., Punia, J.S. (2013). Preliminary acute toxicity study on imidacloprid in Swiss albino mice. *Veterinary World, 6*(December).

Bal, R., Turk, G., Tuzcu, M., Yilmaz, O., Kuloglu, T., Gundogdu, R., . . . Etem, E. (2012). Assessment of imidacloprid toxicity on reproductive organ system of adult male rats. *J Environ Sci Health B, 47*(5), 434-444.

Bhardwaj, S., Srivastava, M. K., Kapoor, U., & Srivastava, L. P. (2010). A 90 day oral toxicity of imidacloprid in female rats: morphological, biochemical and histopathological evaluations. *Food Chem Toxicol, 48*(5), 1185-1190.

Bhaskar, R., Mishra, A. K., & Mohanty, B. (2017). Neonatal Exposure to Endocrine Disrupting Chemicals Impairs Learning Behaviour by Disrupting Hippocampal Organization in Male Swiss Albino Mice. *Basic Clin Pharmacol Toxicol, 121*(1), 44-52.

Burke, A. P., Niibori, Y., Terayama, H., Ito, M., Pidgeon, C., Arsenault, J., . . . Hampson, D. R. (2018). Mammalian Susceptibility to a Neonicotinoid Insecticide after Fetal and Early Postnatal Exposure. *Sci Rep, 8*(1), 16639.

California EPA. (2006). *Imidacloprid: Risk Characterization Document - Dietary and Drinking Water Exposure*. Retrieved from https://www.cdpr.ca.gov/docs/risk/rcd/imidacloprid.pdf

Caron-Beaudoin, E., Viau, R., Hudon-Thibeault, A. A., Vaillancourt, C., & Sanderson, J. T. (2017). The use of a unique co-culture model of fetoplacental steroidogenesis as a screening tool for endocrine disruptors: The effects of neonicotinoids on aromatase activity and hormone production. *Toxicol Appl Pharmacol, 332*, 15-24.

Chakroun, S., Grissa, I., Ezzi, L., Ammar, O., Neffati, F., Kerkeni, E., Najjar, M.F., Haouas, Z., & Ben Cheikh, H. (2017). Imidacloprid Enhances Liver Damage in Male Wistar Rats: Biochemical, Oxidative Damage and Histological Assessment. *Journal of Coast Life Medicine*.

Demsia, G., Vlastos, D., Goumenou, M., & Matthopoulos, D. P. (2007). Assessment of the genotoxicity of imidacloprid and metalaxyl in cultured human lymphocytes and rat bone-marrow. *Mutat Res, 634*(1-2), 32-39.

Duzguner, V., & Erdogan, S. (2012). Chronic exposure to imidacloprid induces inflammation and oxidative stress in the liver and central nervous system of rats. *Pesticide Biochemistry and Physiology, 104*, 58-64.

EFSA. (2008). Conclusion Regarding the Peer Review of the Pesticide Risk Assessment of the Active Substance Imidacloprid. *EFSA Journal, 6*(7).

Gawade, L., Dadarkar, S. S., Husain, R., & Gatne, M. (2013). A detailed study of developmental immunotoxicity of imidacloprid in Wistar rats. *Food Chem Toxicol, 51*, 61-70.

Harada, K. H., Tanaka, K., Sakamoto, H., Imanaka, M., Niisoe, T., Hitomi, T., . . . Koizumi, A. (2016). Biological Monitoring of Human Exposure to Neonicotinoids Using Urine Samples, and Neonicotinoid Excretion Kinetics. *PLoS One, 11*(1), e0146335.

Kapoor, U., Srivastava, M. K., Bhardwaj, S., & Srivastava, L. P. (2010). Effect of imidacloprid on antioxidant enzymes and lipid peroxidation in female rats to derive its No Observed Effect Level (NOEL). *J Toxicol Sci, 35*(4), 577-581.

Kapoor, U., Srivastava, M. K., & Srivastava, L. P. (2011). Toxicological impact of technical imidacloprid on ovarian morphology, hormones and antioxidant enzymes in female rats. *Food Chem Toxicol, 49*(12), 3086-3089.

Kapoor, U., Srivastava, M. K., Trivedi, P., Garg, V., & Srivastava, L. P. (2014). Disposition and acute toxicity of imidacloprid in female rats after single exposure. *Food Chem Toxicol, 68*, 190-195.

Kara, M., Yumrutas, O., Demir, C. F., Ozdemir, H. H., Bozgeyik, I., Coskun, S., . . . Bal, R. (2015). Insecticide imidacloprid influences cognitive functions and alters learning performance and related gene expression in a rat model. *Int J Exp Pathol, 96*(5), 332-337.

Kataria, S. K., Chhillar, A. K., Kumar, A., Tomar, M., & Malik, V. (2016). Cytogenetic and hematological alterations induced by acute oral exposure of imidacloprid in female mice. *Drug Chem Toxicol, 39*(1), 59-65.

Kennel, P. (2010). Imidacloprid 28-Day Immunotoxicity Study in the Male Wistar Rat by Dietary Administration. Bayer S.A.S., Bayer CropScience. MRID: 48298701.

Kimura-Kuroda, J., Komuta, Y., Kuroda, Y., Hayashi, M., & Kawano, H. (2012). Nicotine-like effects of the neonicotinoid insecticides acetamiprid and imidacloprid on cerebellar neurons from neonatal rats. *PLoS One, 7*(2), e32432.

Lin, P. C., Lin, H. J., Liao, Y. Y., Guo, H. R., & Chen, K. T. (2013). Acute poisoning with neonicotinoid insecticides: a case report and literature review. *Basic Clin Pharmacol Toxicol, 112*(4), 282-286.

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

Mohamed, F., Gawarammana, I., Robertson, T. A., Roberts, M. S., Palangasinghe, C., Zawahir, S., . . . Roberts, D. M. (2009). Acute human self-poisoning with imidacloprid compound: a neonicotinoid insecticide. *PLoS One, 4*(4), e5127.

Moser, V. C., Stewart, N., Freeborn, D. L., Crooks, J., MacMillan, D. K., Hedge, J. M., . . . Herr, D. W. (2015). Assessment of serum biomarkers in rats after exposure to pesticides of different chemical classes. *Toxicol Appl Pharmacol, 282*(2), 161-174.

Najafi, G. R., M; Hoshyar, A.; Shahmohamadloo, S.; Feyzi, S. (2010). The Effect of Chronic Exposure with Imidacloprid Insecticide on Fertility in Mature Male Rats. *International Journal of Fertility and Sterility, 4*(1), 9-16.

Sheets, L. P., Li, A. A., Minnema, D. J., Collier, R. H., Creek, M. R., & Peffer, R. C. (2016). A critical review of neonicotinoid insecticides for developmental neurotoxicity. *Crit Rev Toxicol, 46*(2), 153-190.

Soujanya, S., Lakshman, M., Kumar, A. A., & Reddy, A. G. (2013). Evaluation of the protective role of vitamin C in imidacloprid-induced hepatotoxicity in male Albino rats. *J Nat Sci Biol Med, 4*(1), 63-67.

Stivaktakis, P. D., Kavvalakis, M. P., Tzatzarakis, M. N., Alegakis, A. K., Panagiotakis, M. N., Fragkiadaki, P., . . . Tsatsakis, A. M. (2016). Long-term exposure of rabbits to imidaclorpid [*sic*] as quantified in blood induces genotoxic effect. *Chemosphere, 149*, 108-113.

Syracuse Environmental Research Associates Inc. - Patrick R. Durkin. (2016). *Imidacloprid: Human Health and Ecological Risk Assessment Corrected Final Report - submitted to USDA Forest Service*. Malinus, New York Retrieved from https://www.fs.fed.us/foresthealth/pesticide/pdfs/ImidaclopridFinalReport.pdf

Toor, H. K., Sangha, G. K., & Khera, K. S. (2013). Imidacloprid induced histological and biochemical alterations in liver of female albino rats. *Pestic Biochem Physiol, 105*(1), 1-4.

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. EPA. (1993a). *Data Evaluation Report Imidacloprid. Study Type: Metabolism*. Arlington, VA Retrieved from https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/129099/129099-027.pdf

U.S. EPA. (1993b). *Data Evaluation Report: Imidacloprid (Reproductive Toxicity)*. Arlington, VA. Retrieved from https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/129099/129099-025.pdf

U.S. EPA. (1993c). *I.D. #003125-UER: NTN 33893 75 WP-WS. Evaluation of Acute Toxicity Data Submitted (Also NTN 33893 Mutagenicity Data - Attached).* Washington, D.C. Retrieved from https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/129099/129099-026.pdf

U.S. EPA. (1993d). *I.D. Nos. 003125-URU, 003125-URL, 003125-URI, 003125-URT, 003125-URA: NTN 33893. Evaluation of Toxicity Data Submitted and Identification of Outstanding Toxicology Data Requirements.* Washington, D.C. Retrieved from https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/129099/129099-017.pdf

U.S. EPA. (1993e). *I.D. Nos.: 003125-UEE, 003125-UEG, 3F04169, 3H05655. Imidacloprid. Evaluation of Toxicity Data Submitted and Identification of Outstanding Toxicology Data Requirements.* Washington, D.C. Retrieved from https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/129099/129099-041.pdf

U.S. EPA. (1995). *EPA ID# 003125-00414. Imidacloprid. Review of the series 81-8 acute neurotoxicity and 82-7 subchronic neurotoxicity screen studies.* Washington, D.C. Retrieved from

https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/129099/129099-076.pdf

U.S. EPA. (2002). *Data Evaluation Record: Imidacloprid. Developmental Neurotoxicity Study - Rat.* Arlington, VA Retrieved from https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/129099/129099-0000-00-00a.pdf

U.S. EPA. (2010). *Imidacloprid: Revised Human Health Risk Assessment for Proposed Section 3 Seed Treatment Uses on Bulb Vegetables (Crop Group 3); Cereal Grains (Crop Group 15); Root and Tuber Vegetables; Except Sugar Beet (Crop Subgroup 1B): Tuberous and Corm Vegetables (Crop Subgroup 1C); Leafy Vegetables, Except Brassica (Crop Subgroup 4A); Brassica Vegetables (Crop Group 5); Fruiting Vegetables (Crop Group 8); Cucurbit Vegetables (Crop Group 9); and Residential Crack and Crevice and Bed-Bug Uses.* Washington, D.C. Retrieved from https://www3.epa.gov/pesticides/chem_search/hhbp/R181434.pdf

U.S.EPA. (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. EPA. (2017a). *Imidacloprid: Human Health Draft Risk Assessment for Registration Review.* Washington, D.C. Retrieved from https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0844-1235

U.S. EPA. (2017b). Office of Pesticide Programs. Human Health Benchmarks for Pesticides. Retrieved from https://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3. Update 2019. Retrieved from http://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Wang, X., Anadon, A., Wu, Q., Qiao, F., Ares, I., Martinez-Larranaga, M. R., . . . Martinez, M. A. (2018). Mechanism of Neonicotinoid Toxicity: Impact on Oxidative Stress and Metabolism. *Annu Rev Pharmacol Toxicol, 58*, 471-507.

Xiang, D., Han, J., Yao, T., Wang, Q., Zhou, B., Mohamed, A. D., & Zhu, G. (2017). Editor's Highlight: Structure-Based Investigation on the Binding and Activation of Typical Pesticides With Thyroid Receptor. *Toxicol Sci, 160*(2), 205-216.

Toxicological Summary for: Manganese

CAS: **7439-96-5**

MDH has updated manganese guidance to a Health Based Value (HBV), and is removing the tiered Risk Assessment Advice. The Short-term Health-Based Value for Manganese is 100 ug/L. This value is protective of bottle-fed infants less than one year of age, the most sensitive population, as well as other populations.

MDH continues to support the U.S. Environmental Protection Agency (EPA) Lifetime Health Advisory (HA) of 300 µg/L for children older than one year of age and adults See Drinking Water Health Advisory for Manganese (PDF) (https://www.epa.gov/sites/production/files/2014-09/documents/support_cc1_magnese_dwreport_0.pdf)

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

Short-term Non-Cancer Health-Based Value (nHBV$_{Short-term}$) = 100 µg/L

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

$$= \frac{(0.083 \text{ mg/kg-d}) \text{ x } (0.5)^* \text{ x } (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

= 143 rounded to **100 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 25/300 = 0.083 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2012
Point of Departure (POD):	25 mg/kg-d (LOAEL, Kern 2010)
Dose Adjustment Factor (DAF):	Not applicable (Insufficient data to support use of DAFs for neonatal period) (MDH, 2017) (U.S. EPA, 2011)
Human Equivalent Dose (HED):	Not applicable
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	10 for interspecies differences, 10 for intraspecies variability, and 3 for LOAEL-to-NOAEL extrapolation (due to mild effects seen at LOAEL)
Critical effect(s):	Neurological effects including increased distance traveled in open arena, decreased number of animals meeting

learning criteria, increased learning errors, shift in goal-oriented behavior, altered dopamine receptor levels

Co-critical effect(s): Neurological effects including increased startle response
Additivity endpoint(s): Developmental, Nervous System

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = Not Derived (Insufficient Information)*

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = Not Derived (Insufficient Information)*

*MDH recommends the US Environmental Protection Agency's (EPA) health advisory value of 300 µg/L for older children and adults experiencing subchronic or chronic duration exposures. The EPA health advisory value is based on a high end dietary intake level at which no health effects were observed. For additional information see: https://www.health.state.mn.us/communities/environment/water/docs/contaminants/mangnsefctsht.pdf.

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification: Group D – Not classifiable as to human carcinogenicity (U.S. EPA, 2011)
Slope factor (SF): Not Applicable
Source of cancer slope factor (SF): Not Applicable
Tumor site(s): Not Applicable

Volatile: No

Summary of Guidance Value History:
A non-cancer Health Risk Limit (HRL) of 100 µg/L was promulgated in 1993. New guidance of 1,000 µg/L based on an updated U.S. EPA assessment was developed in 1997. A Health Based Value (HBV) of 300 µg/L based on U.S. EPA's Lifetime Health Advisory value of 300 µg/L was developed in 2008. In 2011, based on new information and risk assessment methodology, MDH reverted to recommending the 1993 HRL value of 100 µg/L for infants until guidance could be re-evaluated. In 2012, MDH again reviewed manganese and established Risk Assessment Advice (RAA) of 100 µg/L that used tiered guidance based on age instead of MDH's typical duration-specific guidance. In 2017, MDH re-evaluated the available information and updated the risk assessment methodology, which resulted in no change to the existing RAAs. In 2018, the tiered guidance methodology was removed and the guidance value was converted from RAA of 100/300 µg/L to an HBV of 100 µg/L for the short-term duration. The toxicological information available supports guidance at the level of HBV. MDH also continues to support the U.S. EPA HA of 300 µg/L for adult, infants older than one year of age, and children. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	Yes
Effects observed?	No	No	Yes[1]	Yes[2]	Yes[3]

Comments on extent of testing or effects:

Note: Effects reported in dietary animal studies have limited relevance to humans because humans are known to have tightly regulated controls that limit absorption and excretion of manganese from the diet.

[1] There was some evidence of delayed fetal skeletal and organ development in offspring born to pregnant rats exposed to manganese by gavage at a dose of 33 mg/kg-day, which is similar to the critical short-term LOAEL of 25 mg/kg-day. However, these effects were not present in the same offspring when they were observed at 100 days old, so these effects may be transient. Neurodevelopmental effects are a concern following manganese exposure from drinking water during early life. Neurodevelopmental effects were selected as the basis of the short-term RfD in this assessment and are discussed in footnote 3.

[2] Some male and female reproductive effects were reported in subchronic duration rodent studies (and one developmental study) following oral exposures to manganese. The information available about these effects is very limited, which makes it difficult to establish a strong level of confidence in the results. Male reproductive effects (decreased testicular weight and increased testicular degeneration) were reported at doses 2 times to 5 times higher than the short-term critical LOAEL. Most toxicity studies did not report female reproductive toxicity. Post-implantation loss was observed in female rats as a dose slightly above the short-term critical LOAEL but this effect was not reported in other rodent studies.

[3] Neurodevelopmental effects in animals form the basis of the short-term RfD. Subtle neurodevelopmental effects (biochemical, behavioral, and cognitive changes) have been observed in neonatal rats and non-human primates following oral manganese exposure at exposure levels equal to and above the short-term critical LOAEL of 25 mg/kg-day. Manganese is well established as a neurotoxin following inhalation by humans in occupational settings with the central nervous system appearing to be the primary target for manganese toxicity.

Several epidemiology studies have suggested there could be subtle IQ and memory effects in children exposed to manganese in drinking water at concentrations >200 µg/L. Manganese has also been associated with neurological effects in adults exposed to manganese in drinking water for over 10 years at concentrations of 1,800 to 2,300 µg/L.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR) - MRLs. (2009). Minimal Risk Levels for Hazardous Substances (MRLs). Retrieved from https://www.atsdr.cdc.gov/mrls/mrllist.asp

Agency for Toxic Substances and Disease Registry (ATSDR) - Toxicological Profiles. Toxicological Profile Information Sheet.   Retrieved from https://www.atsdr.cdc.gov/toxprofiledocs/index.html

Agency for Toxic Substances and Disease Registry (ATSDR). (2009). Draft Toxicological Profile for Manganese.   Retrieved from http://www.atsdr.cdc.gov/toxprofiles/tp151.pdf

Andersen, M. E., Dorman, D. C., Clewell, H. J., 3rd, Taylor, M. D., & Nong, A. (2010). Multi-dose-route, multi-species pharmacokinetic models for manganese and their use in risk assessment. *J Toxicol Environ Health A, 73*(2), 217-234. doi:918613622

Aschner, J. L., & Aschner, M. (2005). Nutritional aspects of manganese homeostasis. *Mol Aspects Med, 26*(4-5), 353-362. doi:S0098-2997(05)00038-5

Aschner, M., Erikson, K. M., & Dorman, D. C. (2005). Manganese dosimetry: species differences and implications for neurotoxicity. *Crit Rev Toxicol, 35*(1), 1-32.

Bouchard, M., Laforest, F., Vandelac, L., Bellinger, D., & Mergler, D. (2007). Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. *Environ Health Perspect, 115*(1), 122-127.

Bouchard, M. F., Sauve, S., Barbeau, B., Legrand, M., Brodeur, M. E., Bouffard, T., . . . Mergler, D. (2010). Intellectual Impairment in School-Age Children Exposed to Manganese from Drinking Water. *Environ Health Perspect*. doi:10.1289/ehp.1002321

Brenneman, K. A., Cattley, R. C., Ali, S. F., & Dorman, D. C. (1999). Manganese-induced developmental neurotoxicity in the CD rat: is oxidative damage a mechanism of action? *Neurotoxicology, 20*(2-3), 477-487.

California Environmental Protection Agency-OEHHA Toxicity Criteria Database.   Retrieved from http://www.oehha.ca.gov/risk/ChemicalDB/index.asp

California Environmental Protection Agency - OEHHA Cancer Potency Values. (2005). OEHHA Toxicity Criteria Database.

Chandra, S. V., Shukla, G. S., & Saxena, D. K. (1979). Manganese-induced behavioral dysfunction and its neurochemical mechanism in growing mice. *J Neurochem, 33*(6), 1217-1221.

Claus Henn, B., Ettinger, A. S., Schwartz, J., Tellez-Rojo, M. M., Lamadrid-Figueroa, H., Hernandez-Avila, M., . . . Wright, R. O. (2010). Early postnatal blood manganese levels and children's neurodevelopment. *Epidemiology, 21*(4), 433-439.

Collipp, P. J., Chen, S. Y., & Maitinsky, S. (1983). Manganese in infant formulas and learning disability. *Ann Nutr Metab, 27*(6), 488-494.

Davis, C. D., Zech, L., & Greger, J. L. (1993). Manganese metabolism in rats: an improved methodology for assessing gut endogenous losses. *Proc Soc Exp Biol Med, 202*(1), 103-108.

Dorman, D. C., Struve, M. F., Vitarella, D., Byerly, F. L., Goetz, J., & Miller, R. (2000). Neurotoxicity of manganese chloride in neonatal and adult CD rats following subchronic (21-day) high-dose oral exposure. *J Appl Toxicol, 20*(3), 179-187. doi:10.1002/(SICI)1099-1263(200005/06)20:3<179::AID-JAT631>3.0.CO;2-C

Ericson, J. E., Crinella, F. M., Clarke-Stewart, K. A., Allhusen, V. D., Chan, T., & Robertson, R. T. (2007). Prenatal manganese levels linked to childhood behavioral disinhibition. *Neurotoxicol Teratol, 29*(2), 181-187. doi:S0892-0362(06)00114-0

Golub, M. S., Hogrefe, C. E., Germann, S. L., Tran, T. T., Beard, J. L., Crinella, F. M., & Lonnerdal, B. (2005). Neurobehavioral evaluation of rhesus monkey infants fed cow's milk formula, soy formula, or soy formula with added manganese. *Neurotoxicol Teratol, 27*(4), 615-627. doi:S0892-0362(05)00055-3

Hafeman, D., Factor-Litvak, P., Cheng, Z., van Geen, A., & Ahsan, H. (2007). Association between manganese exposure through drinking water and infant mortality in Bangladesh. *Environ Health Perspect, 115*(7), 1107-1112. doi:10.1289/ehp.10051

He, P., Liu, D. H., & Zhang, G. Q. (1994). Effects of high-level-manganese sewage irrigation on children's neurobehavior. *Zhonghua Yu Fang Yi Xue Za Zhi, 28*(4), 216-218.

Health Canada Guidelines for Canadian Drinking Water Quality. Guidelines for Canadian Drinking Water Quality.   Retrieved from http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/index-eng.php#tech_doc

Institute of Medicine (IOM). (2001). Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. In Food and Nutrition Board (Ed.). Washington, D.C.: National Academy Press.

Kern, C. H., Stanwood, G. D., & Smith, D. R. (2010). Preweaning manganese exposure causes hyperactivity, disinhibition, and spatial learning and memory deficits associated with altered dopamine receptor and transporter levels. *Synapse, 64*(5), 363-378. doi:10.1002/syn.20736

Kim, Y., Kim, B. N., Hong, Y. C., Shin, M. S., Yoo, H. J., Kim, J. W., . . . Cho, S. C. (2009). Co-exposure to environmental lead and manganese affects the intelligence of school-aged children. *Neurotoxicology, 30*(4), 564-571. doi:S0161-813X(09)00075-8

Kondakis, X. G., Makris, N., Leotsinidis, M., Prinou, M., & Papapetropoulos, T. (1989). Possible health effects of high manganese concentration in drinking water. *Arch Environ Health, 44*(3), 175-178.

Malecki, E. A., Radzanowski, G. M., Radzanowski, T. J., Gallaher, D. D., & Greger, J. L. (1996). Biliary manganese excretion in conscious rats is affected by acute and chronic manganese intake but not by dietary fat. *J Nutr, 126*(2), 489-498.

Menezes-Filho, J. A., Bouchard, M., Sarcinelli Pde, N., & Moreira, J. C. (2009). Manganese exposure and the neuropsychological effect on children and adolescents: a review. *Rev Panam Salud Publica, 26*(6), 541-548. doi:S1020-49892009001200010

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017).   Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

Narayanaswamy, M., & Piler, M. B. (2010). Effect of maternal exposure of fluoride on biometals and oxidative stress parameters in developing CNS of rat. *Biol Trace Elem Res, 133*(1), 71-82. doi:10.1007/s12011-009-8413-y

National Toxicology Program (NTP). (1993). Toxicology and Carcinogenesis Studies of Manganese (II) Sulfate monohydrate (CAS No. 10034-96-5) in F344/N Rats and B6C3F Mice (Feed Studies) Retrieved from http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr428.pdf

Pappas, B. A., Zhang, D., Davidson, C. M., Crowder, T., Park, G. A., & Fortin, T. (1997). Perinatal manganese exposure: behavioral, neurochemical, and histopathological effects in the rat. *Neurotoxicol Teratol, 19*(1), 17-25. doi:S0892036296001857 [pii]

Reichel, C. M., Wacan, J. J., Farley, C. M., Stanley, B. J., Crawford, C. A., & McDougall, S. A. (2006). Postnatal manganese exposure attenuates cocaine-induced locomotor activity and reduces dopamine transporters in adult male rats. *Neurotoxicol Teratol, 28*(3), 323-332. doi:S0892-0362(06)00035-3

Rodriguez-Agudelo, Y., Riojas-Rodriguez, H., Rios, C., Rosas, I., Sabido Pedraza, E., Miranda, J., . . . Santos-Burgoa, C. (2006). Motor alterations associated with exposure to manganese in the environment in Mexico. *Sci Total Environ, 368*(2-3), 542-556. doi:S0048-9697(06)00255-5

Santamaria, A. B., & Sulsky, S. I. (2010). Risk assessment of an essential element: manganese. *J Toxicol Environ Health A, 73*(2), 128-155. doi:918612614 [pii]

Santos-Burgoa, C., Rios, C., Mercado, L. A., Arechiga-Serrano, R., Cano-Valle, F., Eden-Wynter, R. A., . . . Montes, S. (2001). Exposure to manganese: health effects on the general population, a pilot study in central Mexico. *Environ Res, 85*(2), 90-104. doi:10.1006/enrs.2000.4108

Syracuse Research PhysProp Database.   Retrieved from http://www.syrres.com/what-we-do/databaseforms.aspx?id=386

Tran, T. T., Chowanadisai, W., Crinella, F. M., Chicz-DeMet, A., & Lonnerdal, B. (2002a). Effect of high dietary manganese intake of neonatal rats on tissue mineral accumulation, striatal dopamine

levels, and neurodevelopmental status. *Neurotoxicology, 23*(4-5), 635-643. doi:S0161-813X(02)00091-8

Tran, T. T., Chowanadisai, W., Lonnerdal, B., Le, L., Parker, M., Chicz-Demet, A., & Crinella, F. M. (2002b). Effects of neonatal dietary manganese exposure on brain dopamine levels and neurocognitive functions. *Neurotoxicology, 23*(4-5), 645-651. doi:S0161-813X(02)00068-2

U.S. Environmental Protection Agency - IRIS. Integrated Risk Information Systems (IRIS) A-Z List of Substances.   Retrieved from http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList

U.S. Environmental Protection Agency - National Center for Environmental Assessment.   Retrieved from http://cfpub.epa.gov/ncea/cfm/archive_whatsnew.cfm

U.S. Environmental Protection Agency - Office of Drinking Water. (2011). 2011 Edition of the Drinking Water Standards and Health Advisories.   Retrieved from http://water.epa.gov/action/advisories/drinking/drinking_index.cfm#dw-standards

U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). Recommended Use of Body Weight¾ 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 - Regional Screening Tables. Mid-Atlantic Risk Assessment - Regional Screening Table.   Retrieved from http://www.epa.gov/reg3hwmd/risk/human/rb-concentration_table/Generic_Tables/index.htm

U.S. Environmental Protection Agency - Toxicity and Exposure Assessment for Children's Health (TEACH).   Retrieved from https://archive.epa.gov/region5/teach/web/html/index.html

U.S. Environmental Protection Agency (EPA). (2004). Drinking Water Health Advisory for Manganese. Retrieved from https://www.epa.gov/sites/production/files/2014-09/documents/support_cc1_magnese_dwreport_0.pdf

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

U.S. Geological Survey - Health-Based Screening Levels.   Retrieved from https://cida.usgs.gov/hbsl/apex/f?p=104:1

Wasserman, G. A., Liu, X., Parvez, F., Ahsan, H., Levy, D., Factor-Litvak, P., . . . Graziano, J. H. (2006). Water manganese exposure and children's intellectual function in Araihazar, Bangladesh. *Environ Health Perspect, 114*(1), 124-129.

Wasserman, G. A., Liu, X., Parvez, F., Factor-Litvak, P., Ahsan, H., Levy, D., . . . Graziano, J. H. (2011). Arsenic and manganese exposure and children's intellectual function. *Neurotoxicology, 32*(4), 450-457. doi:S0161-813X(11)00056-8

Woolf, A., Wright, R., Amarasiriwardena, C., & Bellinger, D. (2002). A child with chronic manganese exposure from drinking water. *Environ Health Perspect, 110*(6), 613-616. doi:sc271_5_1835

World Health Organization - Guidelines for Drinking-Water Quality. (2008). Retrieved from http://www.who.int/water_sanitation_health/publications/gdwq3rev/en/

World Health Organization (WHO). (2004). Manganese in drinking water - background document for development of WHO *Guidelines for drinking-water quality*. Retrieved from http://www.who.int/water_sanitation_health/dwq/chemicals/manganese.pdf

Yoon, M., Schroeter, J. D., Nong, A., Taylor, M. D., Dorman, D. C., Andersen, M. E., & Clewell, H. J., 3rd. (2011). Physiologically Based Pharmacokinetic Modeling of Fetal and Neonatal Manganese Exposure in Humans: Describing Manganese Homeostasis during Development. *Toxicological Sciences: an official journal of the Society of Toxicology, 122*(2), 297-316. doi:10.1093/toxsci/kfr141

Zota, A. R., Ettinger, A. S., Bouchard, M., Amarasiriwardena, C. J., Schwartz, J., Hu, H., & Wright, R. O. (2009). Maternal blood manganese levels and infant birth weight. *Epidemiology, 20*(3), 367-373. doi:10.1097/EDE.0b013e31819b93c0

Toxicological Summary for: Metolachlor and s-Metolachlor

CAS: **51218-45-2 and 87392-12-9**

Synonyms: Metolachlor: **2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(1-methoxypropan-2-yl)acetamide)**

s-Metolachlor: **2-Chloro-N-(2-ethyl-6-methylphenyl)-N-[(2S)-1-methoxypropan-2-yl]acetamide**

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 300 µg/L

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

$$= \frac{\text{(0.19 mg/kg-d) x (0.5)}^* \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

$$= 327 \text{ rounded to } \textbf{300 µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 5.72/30 = 0.19 mg/kg-d (laboratory rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	26 mg/kg-d (NOAEL, MRID 00080897 (Smith, 1981 (Ciba-Geigy)) aci (EPA, 1995))
Dose Adjustment Factor (DAF):	0.22 (Body weight scaling, default) (EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 26 mg/kg-d x 0.22 = 5.72 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased body weight in pups
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 300 µg/L

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

$$= \frac{\text{(0.19 mg/kg-d) x (0.2)}^* \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 513 rounded to 500 µg/L

Reference Dose/Concentration:	HED/Total UF = 5.72/30= 0.19 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	9.7 mg/kg-d (NOAEL, MRID 409807 (Hazelette, 1989) aci (USEPA, 1995))
Dose Adjustment Factor (DAF):	0.59 (Body weight scaling, default) (EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 9.7 mg/kg-d x 0.59 = 5.72 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased body weight gain in adults
Co-critical effect(s):	Decreased body weight in pups
Additivity endpoint(s):	Developmental

The Subchronic nHBV must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 300 µg/L. Additivity endpoints: Developmental

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = nHBV$_{Short-term}$ = 300 µg/L

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

$$= \frac{(0.19 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 844 rounded to 800 µg/L

Reference Dose/Concentration:	HED/Total UF = 5.72/30 = 0.19 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	9.7 mg/kg-d (NOAEL, MRID 409807 (Hazelette, 1989) aci (EPA, 1995)) (subchronic exposure)
Dose Adjustment Factor (DAF):	0.59 (Body weight scaling, default) (EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 9.7 mg/kg-d x 0.59 = 5.72 mg/kg-d
Total uncertainty factor (UF):	30

Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability (subchronic-to-chronic uncertainty factor not selected as toxicity did not increase with longer durations of related studies)
Critical effect(s):	Decreased body weight gain in adults
Co-critical effect(s):	Decreased body weight in pups
Additivity endpoint(s):	Developmental

The Chronic nHBV must be protective of the acute, 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 300 µg/L. Additivity endpoints: Developmental

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Group C (possible human carcinogen) (EPA, 2006)
Slope factor (SF):	Non-linear approach recommended by US EPA 0.0092 (mg/kg-d)$^{-1}$ (EPA, 1995) (EPA, 2002) (EPA, 2006)
Source of cancer slope factor (SF):	US EPA, 2006
Tumor site(s):	liver tumors in rats

Statement for non-linear carcinogens:
At this time, MDH's non-cancer health-based guidance values are considered to be protective for possible cancer risks associated with metolachlor in drinking water. Neither the International Agency for Research on Cancer (IARC) nor the National Toxicology Program (NTP) have classified metolachlor as a carcinogen. Metolachlor has been identified as a nonlinear carcinogen by the US Environmental Protection Agency (EPA). Three long-term animal studies have been conducted with metolachlor, and tumors were reported in only one of these studies at the highest dose level tested (over 200 times higher than the MDH Chronic RfD). Additionally, as part of the 2008 HRL revision, the MDH Group C review committee evaluated the weight of evidence regarding the carcinogenicity and determined that no Group C uncertainty factor was needed and agreed that the data do not support derivation of a cancer specific value. (MDH, 2008)

Volatile: No

Summary of Guidance Value History:
A noncancer chronic Health Risk Limit (HRL) of 100 µg/L was promulgated in 1993. Acute, Short-term, Subchronic, and Chronic Health-Based Values (HBV) of 400, 400, 300, and 300 µg/L were derived in 2009 and promulgated as HRLs in 2011. In 2017, MDH re-evaluated the non-cancer HRLs, resulting in the removal of the acute HRL, an updated short-term HBV of 300 µg/L, and updated subchronic and chronic HBVs set to the short-term HBV of 300 µg/L. The short-term, subchronic, and chronic values were updated and the acute guidance removed as a result of 1) using MDH's most recent risk assessment methodology and 2) rounding to one significant digit. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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?	Yes	No	Yes	Yes	No
Effects observed?	Yes[1]	-	Yes[2]	Yes[3]	-[4]

Comments on extent of testing or effects:

[1] Serum levels of testosterone, estradiol, and other hormones were altered in rats after pubertal exposure (PND 23-53) at levels 60 times higher than the short-term RfD. Increased relative thyroid weights were observed in F1 males in a multigenerational study in rats. A related compound, Acetochlor, caused thyroid effects in laboratory studies.

[2] The short-term reference dose is based on developmental effects (decreased body weight in pups) observed in the critical study.

[3] Decreased implantations, increased resorptions, decreased litter size, and increased post-implantation loss has been observed at doses ~1,000 higher than the short-term reference dose.

[4] Neurotoxicity of metolachlor has not be studied. However, a related compound, acetochlor, causes neurological effects.

Resources Consulted During Review:

Australian Natural Resource Management Ministerial Council; Environmental Protection and Heritage Council; and National Health and Medical Research Council (2008). "Australian Guidelines for Water Recycling. Augmentation of Drinking Water Supplies." from https://www.waterquality.gov.au/sites/default/files/documents/water-recycling-guidelines-augmentation-drinking-22.pdf

Barr, D. B., Anath, C.V., Lashley, S., Smulian, J.C., Ledoux, T.A., Hore, P., Robson, M.G. (2010). "Pesticide concentrations in maternal and umbilical cord sera and their relation to birth outcomes in a population of pregnant women and newborns in New Jersey." Science of the Total Environment(408): 790-795.

ChemFinder. Retrieved 2/28/2017, from http://www.cambridgesoft.com/services/documentation/sdk/chemfinder

Coleman, S., Linderman, R., Hodgson, E., Rose, R.L. (2000). "Comparative metabolism of chloroacetamide herbicides and selected metabolites in human and rat liver microsomes." Environmental Health Perspectives **108**(12): 1151-1157.

Federal Register 40 CFR Part 180 (2006). "S-metolachlor Pesticide Tolerance [EPA-HQ-OPP-2006-0292; FRL-8090-2]." **71**(168): 51505-51510.

Health Canada (1986). "Guidelines for Canadian Drinking Water Quality - Guideline Technical Document for Metolachlor." from https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-metolachlor.html

Mathias, F. T., Romano, R.M., Sleiman, H.K., de Oliveira, C.A., Romano, M.A. (2012). "Herbicide Metolachlor Causes Changes in Reproductive Endocrinology of Male Wistar Rats." Internation Scholarly Research Notices **2012**.

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". from https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH) (2017). "MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017)." from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

New York State Department of Health (Dr. Kenneth Bogdan) (2003). Human Health Fact Sheet for Metolachlor: Ambient Water Quality Value for Protection of Human Health and Sources of Potable Water.

Personal Correspondence with Steve Snyderman (EPA) on 8/8/2017. Status of Metolachlor Re-registration.

Syracuse Research PhysProp Database. from http://www.syrres.com/what-we-do/databaseforms.aspx?id=386

U.S. Environmental Protection Agency (EPA). " Regional Screening Levels (RSLs) Table." https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables-november-2017

U.S. Environmental Protection Agency (EPA) (1988). "Integrated Risk Information System: Chemical Assessment Summary for Metolachlor." from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0074_summary.pdf

U.S. Environmental Protection Agency (EPA) (1991). Memorandum: Review additional discussion on Metolachlor's carcinogenicity potential, a chronic dog study with additional data and additional metabolism data. Data Evaluation Records (DERs) for Metolachlor metabolism in the rat and Metolachlor 13/52 week oral toxicity study in dogs.

U.S. Environmental Protection Agency (EPA) (1993a). Data Evaluation Record. Metolachlor: Rat chronic toxicity/carcinogenicity study and subchronic dog study - re-review of data.

U.S. Environmental Protection Agency (EPA) (1993b). Data Evaluation Record. Metolachlor: Re-review of chronic dog study, 2-generation reproduction study, and rabbit developmental toxicity (teratology) study.

U.S. Environmental Protection Agency (EPA) (1995). "Metolachlor Reregistration Eligibility Decision." from https://archive.epa.gov/pesticides/reregistration/web/pdf/0001.pdf

U.S. Environmental Protection Agency (EPA) (1997). Health Effects Assessment Summary Table (HEAST).

U.S. Environmental Protection Agency (EPA) (2002). Metolachlor: Revised HED Science Assessment for Tolerance Reassessment Eligibility Decision (RED). PC Code 108801. (May 23, 2002).

U.S. Environmental Protection Agency (EPA) (2002). "Report on the Food Quality Protection Act (FWPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Metolachlor (6/17/2002)." from https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/tred_PC-108801_1-Oct-02.pdf

U.S. Environmental Protection Agency (EPA) (2002). Revised Toxicology Chapter for Metolachlor/s-Metolachlor (May 13, 2002).

U.S. Environmental Protection Agency (EPA) (2006). S-metolachlor: Human Health Risk Assessment for Proposed Section 18 Uses on Cilantro, Collards, Kale, and Mustard Greens; Section 3 use on Pumpkin and Tolerance of Winter Squash without US Registration. PC Code 108800 s-metolachlor and 108801 Metolachlor (7/13/2006).

U.S. Environmental Protection Agency (EPA) (2007). Fifth Report of the Cancer Assessment Review Committee.

U.S. Environmental Protection Agency (EPA) (2008). Regulatory Determinations Support Document for Selected Contaminants from the Second Drinking Water Contaminant Candidate List (CCL2): Chapter 12 Metolachlor. https://www.epa.gov/sites/production/files/2014-09/documents/report_ccl2-reg2_supportdocument_full.pdf

U.S. Environmental Protection Agency (EPA) (2011). "Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor." from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA) (2012). "Office of Drinking Water. 2012 Edition of the Drinking Water Standards and Health Advisories." from https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100N01H.TXT

U.S. Environmental Protection Agency (EPA) (2019). "Exposure Factors Handbook Chapter 3 Update 2019." from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

U.S. Geological Survey - Health-Based Screening Levels. from https://cida.usgs.gov/hbsl/apex/f?p=104:1

World Health Organization (WHO) (1996 (updated 2003)). "Metolachlor in Drinking Water: Background document for development of WHO Guidelines for Drinking Water." from http://www.who.int/water_sanitation_health/water-quality/guidelines/chemicals/metolachlor.pdf?ua=1

World Health Organization (WHO) (2011). "Guidelines for Drinking-Water Quality." from http://apps.who.int/iris/bitstream/10665/44584/1/9789241548151_eng.pdf

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Toxicological Summary for: Metolachlor ESA

CAS**: 171118-09-5**

Synonyms: Ethanesulfonate degradate of metolachlor; Metolachlor ethane sulfonic acid

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = 7,000 µg/L

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

$$= \frac{\text{(2.7 mg/kg-d) x (0.2)}^* \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 7,297 rounded to **7,000 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 265/100 = 2.7 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2009
Point of Departure (POD):	500 mg/kg-d (NOAEL, MRID 44931709 Data Evaluation Report, US EPA 2000)
Dose Adjustment Factor (DAF):	0.53 (Body weight scaling, default) (US EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 500 mg/kg-d x 0.53 = 265 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 (lack of two-generation study)
Critical effect(s):	Increased liver weight and increased serum liver enzymes
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = 1,000 µg/L

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

$$= \frac{(0.27 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 1,200 \text{ rounded to } \textbf{1,000 µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 265/1000 = 0.27 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2009
Point of Departure (POD):	500 mg/kg-d (NOAEL, MRID 44931709 Data Evaluation Report, US EPA 2000, subchronic exposure)
Dose Adjustment Factor (DAF):	0.53 (Body weight scaling, default) (US EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 500 mg/kg-d x 0.53 = 265 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for subchronic-to-chronic extrapolation, and 3 for database uncertainty (lack of two-generation study)
Critical effect(s):	Increased liver weight and increased serum liver enzymes
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not Classified
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: No

Summary of Guidance Value History

A noncancer Health Based Value (HBV) of 1,000 µg/L was derived in 2004. Updated noncancer subchronic and chronic Health Risk Limits (HRL) of 4,000 and 800 µg/L, respectively, were promulgated in 2011. In 2018, MDH re-evaluated the noncancer HRLs, resulting in updated values for the subchronic and chronic durations of 8,000 and 1,000 µg/L, respectively. The noncancer HBVs are higher as a result of 1) using MDH's most recent risk assessment methodology, and 2) rounding to one significant digit. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in a decrease in the subchronic duration water guidance value from 8,000 µg/L to 7,000 µg/L. The chronic water guidance value did not change.

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	No	No
Effects observed?	-	-	No[1]	-	-

Comments on extent of testing or effects:

[1] The single available developmental study reported no treatment related effects to pregnant animals or fetuses at the highest dose tested, a dose 80 times higher than the subchronic RfD. However, the database for the parent compound demonstrated that developmental toxicity observed in the two-generation reproductive study occurred at lower doses than the standard developmental study. As no two-generation reproductive study has been conducted for metolachlor ESA, a database uncertainty factor was incorporated into the RfD derivation to address this data gap.

Resources Consulted During Review:

California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) (2017). "Metolachlor and Metolachlor Degradates Ethanesulfonic Acid and Oxanilic Acid in Groundwater." from https://oehha.ca.gov/media/downloads/pesticides/report/metolachlor05312017.pdf.

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

U.S. Environmental Protection Agency (EPA) (2000). "Data Evaluation Report, Metolachlor ESA Developmental Toxicity - rat. MRID 44931711. January 2000." from

https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/108801/108801-227.pdf.

U.S. Environmental Protection Agency (EPA) (2000). "Data Evaluation Report, Metolachlor ESA subchronic oral toxicity feeding - dog. MRID 44931709. January 2000." from https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/108801/108801-229.pdf.

U.S. Environmental Protection Agency (EPA) (2000). "Data Evaluation Report, Metolachlor ESA subchronic oral toxicity feeding - rat. MRID 44931710." from https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/108801/108801-230.pdf.

U.S. Environmental Protection Agency (EPA) (2001). Memo: Metolachlor and s-Metolachlor - Report of the Hazard Identification Assessment Review Committee. Memo from Virginia Debozy dated September 28, 2001.

U.S. Environmental Protection Agency (EPA) (2001). Memo: Metolachlor and s-Metolachlor. Results of the Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Meeting held on 14-August-2001. Memo from Virginia Debozy dated August 14, 2001.

U.S. Environmental Protection Agency (EPA) (2001). Memo: Review of toxicity studies with Metolachlor/S-Metolachlor metabolites updated executive summaries for metolachlor DERs. Memo from Virginia Debozy dated December 12, 2001.

U.S. Environmental Protection Agency (EPA) (2002). Memo Revised Toxicology Chapter for Metolachlor/s-Metolachlor. PC Code 108801/108800. Memo from Virginia Debozy dated (May 13, 2002).

U.S. Environmental Protection Agency (EPA) (2002). Metolachlor: Revised HED Science Assessment for Tolerance Reassessment Eligibility Decision (RED). PC Code 108801. (May 23, 2002).

U.S. Environmental Protection Agency (EPA) (2003). Metolachlor. Revised HED Science Assessment for the Tolerance Reassessment Eligibility Decision, Including Various Pending Petitions. PC CODE 108801. Memo from Sherrie Kinard dated (February 12, 2003).

U.S. Environmental Protection Agency (EPA) (2019). Exposure Factors Handbook Chapter 3, Update 2019. Retrieved from http://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Toxicological Summary for: Metolachlor OXA

CAS: **152019-73-3**

Synonyms: Oxanilic acid degradates of metolachlor, metolachlor OA, Metolachlor oxanilic acid

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 5,000 µg/L

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

$$= \frac{\text{(2.7 mg/kg-d) x (0.5)}^* \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 4,655 rounded to **5,000 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 265/100 = 2.7 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2009
Point of Departure (POD):	500 mg/kg-d (NOAEL, Syngenta, 2004)
Dose Adjustment Factor (DAF):	0.53 (Body weight scaling, default) (US EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 500 mg/kg-d x 0.53 = 265 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 (lack of two generation study)
Critical effect(s):	Changes in blood chemistry parameters without identified specific target organs
Co-critical effect(s):	None
Additivity endpoint(s):	None

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 5,000 µg/L

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

$$= \frac{\text{(2.7 mg/kg-d) x (0.2)}^* \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 7,297 rounded to 7,000 µg/L

Reference Dose/Concentration:	HED/Total UF = 265/100 = 2.7 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2009
Point of Departure (POD):	500 mg/kg-d (NOAEL, Syngenta, 2004)
Dose Adjustment Factor (DAF):	0.53 (Body weight scaling, default) (US EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 500 mg/kg-d x 0.53 = 265 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 (lack of a two-generation study)
Critical effect(s):	Changes in blood chemistry parameters without identified specific target organs
Co-critical effect(s):	None
Additivity endpoint(s):	None

The Subchronic nHBV must be protective of the acute, and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 5,000 µg/L. Additivity endpoints: None

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = 1,000 µg/L

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

$$= \frac{\text{(0.27 mg/kg-d) x (0.2)}^* \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 1,200 rounded to **1,000 µg/L**

Reference Dose/Concentration:	HED/Total UF = 265/1000 = 0.27 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2009
Point of Departure (POD):	500 mg/kg-d (NOAEL, Syngenta, 2004 (subchronic exposure))
Dose Adjustment Factor (DAF):	0.53 (Body weight scaling, default) (US EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 500 mg/kg-d x 0.53 = 265 mg/kg-d
Total uncertainty factor (UF):	1000

Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for subchronic-to-chronic extrapolation, and 3 for database uncertainty (lack of two-generation study)
Critical effect(s):	Changes in blood chemistry parameters without identified specific target organs
Co-critical effect(s):	None
Additivity endpoint(s):	None

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not Classified
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: No

Summary of Guidance Value History:

A noncancer Health Based Value (HBV) of 1,000 µg/L was derived in 2004. Updated noncancer short-term, subchronic and chronic Health Risk Limits (HRL) of 3,000, 3,000, and 800 µg/L, respectively, were promulgated in 2011. In 2018, MDH re-evaluated the noncancer HRLs, resulting in updated values for the short-term, subchronic, and chronic durations of 5,000, 5,000, and 1,000 µg/L, respectively. The noncancer HBVs are higher as a result of 1) using MDH's most recent risk assessment methodology, and 2) rounding to one significant digit. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	No	No
Effects observed?	-	-	No[1]	-	-

Comments on extent of testing or effects:

[1] The single available developmental study reported no treatment related effects to pregnant animals or fetuses at the highest dose tested, a dose 80 times higher than the short-term RfD. However, the database for the parent compound demonstrated that developmental toxicity observed in the two-

generation reproductive/developmental study occurred at lower doses than the standard developmental study. As no two generation reproductive study has been conducted for metolachlor OXA, a database uncertainty factor was incorporated into the RfD derivation to address this data gap.

Resources Consulted During Review:

California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) (2017). "Metolachlor and Metolachlor Degradates Ethanesulfonic Acid and Oxanilic Acid in Groundwater." from https://oehha.ca.gov/media/downloads/pesticides/report/metolachlor05312017.pdf.

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Syngenta (personal communication from Patrick McCain, J., 2004). (2004). Metolachlor metabolite - oxanilic acid 90-day oral toxicity study in dogs. Central Toxicology Laboratory CTL/PTD1240/Regulatory/Report. March 16, 2004.

U.S. Environmental Protection Agency (EPA) (2000). "Data Evaluation Report, Metolachlor OA subchronic oral toxicity feeding - rat. MRID 44929509. January 2000. Reviewed by EPA in 2001.". from https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-108801_25-Apr-01_228.pdf.

U.S. Environmental Protection Agency (EPA) (2000). "Data Evaluation Report: Metolachlor OA Developmental Toxicity - Rat. MRID 44929510. Prepared 2000, Reviewed 2001." from https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/108800/108800-019.pdf.

U.S. Environmental Protection Agency (EPA) (2001). Memo: Metolachlor and s-Metolachlor - Report of the Hazard Identification Assessment Review Committee. Memo from Virginia Debozy dated September 28, 2001.

U.S. Environmental Protection Agency (EPA) (2001). Memo: Metolachlor and s-Metolachlor. Results of the Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Meeting held on 14-August-2001. Memo from Virginia Debozy dated August 14, 2001.

U.S. Environmental Protection Agency (EPA) (2001). Memo: Review of toxicity studies with Metolachlor/S-Metolachlor metabolites updated executive summaries for metolachlor DERs. Memo from Virginia Debozy dated December 12, 2001.

U.S. Environmental Protection Agency (EPA) (2002). Memo Revised Toxicology Chapter for Metolachlor/s-Metolachlor. PC Code 108801/108800. Memo from Virginia Debozy dated (May 13, 2002).

U.S. Environmental Protection Agency (EPA) (2002). Metolachlor: Revised HED Science Assessment for Tolerance Reassessment Eligibility Decision (RED). PC Code 108801. (May 23, 2002).

U.S. Environmental Protection Agency (EPA) (2003). Metolachlor. Revised HED Science Assessment for the Tolerance Reassessment Eligibility Decision, Including Various Pending Petitions. PC CODE 108801. Memo from Sherrie Kinard dated (February 12, 2003).

U.S. Environmental Protection Agency (EPA) (2019). Exposure Factors Handbook Chapter 3, Update 2019. Retrieved from http://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Web Publication Date: September 2020

Toxicological Summary for: *p*-Nonylphenol, branched isomers

CAS: **84852-15-3**

Synonyms: 4-Nonylphenol; Phenol, *p*-nonyl-; 4-*p*-Nonyl phenol; Phenol, 4-nonyl-; *para* Nonyl phenol, branched (mixed isomers)

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 100 µg/L

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

$$= \frac{(0.21 \text{ mg/kg-d) x } (0.2)^* \text{ x } (1000 \text{ µg/mg)}}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 144 \text{ rounded to } \textbf{100 µg/L}$$

*The available data indicate that infant exposures, from sources such as breast milk and baby food, are not lower than adult exposures. As infant exposures are equal to or exceed adult exposures based on the available exposure data, a relative source contribution of 0.2 has been selected for all durations

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 6.27/30 = 0.21 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	33 mg/kg-d (administered dose NOAEL; NTP 1997/Chapin 1999)
Dose Adjustment Factor (DAF):	0.19, Body weight scaling, study-specific (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 33 mg/kg-d x 0.19 = 6.27 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Accelerated vaginal opening
Co-critical effect(s):	Decreased pup body weight and increased duration of estrous cycle
Additivity endpoint(s):	Developmental, Female Reproductive system

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = 40 µg/L

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

$$= \underline{(0.016 \text{ mg/kg-d) x } (0.2)^* \text{ x } (1000 \text{ µg/mg})}$$

$$(0.074 \text{ L/kg-d})^{**}$$

$$= 43.2 \text{ rounded to } \textbf{40 µg/L}$$

Reference Dose/Concentration:	HED/Total UF = 0.485/30 = 0.016 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	1.94 mg/kg-d (administered dose $BMDL_{10}$, NTP 1997/Chapin 1999)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.94 mg/kg-d x 0.25 = 0.485 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Renal mineralization in male rats
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = 20 µg/L

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

$$= \frac{(0.0049 \text{ mg/kg-d}) \text{ x } (0.2)^{*} \text{ x } (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 21.7 \text{ rounded to } \textbf{20 µg/L}$$

Reference Dose/Concentration:	HED/Total UF = 0.485/100 = 0.0049 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	1.94 mg/kg-d (administered dose $BMDL_{10}$, NTP 1997/Chapin 1999, subchronic exposure)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.94 mg/kg-d x 0.25 = 0.485 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability and 3 for subchronic to chronic extrapolation
Critical effect(s):	Renal mineralization in male rats

Co-critical effect(s):   None
Additivity endpoint(s):   Renal (kidney) system

Cancer Health-Based Value (cHBV) = Not Applicable

Volatile: Yes (low)

Summary of Guidance Value History:
MDH developed non-cancer Health-Based Values for Short-term, Subchronic and Chronic durations of 100, 40, and 20 ug/L, respectively, for p-nonylphenol in 2015. In 2020, MDH incorporated updated intake rates (US EPA 2019) and performed a re-evaluation of p-Nonylphenol. Use of the updated intake rates and results from the re-evaluation did not result in any changes to the 2015 guidance values. Recent detections of *p*-nonylphenol in Minnesota's groundwater make it eligible for promulgation as a Health Risk Limit.

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?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:
[1]The short-term reference dose (RfD) is based on a developmental and endocrine-mediated effect (accelerated vaginal opening). Endocrine effects have been well studied. Hormone level changes in adult rats have been observed at approximately 60 times higher than the current short-term reference dose. Endocrine-mediated alterations in development and reproduction were not observed, at doses up to 160 times the short-term reference dose, in three multiple generation studies.
[2]Immunotoxicity has been evaluated in two studies. Subtle alterations in immune cell populations were observed at a dose approximately 30 times higher than the current subchronic reference dose. More overt effects on immune system organ weights and immune cellular parameters were not observed until doses reached over 2000 times the current subchronic reference dose.
[3]Development effects have been well studied. The critical effect for the short-term duration is accelerated vaginal opening, a developmental effect. The only other consistent developmental effect seen was decreased pup body weight at weaning occurring at doses over 150 times higher than the current short-term reference dose.
[4]Reproductive effects have been well studied. Altered hormone levels in female rats, identified as a co-critical effect, was observed at 50 times higher than the short-term reference dose. Male reproductive toxicity noted as altered sperm and decreased testes weight was observed at 800 times up to 3500 times the subchronic reference dose.

[5]Both neurotoxicity and developmental neurotoxicity have been studied. Small alterations in maze performance tests on rodents were noted at 800 times the subchronic reference dose. At doses 2000 times the subchronic reference dose, no effects were seen on neurobehavioral endpoints. Certain gender-specific behaviors may be altered by nonylphenol exposure, but not until doses reach over 900 times the subchronic reference dose.

Resources Consulted During Review:

Ademollo, N., Ferrara, F., Delise, M., Fabietti, F., & Funari, E. (2008). Nonylphenol and octylphenol in human breast milk. *Environ Int, 34*(7), 984-987. doi: 10.1016/j.envint.2008.03.001

Chapin, R. E., Delaney, J., Wang, Y., Lanning, L., Davis, B., Collins, B., Mintz, N., & Wolfe, G. (1999). The effects of 4-nonylphenol in rats: a multigeneration reproduction study. *Toxicol Sci, 52*(1), 80-91.

Cooper, S., Latendresse, J. R., Doerge, D. R., Twaddle, N. C., Fu, X., & Delclos, K. B. (2006). Dietary modulation of p-nonylphenol-induced polycystic kidneys in male Sprague-Dawley rats. *Toxicol Sci, 91*(2), 631-642. doi: 10.1093/toxsci/kfj171

Cunny, H. C., Mayes, B. A., Rosica, K. A., Trutter, J. A., & Van Miller, J. P. (1997). Subchronic toxicity (90-day) study with para-nonylphenol in rats. *Regul Toxicol Pharmacol, 26*(2), 172-178. doi: 10.1006/rtph.1997.1154

Danish Environmental Protection Agency. (1999). Toxicological Evaluation and Limit Values for Nonylphenol, Nonylphenol Ethoxylates, Tricresyl, Phosphates and Benzoic Acid.   Retrieved June 17, 2014, from https://www2.mst.dk/Udgiv/publications/1999/87-7909-566-6/pdf/87-7909-565-8.pdf

de Jager, C., Bornman, M. S., & Oosthuizen, J. M. (1999). The effect of p-nonylphenol on the fertility potential of male rats after gestational, lactational and direct exposure. *Andrologia, 31*(2), 107-113.

Delclos, K. B., Weis, C., & Newbold, R. (2009). para-Nonylphenol: Evaluation of Reproductive Effects over Multiple Generations *NCTR GLP/NTP Technical Report* (pp. 85).

Doerge, D. R., Twaddle, N. C., Churchwell, M. I., Chang, H. C., Newbold, R. R., & Delclos, K. B. (2002). Mass spectrometric determination of p-nonylphenol metabolism and disposition following oral administration to Sprague-Dawley rats. *Reprod Toxicol, 16*(1), 45-56.

European Chemicals Agency (ECHA). (2014). Background Document to RAC and SEAC Opinions on Nonylphehol ethoxylate. from http://echa.europa.eu/documents/10162/8bdb40dc-1367-480e-8d81-b5d308bc5f81

European Chemicals Bureau (ECB). (2002). European Union Risk Assessment Report for 4-nonylphenol (branched) and nonylphenol. 10, from http://echa.europa.eu/documents/10162/6c460d8a-9f18-475f-823c-b8941e18fa3a

Ferguson, S. A., Delclos, K. B., Newbold, R. R., & Flynn, K. M. (2009). Few effects of multi-generational dietary exposure to genistein or nonylphenol on sodium solution intake in male and female Sprague-Dawley rats. *Neurotoxicol Teratol, 31*(3), 143-148.

Ferguson, S. A., Flynn, K. M., Delclos, K. B., & Newbold, R. R. (2000). Maternal and offspring toxicity but few sexually dimorphic behavioral alterations result from nonylphenol exposure. *Neurotoxicol Teratol, 22*(4), 583-591.

Ferguson, S. A., Flynn, K. M., Delclos, K. B., Newbold, R. R., & Gough, B. J. (2002). Effects of lifelong dietary exposure to genistein or nonylphenol on amphetamine-stimulated striatal dopamine release in male and female rats. *Neurotoxicol Teratol, 24*(1), 37-45.

Flynn, K. M., Newbold, R. R., & Ferguson, S. A. (2002). Multigenerational exposure to dietary nonylphenol has no severe effects on spatial learning in female rats. *Neurotoxicology, 23*(1), 87-94.

Guo, T. L., Germolec, D. R., Musgrove, D. L., Delclos, K. B., Newbold, R. R., Weis, C., & White, K. L., Jr. (2005). Myelotoxicity in genistein-, nonylphenol-, methoxychlor-, vinclozolin- or ethinyl estradiol-exposed F1 generations of Sprague-Dawley rats following developmental and adult exposures. *Toxicology, 211*(3), 207-219. doi: 10.1016/j.tox.2005.03.008

Huang, Y. F., Wang, P. W., Huang, L. W., Yang, W., Yu, C. J., Yang, S. H., Chiu, H. H., & Chen, M. L. (2014). Nonylphenol in pregnant women and their matching fetuses: placental transfer and potential risks of infants. *Environ Res, 134*, 143-148. doi: 10.1016/j.envres.2014.07.004

Karrow, N. A., Guo, T. L., Delclos, K. B., Newbold, R. R., Weis, C., Germolec, D. R., White, K. L., Jr., & McCay, J. A. (2004). Nonylphenol alters the activity of splenic NK cells and the numbers of leukocyte subpopulations in Sprague-Dawley rats: a two-generation feeding study. *Toxicology, 196*(3), 237-245. doi: 10.1016/j.tox.2003.11.009

Kazemi S, Khalili-Fomeshi M, Akbari A, Kani SNM, Ahmadian SR, Ghasemi-Kasman M. The correlation between nonylphenol concentration in brain regions and resulting behavioral impairments. *Brain Res Bull*. 2018;139:190-196. doi:10.1016/j.brainresbull.2018.03.003

Latendresse, J. R., Newbold, R. R., Weis, C. C., & Delclos, K. B. (2001). Polycystic kidney disease induced in F(1) Sprague-Dawley rats fed para-nonylphenol in a soy-free, casein-containing diet. *Toxicol Sci, 62*(1), 140-147.

Laurenzana, E. M., Balasubramanian, G., Weis, C., Blaydes, B., Newbold, R. R., & Delclos, K. B. (2002). Effect of nonylphenol on serum testosterone levels and testicular steroidogenic enzyme activity in neonatal, pubertal, and adult rats. *Chem Biol Interact, 139*(1), 23-41.

Laurenzana, E. M., Weis, C. C., Bryant, C. W., Newbold, R., & Delclos, K. B. (2002). Effect of dietary administration of genistein, nonylphenol or ethinyl estradiol on hepatic testosterone metabolism, cytochrome P-450 enzymes, and estrogen receptor alpha expression. *Food Chem Toxicol, 40*(1), 53-63.

Li M, You M, Li S, Qiu Z, Wang Y. Effects of maternal exposure to nonylphenol on learning and memory in offspring involve inhibition of BDNF-PI3K/Akt signaling. *Brain Res Bull*. 2019;146:270-278. doi:10.1016/j.brainresbull.2019.01.014

Lu WC, Wang AQ, Chen XL, et al. 90d Exposure to Nonylphenol has Adverse Effects on the Spermatogenesis and Sperm Maturation of Adult Male Rats. *Biomed Environ Sci*. 2014;27(11):907-911. doi:10.3967/bes2014.128

Minnesota Department of Health (MDH). (2011). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses. from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Toxicology Program (NTP). (1997). Final Report on the Reproductive Toxicity of Nonylphenol (CAS #84852-15-3) (Vol. RACB No. 94-021, pp. 576): National Institute of Environmental Health Sciences.

Raecker, T., Thiele, B., Boehme, R. M., & Guenther, K. (2011). Endocrine disrupting nonyl- and octylphenol in infant food in Germany: considerable daily intake of nonylphenol for babies. *Chemosphere, 82*(11), 1533-1540. doi: 10.1016/j.chemosphere.2010.11.065

Scallet, A. C., Divine, R. L., Newbold, R. R., & Delclos, K. B. (2004). Increased volume of the calbindin D28k-labeled sexually dimorphic hypothalamus in genistein and nonylphenol-treated male rats. *Toxicol Sci, 82*(2), 570-576. doi: 10.1093/toxsci/kfh297

Snyder, SA, RA Trenholm, EM Snyder, GM Bruce, RC Pleus, and JDC Hemming,. (2008). Toxicological Relevance of EDCs and Pharmaceuticals in Drinking Water. In AWWA Research Foundation (Ed.).

Tyl, R. W., Myers, C. B., Marr, M. C., Castillo, N. P., Seely, J. C., Sloan, C. S., Veselica, M. M., Joiner, R. L., Van Miller, J. P., & Simon, G. S. (2006). Three-generation evaluation of dietary para-nonylphenol in CD (Sprague-Dawley) rats. *Toxicol Sci, 92*(1), 295-310. doi: 10.1093/toxsci/kfj203

U.S. Environmental Protection Agency - Office of Research and Development. (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. from https://www.epa.gov/sites/production/files/2013-09/documents/recommended-use-of-bw34.pdf

U.S. Environmental Protection Agency. (2009). *Screening Level Hazard Characterization: Alkylphenols Category*. Environmental Protection Agency Retrieved from https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.175.5613&rep=rep1&type=pdf.

U.S. Environmental Protection Agency. (2010a). Memorandum to Kerry Leifer and PV Shah, Inert Ingredient Assessment Branch, Registration Division. Subject: Nonylphenol Ethoxylates and

Their Phosphate and Sulfate Derivatives (NPEs - JITF CST 9 Inert Ingredients). Revised Human Health Risk Assessment to Support Proposed Exemption from the Requirement of a Tolerance When Used as Inert Ingredients in Pesticide Formulations. March 31, 2010.

U.S. Environmental Protection Agency. (2010b). Nonylphenol (NP) and Nonylphenol Ethoxylates (NPEs) Action Plan [RIN 2070-ZA09]. from https://www.epa.gov/sites/production/files/2015-09/documents/rin2070-za09_np-npes_action_plan_final_2010-08-09.pdf

U.S. Environmental Protection Agency. (2011). High Production Volume Information System (HPVIS) (Water Solubility). High Production Volume Information System. (Study 1). Retrieved September 20, 2011, from Enviornmental Protection Agency http://iaspub.epa.gov/oppthpv/Public_Search.PublicTabs?SECTION=1&epcount=2&v_rs_list=24982539,24975244

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

United States Geologic Survey. (2014). Health-Based Screening Levels for Evaluating Water-Quality Data. Retrieved June 17, 2014, from https://water.usgs.gov/water-resources/hbsl/

Woo, G. H., Shibutani, M., Ichiki, T., Hamamura, M., Lee, K. Y., Inoue, K., & Hirose, M. (2007). A repeated 28-day oral dose toxicity study of nonylphenol in rats, based on the 'Enhanced OECD Test Guideline 407' for screening of endocrine-disrupting chemicals. *Arch Toxicol, 81*(2), 77-88. doi: 10.1007/s00204-006-0129-6

Yen, C. H., Sun, C. K., Leu, S., Wallace, C. G., Lin, Y. C., Chang, L. T., Chen, Y. L., Tsa, T. H., Kao, Y. H., Shao, P. L., Hsieh, C. Y., Chen, Y. T., & Yip, H. K. (2012). Continuing exposure to low-dose nonylphenol aggravates adenine-induced chronic renal dysfunction and role of rosuvastatin therapy. *J Transl Med, 10*, 147. doi: 10.1186/1479-5876-10-147

Toxicological Summary for: 4-*tert*-Octylphenol

CAS**: 140-66-9**

Synonyms: 4-(1,1,3,3-Tetramethylbutyl)phenol, *p*-(1,1,3,3-Tetramethylbutyl)phenol, *p-tert*-Octylphenol, 4-(2,4,4-trimethylpentan-2-yl)phenol

Acute Non-Cancer Health Based Value (nHBVAcute) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value (nHBVShort-term) = 100 µg/L

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

$$= \frac{\text{(0.17 mg/kg-d) x (0.2*) x (1000 µg/mg)}}{\text{(0.290 L/kg-d)**}}$$

= 117 rounded to **100 µg/L**

*The available data indicate that infant exposures, from sources such as breast milk and baby food, are not lower than adult exposures. As infant exposures are equal to or exceed adult exposures based on the available exposure data, a relative source contribution of 0.2 has been selected for all durations.

** Intake rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 5.06/30 = 0.17 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	22 mg/kg-d (administered dose NOAEL, 2-generation reproductive study, Tyl *et al.* 1999)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD X DAF = 22 mg/kg-d x 0.23 = 5.06 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Decreased pup body weight and increased time to preputial separation
Co-critical effect(s):	Decreased adult body weight
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 100 µg/L

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

$$= \frac{\text{(0.17 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.074 L/kg-d)**}}$$

= 459 rounded to 500 µg/L

** Intake rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 5.06/30 = 0.17 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	22 mg/kg-d (administered dose NOAEL, 2-generation reproductive study, Tyl *et al.* 1999)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD X DAF = 22 mg/kg-d x 0.23 = 5.06 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Decreased uterine weight
Co-critical effect(s):	Decreased adult body weight
Additivity endpoint(s):	Female Reproductive system

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 100 µg/L. Additivity endpoints: Developmental

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = nHBV$_{Short-term}$ = 100 µg/L

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

$$= \frac{\text{(0.051 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.045 L/kg-d)**}}$$

= 226 rounded to 200 µg/L

** Intake rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 5.06/100 = 0.051 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	22 mg/kg-d (administered dose NOAEL, 2-generation reproductive study, Tyl *et al.* 1999, subchronic exposure)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 22 mg/kg-d x 0.23 = 5.06 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for subchronic to chronic extrapolation
Critical effect(s):	Decreased uterine weight
Co-critical effect(s):	Decreased adult body weight
Additivity endpoint(s):	Female Reproductive system

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 100 µg/L. Additivity endpoints: Developmental

Cancer Health Based Value (cHBV) = **Not Applicable**

Volatile: Yes (low)

Summary of Guidance Value History:
An HBV of 100 µg/L for all durations was developed in 2015. In 2020, MDH re-evaluated 4-tert-octylphenol resulting in no changes to the guidance value, however, the recent detections of 4-tert-octylphenol in Minnesota groundwater made it eligible for rule. Also in 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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?	Yes	No	Yes	Yes	Yes
Effects observed?	Yes[1]	--[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:
[1]Endocrine effects such as increased uterine weights, increased vaginal and uterine thickness, and changes in estrus cyclicity were reported in female rats receiving doses approximately 35-275 times

higher than the short-term RfD. In addition, male animals receiving doses approximately 225 times higher than the short-term RfD had increased prolactin levels.

[2] No oral studies specifically evaluating immunotoxicity have been conducted. Studies examining other endpoints reported reduced thymus and spleen weights at approximately 300 times higher than the short-term RfD, and increased white blood cell/platelet counts around 650-700 times higher than the short-term RfD.

[3] The short-term RfD is based on reduced pup body weights and delayed preputial separation after rats were exposed to 4-*tert*-Octylphenol through their diet. Precocious vaginal patency was observed at doses more than 250 times the short-term RfD.

[4] The subchronic and chronic reference doses are based on reduced uterine weights of rats exposed to 4-*tert*-Octylphenol through their diet. In other studies, doses more than 650 times higher than the short-term RfD resulted in changes in epididymis and prostate weights. In addition, an increase in post-implantation loss and the reduction of number of live fetuses per litter were observed at doses 41-160 times higher than the short-term RfD.

[5] Neurobehavioral effects, including effects on a variety of sexually dimorphic behaviors and water maze performance, were evaluated in a single oral study. The effects occurred at an estimated dose approximately 150 times higher than the short-term RfD.

Resources Consulted During Review:

Anderson, P., Denslow, N., Drewes, J. E., Olivieri, A., Schlenk, D., & Snyder, S. (2010). Final Report: Monitoring Strategies for Chemicals of Emerging Concern (CECs) in Recycled Water, Recommendations of a Science Advisory Panel.

Australian Environment Protection and Heritage Council, Australian National Health and Medical Research Council, & Australian Natural Resource Management Ministerial Council. (2008). Australian Guidelines for Water Recycling: Managing Health and Environmental Risks (Phase 2), Augmentation of Drinking Water Supplies. Retrieved from: https://www.waterquality.gov.au/sites/default/files/documents/water-recycling-guidelines-augmentation-drinking-22.pdf

Barber, L. B., Loyo-Rosales, J. E., Rice, C. P., Minarik, T. A., & Oskouie, A. K. (2015). Endocrine disrupting alkylphenolic chemicals and other contaminants in wastewater treatment plant effluents, urban streams, and fish in the Great Lakes and Upper Mississippi River Regions. *Sci Total Environ, 517C*, 195-206.

Bian, Q., Qian, J., Xu, L., Chen, J., Song, L., & Wang, X. (2006). The toxic effects of 4-tert-octylphenol on the reproductive system of male rats. *Food Chem Toxicol, 44*(8), 1355-1361.

Blake, C. A., Boockfor, F. R., Nair-Menon, J. U., Millette, C. F., Raychoudhury, S. S., & McCoy, G. L. (2004). Effects of 4-tert-octylphenol given in drinking water for 4 months on the male reproductive system of Fischer 344 rats. *Reprod Toxicol, 18*(1), 43-51.

Calafat, A. M., Ye, X., Wong, L. Y., Reidy, J. A., & Needham, L. L. (2008). Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Environ Health Perspect, 116*(1), 39-44.

Certa, H., Fedtke, N., Wiegand, H. J., Muller, A. M., & Bolt, H. M. (1996). Toxicokinetics of p-tert-octylphenol in male Wistar rats. *Arch Toxicol, 71*(1-2), 112-122.

Chalubinski, M., & Kowalski, M. L. (2006). Endocrine disrupters--potential modulators of the immune system and allergic response. *Allergy, 61*(11), 1326-1335.

ChemIDplus. 4-(1,1,3,3-Tetramethylbutyl)phenol. *TOXNET.* From https://chem.nlm.nih.gov/chemidplus/rn/140-66-9

Diel, P., Schmidt, S., Vollmer, G., Janning, P., Upmeier, A., Michna, H., . . . Degen, G. H. (2004). Comparative responses of three rat strains (DA/Han, Sprague-Dawley and Wistar) to treatment with environmental estrogens. *Arch Toxicol, 78*(4), 183-193.

European Chemicals Agency. (2011). Annex XV Dossier including Member state committee support document for indentification of 4-(1,1,3,3-tetramethylbutyl)phenol, 4-tert-octylphenol). Retrieved from: http://echa.europa.eu/documents/10162/397abe32-ecb8-451c-87d2-33af413687dd

Gregory, M., Lacroix, A., Haddad, S., Devine, P., Charbonneau, M., Tardif, R., . . . Cyr, D. G. (2009). Effects of chronic exposure to octylphenol on the male rat reproductive system. *J Toxicol Environ Health A, 72*(23), 1553-1560.

Hamelin, G., Charest-Tardif, G., Krishnan, K., Cyr, D., Charbonneau, M., Devine, P. J., . . . Tardif, R. (2009). Toxicokinetics of p-tert-octylphenol in male and female Sprague-Dawley rats after intravenous, oral, or subcutaneous exposures. *J Toxicol Environ Health A, 72*(8), 541-550.

Hamelin, G., Charest-Tardif, G., Krishnan, K., Cyr, D. G., Charbonneau, M., Devine, P. J., . . . Tardif, R. (2008). Determination of p-tert-octylphenol in blood and tissues by gas chromatography coupled with mass spectrometry. *J Anal Toxicol, 32*(4), 303-307.

Hanioka, N., Jinno, H., Chung, Y. S., Nishimura, T., Tanaka-Kagawa, T., & Ando, M. (2000). Effect of 4-tert-octylphenol on cytochrome P450 enzymes in rat liver. *Arch Toxicol, 73*(12), 625-631.

Harazono, A., & Ema, M. (2001). Effects of 4-tert-octylphenol on initiation and maintenance of pregnancy following oral administration during early pregnancy in rats. *Toxicol Lett, 119*(1), 79-84.

Hejmej, A., Kotula-Balak, M., Galas, J., & Bilinska, B. (2011). Effects of 4-tert-octylphenol on the testes and seminal vesicles in adult male bank voles. *Reprod Toxicol, 31*(1), 95-105.

Hossaini, A., Dalgaard, M., Vinggaard, A. M., Pakarinen, P., & Larsen, J. J. (2003). Male reproductive effects of octylphenol and estradiol in Fischer and Wistar rats. *Reprod Toxicol, 17*(5), 607-615.

ICI Americas Inc. (1996). Screening of Chemicals for Uterine Growth in Immature Female Rats: Nonylphenol, Octylphenol, and Nonylphenoxyacetic Acid: EPA TSCA Test Submission 8EHQ-0596-13647

Kamei, S., Miyawaki, J., Sakayama, K., Yamamoto, H., & Masuno, H. (2008). Perinatal and postnatal exposure to 4-tert-octylphenol inhibits cortical bone growth in width at the diaphysis in female mice. *Toxicology, 252*(1-3), 99-104.

Kim, J., Kang, E. J., Park, M. N., Lee, J. E., Hong, S. H., An, S. M., . . . An, B. S. (2014). Adverse effects of 4-tert-octylphenol on the production of oxytocin and hCG in pregnant rats. *Lab Anim Res, 30*(3), 123-130.

Kuklenyik, Z., Ekong, J., Cutchins, C. D., Needham, L. L., & Calafat, A. M. (2003). Simultaneous measurement of urinary bisphenol A and alkylphenols by automated solid-phase extractive derivatization gas chromatography/mass spectrometry. *Anal Chem, 75*(24), 6820-6825.

Laws, S. C., Carey, S. A., Ferrell, J. M., Bodman, G. J., & Cooper, R. L. (2000). Estrogenic activity of octylphenol, nonylphenol, bisphenol A and methoxychlor in rats. *Toxicol Sci, 54*(1), 154-167.

Lee, H. R., & Choi, K. C. (2013). 4-tert-Octylphenol stimulates the expression of cathepsins in human breast cancer cells and xenografted breast tumors of a mouse model via an estrogen receptor-mediated signaling pathway. *Toxicology, 304*, 13-20.

Lee, M. H., Kim, E., & Kim, T. S. (2004). Exposure to 4-tert-octylphenol, an environmentally persistent alkylphenol, enhances interleukin-4 production in T cells via NF-AT activation. *Toxicol Appl Pharmacol, 197*(1), 19-28.

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2011). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses. From https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

Murono, E. P., Derk, R. C., & de Leon, J. H. (2000). Octylphenol inhibits testosterone biosynthesis by cultured precursor and immature Leydig cells from rat testes. *Reprod Toxicol, 14*(3), 275-288.

Nagao, T., Yoshimura, S., Saito, Y., Nakagomi, M., Usumi, K., & Ono, H. (2001). Reproductive effects in male and female rats from neonatal exposure to p-octylphenol. *Reprod Toxicol, 15*(6), 683-692.

Organisation for Economic Co-operation and Development, U. N. E. P. (1995). Phenol, 4-(1,1,3,3-tetramethylbutyl)- Screening Information Data Sets Initial Assessment Report. Retrieved from: http://www.chem.unep.ch/irptc/sids/OECDSIDS/140669.pdf

Paris, F., Balaguer, P., Terouanne, B., Servant, N., Lacoste, C., Cravedi, J. P., . . . Sultan, C. (2002). Phenylphenols, biphenols, bisphenol-A and 4-tert-octylphenol exhibit alpha and beta estrogen activities and antiandrogen activity in reporter cell lines. *Mol Cell Endocrinol, 193*(1-2), 43-49.

Petroleum Additives Panel, H., Environmental and Regulatory Task Group,. (2006). Group 28 - Phenol, Heptyl Derivatives. Retrieved from: http://iaspub.epa.gov/oppthpv/document_api.download?FILE=Revised Summaries sn265.pdf

Pocock, V. J., Sales, G. D., Wilson, C. A., & Milligan, S. R. (2002). Effects of perinatal octylphenol on ultrasound vocalization, behavior and reproductive physiology in rats. *Physiol Behav, 76*(4-5), 645-653.

Qin, Y., Chen, M., Wu, W., Xu, B., Tang, R., Chen, X., . . . Wang, X. (2013). Interactions between urinary 4-tert-octylphenol levels and metabolism enzyme gene variants on idiopathic male infertility. *PLoS One, 8*(3), e59398.

Sahambi, S. K., Pelland, A., Cooke, G. M., Schrader, T., Tardif, R., Charbonneau, M., . . . Devine, P. J. (2010). Oral p-tert-octylphenol exposures induce minimal toxic or estrogenic effects in adult female Sprague-Dawley rats. *J Toxicol Environ Health A, 73*(9), 607-622.

Schenectady International for U.S. EPA. (2002). Alkylphenols Category, Section Two, Ortho-substituted Mono-alkylphenols, Chemical Right-to-Know Initiative, HPV Challenge Program.

Shalaby, K. F. W., L.F.; El-Sisi, S.F.I. (2011). The Possible Toxic Effect of 4-tert-octylphenol-Polluted Water, on Male Reproductive Hormone of Rat. *Nature and Science, 9*(11), 97-107.

Sharpe, R. M., Fisher, J. S., Millar, M. M., Jobling, S., & Sumpter, J. P. (1995). Gestational and lactational exposure of rats to xenoestrogens results in reduced testicular size and sperm production. *Environ Health Perspect, 103*(12), 1136-1143.

Snyder, S. A., Bruce, G. M., & Drewes, J. E. (2010). Identifying Hormonally Active Compounds, Pharmaceuticals, and Personal Care Product Ingredients of Heatlth Concern from Potential Presence in Water Intended for Indirect Potable Reuse. Retrieved from: https://watereuse.org/download/identifying-hormonally-active-compounds-pharmaceuticals-and-personal-care-product-ingredients-of-health-concern-from-potential-presence-in-water-intended-for-indirect-potable-reuse/

Snyder, S. A., Trenholm, R. A., Snyder, E. M., Bruce, G. M., Pleus, R. C., & Hemming, J. D. C. (2008). Toxicological Relevance of EDCs and Pharmaceuticals in Drinking Water. Retrieved from: http://environmentalhealthcollaborative.org/images/91238_Toxicological_Relevance.pdf

Suberg H., L. E., and Kaliner, G. (1982). Isooctylphenol: Subchronic Toxicological Experiments with Rats. Wuppertal, Germany: Bayer AG Institute for Toxicology.

Tyl, R. W., Myers, C. B., Marr, M. C., Brine, D. R., Fail, P. A., Seely, J. C., & Van Miller, J. P. (1999). Two-generation reproduction study with para-tert-octylphenol in rats. *Regul Toxicol Pharmacol, 30*(2 Pt 1), 81-95.

U.S. Environmental Protection Agency - Office of Research and Development. (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. From http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. From http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf

U.S. Environmental Protection Agency. (2009). Screening-Level Hazard Characterization, Alkylphenols Category. From http://www.epa.gov/hpvis/hazchar/Category_Alkylphenols_Sept2009.pdf

U.S. Environmental Protection Agency. (2010). Alkylphenol Ethoxylates (APEs-JITF CST 5 inert Ingredients). Revised Human Health Risk Assessment to Support Propsed Exemption from the Requirement of a Tolerance When Used as Inert Ingredients in Pesticide Formulations. Washington, D.C. From http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0890-0004

U.S. Environmental Protection Agency. (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

United Nations Environment Programme (UNEP). (1995). 4-(1, 1, 3, 3-Tetramethyl butyl)-Phenol: SIDS Initial Assessment Report for SIAM 3. From http://www.chem.unep.ch/irptc/sids/OECDSIDS/140669.pdf

United States Geological Survey. (2014). Health-Based Screening Levels for Evaluating Water-Quality Data. From http://cida.usgs.gov/hbsl/apex/f?p=104:1:

Upmeier, A., Degen, G. H., Schuhmacher, U. S., Certa, H., & Bolt, H. M. (1999). Toxicokinetics of p-tert-octylphenol in female DA/Han rats after single i.v. and oral application. *Arch Toxicol, 73*(4-5), 217-222.

vom Saal, F. S., Cooke, P. S., Buchanan, D. L., Palanza, P., Thayer, K. A., Nagel, S. C., . . . Welshons, W. V. (1998). A physiologically based approach to the study of bisphenol A and other estrogenic chemicals on the size of reproductive organs, daily sperm production, and behavior. *Toxicol Ind Health, 14*(1-2), 239-260.

White, R., Jobling, S., Hoare, S. A., Sumpter, J. P., & Parker, M. G. (1994). Environmentally persistent alkylphenolic compounds are estrogenic. *Endocrinology, 135*(1), 175-182.

Ye, X., Kuklenyik, Z., Needham, L. L., & Calafat, A. M. (2006). Measuring environmental phenols and chlorinated organic chemicals in breast milk using automated on-line column-switching-high performance liquid chromatography-isotope dilution tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci, 831*(1-2), 110-115.

Yon, J. M., Kwak, D. H., Cho, Y. K., Lee, S. R., Jin, Y., Baek, I. J., . . . Nam, S. Y. (2007). Expression pattern of sulfated glycoprotein-2 (SGP-2) mRNA in rat testes exposed to endocrine disruptors. *J Reprod Dev, 53*(5), 1007-1013.

Yoshida, M., Katsuda, S., Tanimoto, T., Asai, S., Nakae, D., Kurokawa, Y., . . . Maekawa, A. (2002). Induction of different types of uterine adenocarcinomas in Donryu rats due to neonatal exposure to high-dose p-t-octylphenol for different periods. *Carcinogenesis, 23*(10), 1745-1750.

Toxicological Summary for: Perfluorobutane sulfonate

CAS: **45187-15-3 [anion]**
375-73-5 [free acid]
29420-49-3 [potassium salt]
68259-10-9 [ammonium salt]
60453-92-1 [sodium salt]

Synonyms: PFBS ion; Perfluorobutanesulfonate; 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (IUPAC name); Perfluorobutyl sulfonate

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

Short-term Non-Cancer Health-Based Value (nHBV$_{Short-term}$) = 0.1 µg/L

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

$$= \frac{(0.000084 \text{ mg/kg-d}) \times (0.5)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

$$= 0.14 \text{ rounded to } \textbf{0.1 µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.0084/100 = 0.000084 mg/kg-d (Hsd:Sprague Dawley Rats)
Source of toxicity value:	Determined by MDH in 2022
Point of Departure (POD):	6.97 mg/kg-d (administered dose BMDL$_{1SD}$, (National Toxicology Program 2019))
Dose Adjustment Factor (DAF):	Chemical- and Study-Specific Toxicokinetic Adjustment Half-life$_{FemaleRat}$/Half-life$_{Human}$ = 1.3 hr/1050 hr = 0.0012, based on MDH analysis of (Huang, Dzierlenga et al. 2019) for female rats and (Xu, Fletcher et al. 2020) for humans.
Human Equivalent Dose (HED):	POD x DAF = 6.97 mg/kg-d x 0.0012 = 0.0084 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 due to a lack of available immunotoxicity and developmental neurotoxicity studies (known sensitive effects of other

	PFAS) as well as lack of a 2-generation study in a more appropriate species
Critical effect(s):	Decreased total T4
Co-critical effect(s):	None
Additivity endpoint(s):	Thyroid (E)

Subchronic Non-Cancer Health-Based Value (nHBV$_{Subchronic}$) = 0.1 µg/L

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

$$= \frac{(0.000084 \text{ mg/kg-d})^{\#} \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 0.23 \text{ rounded to } 0.2 \text{ µg/L}$$

[#]The calculated Subchronic RfD (0.00054 mg/kg-d) is higher than the Short-Term RfD (0.000084 mg/kg-d), which is based on thyroid 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 when deriving subchronic water guidance.

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

The Subchronic nHBV must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 0.1 µg/L. Additivity endpoints: Thyroid (E)

Chronic Non-Cancer Health-Based Value (nHBV$_{Chronic}$) = 0.1 µg/L

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

$$= \frac{(0.000084 \text{ mg/kg-d})^{\#} \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 0.37 \text{ rounded to } 0.4 \text{ µg/L}$$

[#]The calculated Chronic RfD (0.00018 mg/kg-d) is higher than the Short-Term RfD (0.000084 mg/kg-d), which is based on thyroid effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of shorter exposures, including short-term effects (MDH 2008, page 34). Therefore, the Short-Term RfD is used in place of the calculated Chronic RfD when deriving chronic water guidance.

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

The Chronic nHBV must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-Term nHBV of 0.1 µg/L. Additivity endpoints: Thyroid (E)

Cancer Health-Based Value (cHBV) = Not Applicable

Chemical Mixtures: Exposure to chemicals in combination may cause adverse effects that would not be predicted based on separate exposures to individual chemicals. When multiple contaminants occur as a mixture in water, the cumulative risk should be assessed (MDH 2008, Section IV.E.3). To download the calculator, see
MDH's Water Guidance and Additivity Calculator
https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/guidance.xlsx

Volatile: No

Summary of Guidance Value History:
In 2009, Health-Based Values (HBVs) for PFBS were first derived: 9 µg/L for Subchronic durations and 7 µg/L for Chronic durations. These HBVs were adopted as HRLs in 2011.

In 2017, MDH re-evaluated the 2011 guidance and derived new HBVs of 3 µg/L for Short-Term and Subchronic durations and 2 µg/L for Chronic durations based on new toxicokinetic information in mice, a reassessment of toxicokinetic information in rats, and a new developmental toxicity study in mice.

In 2020, MDH updated the intake rates used in the calculation of water guidance values based on the most recent EPA Exposure Factors Handbook. This update did not change the PFBS 2017 guidance values.

In 2022, MDH re-evaluated the 2020 guidance and derived new HBVs of 0.1 µg/L for Short-Term, Subchronic, and Chronic durations. The 2022 values are lower than the previous values as a result of: 1) new toxicokinetic information in humans and rats, and 2) a new toxicity study in rats evaluating sensitive thyroid endpoints.

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?	Yes	No	Yes	Yes	Yes
Effects observed?	Yes[1]	–[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Male and female rats exposed to PFBS orally had large decreases in various thyroid hormones at a dose 900-fold higher than the Short-Term RfD; the effect on one thyroid hormone (tT4) served as the basis for the Short-Term RfD. A decrease in serum thyroid hormones is an effect consistently observed in other PFAS compounds.

An oral developmental study evaluated female mice exposed in utero to PFBS. Delays in vaginal opening and changes in estrus cycling as well as changes in uterine and ovarian size were reported. Pubertal and adult female offspring exhibited decreases in serum estrogen and progesterone levels with elevation of luteinizing hormone levels. Decreases in serum tT4 and T3 were observed in conjunction with slight increases in TSH in female offspring as well as their mothers. These effects all occurred at doses at least 1400-fold higher than the Short-Term RfD.

[2] An study evaluated the association between 11 PFAS chemicals and immunological markers in children from Taiwan. Associations of several PFAS chemicals, including PFBS, with asthma and asthma related biomarkers were found. Associations for PFBS were fewer and weaker than those for several other PFAS chemicals. Concentrations of individual PFAS were positively correlated, and therefore it is not possible to determine whether associations apply to multiple PFASs or to only a subset of individual PFAS. A more recent study following a cohort of several hundred children in Shanghai, China found an association between PFBS concentration in maternal cord blood with increased frequency of respiratory tract infections and decreased IgG concentration in 5-year-old children, suggesting that pre/perinatal exposures to PFBS impacts future immune function in children.

No PFBS immunotoxicity studies have been conducted in laboratory animals. Immunotoxicity has been identified as a sensitive endpoint for several other PFAS. A database uncertainty factor of 3 was incorporated, in part, to address the need for immunotoxicity testing.

[3] Two oral developmental studies (one in rats and one in mice) and a 2-generation study in rats have been conducted. The developmental effects reported in the mouse study included decreased pup body weight, decreased serum thyroid hormones, delayed eye opening, delayed vaginal opening and first estrus as well as smaller ovarian and uterine size in adult offspring. These effects were observed at doses 1400-fold higher than the Short-Term RfD. The developmental study in rats reported decreased fetal body weight at doses >14000-fold higher than the Short-term RfD. In the 2-generation study in rats, no developmental effects were identified at the highest dose tested (14000-fold higher than the Short-Term RfD). However, female rats excrete PFBS much more quickly than humans, which may limit the applicability of this 2-generation study. A database uncertainty factor of 3 was incorporated, in part, to address the lack of a 2-generation study in a more appropriate species.

[4] Researchers examined the association between PFAS chemicals and endometriosis-related infertility among Chinese reproductive-age women in a case-control study. Women with endometriosis-related infertility had significantly higher median levels of PFBS compared with those without the disease. PFBS was the only PFAS identified with a significant positive association, while several other PFAS chemicals exhibited an inverse association. Limitations of this study include no identification of the time course,

disease survey reported levels may not reflect actual exposure, and no physical exam data was measured for controls.

An oral 2-generation study in rats has been conducted. No treatment related effects on female reproductive parameters were noted. Decreased number of spermatids per gram testes (P0) and increased incidence of abnormal sperm (F1) were noted at HED dose levels 37000-fold higher than the Short-term RfD.

[5]Neurological alterations were reported in the 28-day but not the 90-day oral study in adult rats. The results of the study are difficult to interpret. The longer study did not report any treatment related effects. The effects in the 28-day study occurred at HED dose levels 1400-fold higher than the Short-term RfD.

A database UF was incorporated, in part, to address the need for additional neurological testing, particularly in developmental life stages.

Resources Consulted During Review:
Apelberg, B., LR Goldman, AM Calafat, JB Herbstman, Z Kuklenyik, L Heidler, LL Needham, RU Halden, FR Witter. (2007). "Determinants of Fetal Exposure to Polyfluoroalkyl Compounds in Baltimore, Maryland." Environmental Science & Technology **41**: 3891-3897.
ATSDR (2021). Agency for Toxic Substances and Disease Registry. Toxicological Profile for Perfluoroalkyls.
Australian Department of Health And Ageing NICNAS (2005). Existing Chemical Hazard Assessment Report. Potassium Perfluorobutane Sulfonate.
Bijland, S., PCN Rensen, EJ Pieterman, ACE Mass, JW van der Hoorn, MJ van Erk, KW van Dijk, SC Chang, DJ Ehresman, JL Butenhoff, HMG Princen. (2011). "Perfluoroalkyl Sulfonates Cause Alkyl Chain Length-Dependent Hepatic Steatosis and Hypolipidemia Mainly by Impairing Lipoprotein Production in APOE*3-Leiden CETP Mice." Toxicological Sciences **123**(1): 290-303.
Bogdanska, J., M. Sundström, U. Bergström, D. Borg, M. Abedi-Valugerdi, Å. Bergman, J. DePierre and S. Nobel (2014). "Tissue distribution of 35S-labelled perfluorobutanesulfonic acid in adult mice following dietary exposure for 1-5 days." Chemosphere **98**: 28-36.
Cai, D., QQ Li, C Chu, SZ Wang, YT Tang, AA Appleton, RL Qiu, BY Yang, LW Hu, GH Dong, XW Zeng (2020). "High trans-placental transfer of perfluoroalkyl substances alternatives in the matched maternal-cord blood serum: Evidence from a birth cohort study." Science of the Total Environment **705**: 135885.
Calafat AM, L. W., Z Kuklenyik, JA Reidy, LL Needham (2007). "Polyfluoroalkyl Chemicals in the U.S. Population: Data from the National Health and Nutrition Examination Survey (NHANES) 2003-2004 and Comparison with NHANES 1999-2000." Env Health Perspective **115**: 1596-1602.
CDC (2017). Centers for Disease Control and Prevention. Fourth National Report on Human Exposure to Environmental Chemicals. Updated Tables, January 2017, Volume One.
Chengelis, C., JB Kirkpatrick, NR Myers, M Shinohara, PL Stetson, DW Sved. (2009). "Comparison of the toxicokinetic behavior of perfluoronexanoic acid (PFHxA) and nonafluorobutane-1-sulfonic acid (PFBS) in cynomolgus monkeys and rats." Reproductive Toxicology **27**: 400-406.

Corsini, E., E Sangiovanni, A Avogadro, V Galbiati, B Viviani, M Marinovich, CL Galli, M Dell'Agli, DR Germolec. (2012). "In vitro characterization of the immunotoxic potential of several perfluorinated compounds (PFCs)." Toxicology and Applied Pharmacology **258**: 248-255.

Dong, G., KY Tung, CH Tsai, MM Liu, D Wang, W Liu, YH Jin, WS Hsieh, YL Lee, PC Chen. (2013). "Serum Polyfluoroalkyl Concentrations, Asthma Outcomes, and Immunological Markers in a Case–Control Study of Taiwanese Children." Environmental Health Perspectives **121**: 507-513.

Feng, X., X Cao, S Zhao, X Wang, X Hua, L Chen, L Chen. (2017). "Exposure of Pregnant Mice to Perfluorobutanesulfonate Causes Hypothyroxinemia and Developmental Abnormalities in Female Offspring." Toxicological Sciences **155**(2): 409-419.

Fromme, H., C Mosch, M Morovitz, I Alba-Alejandre, S Boehmer, M Kiranoglu, F Faber, I Hannibal, O Genzel-Boroviczeny, B Koletzko, W Volkel. (2010). "Pre- and Postnatal Exposure to Perfluorinated Compounds (PFCs)." Environmental Science & Technology **44**: 7123-7129.

Gao K, T. Z., X Liu, J Fu, J Zhang, J Fu, L Wang, A Zhang, Y Liang, M Song, G Jiang, (2019). "Prenatal Exposure to Per- and Polyfluoroalkyl Substances (PFASs) and Association between the Placental Transfer Efficiencies and Dissociation Constant of Serum Proteins–PFAS Complexes." Environmental Science and Technology **53**: 6529-6538.

Han, W., Y. Gao, Q. Yao, T. Yuan, Y. Wang, S. Zhao, R. Shi, E. C. Bonefeld-Jorgensen, X. Shen and Y. Tian (2018). "Perfluoroalkyl and polyfluoroalkyl substances in matched parental and cord serum in Shandong, China." Environment International **116**: 206-213.

Holzer J, O. Midasch, K. Rauchfuss, M. Kraft, R. Reupert, J. Angerer, P. Kleeschulte, N. Marschall, M. Wilhelm, (2008). "Biomonitoring of Perfluorinated Compounds in Children and Adults Exposed to Perfluorooctanoate-Contaminated Drinking Water." Env Health Perspective **116**(5): 651-657.

Huang, H., K. Yu, X. Zeng, Q. Chen, Q. Liu, Y. Zhao, J. Zhang, X. Zhang and L. Huang (2020). "Association between prenatal exposure to perfluoroalkyl substances and respiratory tract infections in preschool children." Environ Res **191**: 110156.

Huang, M. C., A. L. Dzierlenga, V. G. Robinson, S. Waidyanatha, M. J. Devito, M. A. Eifrid, C. A. Granville, S. T. Gibbs and C. R. Blystone (2019). "Toxicokinetics of perfluorobutane sulfonate (PFBS), perfluorohexane-1-sulphonic acid (PFHxS), and perfluorooctane sulfonic acid (PFOS) in male and female Hsd:Sprague Dawley SD rats after intravenous and gavage administration." Toxicology Reports **6**: 645-655.

Interstate Technology and Regulatory Council (ITRC). (December 2021). "PFAS Water and Soil Values Table Excel file." from https://pfas-1.itrcweb.org/fact-sheets/.

ITRC. (2021). "Interstate Technology and Regulatory Council Regulations, Guidance, and Advisories. Section 4 Tables (Excel)." Last Update August 2021. Retrieved October 26, 2021, from https://pfas-1.itrcweb.org/fact-sheets/.

Kaiser AM, M. F., R Aro, A Kärrman, C Gundacker, H Zeisler, P Foessleitner, H Salzer, C Hartmann, M Uhl, LWY Yeung, (2021b). "Extractable Organofluorine Analysis in Pooled Human Serum and Placental Tissue Samples from an Austrian Subpopulation - A Mass Balance Analysis Approach." Environ Sci and Technol **55**: 9033-9042.

Kärrman, A., I Ericson, B van Bavel, PO Darnerud, M Aune, A Glynn, S Lignell, G Lindström. (2007). "Exposure of Perfluorinated Chemicals through Lactation: Levels of Matched Human Milk and Serum and a Temporal Trend, 1996-2004, in Sweden." Environmental Health Perspectives **115**: 226-230.

Kärrman A, K. H., K Inoue, T Takasuga, E Ohi, A Koizumi, (2009). "Relationship between dietary exposure and serum perfluorochemical (PFC) levels - A case study." Environ Int **35(4):** 712-7

Kim, S.-K., KT Lee, CS Kang, L Tao, K Kannan, KR Kim, CK Kim, JS Lee, PS Park, YW Yoo, JY Ha, YS Shin, JH Lee. (2011b). "Distribution of perfluorochemicals between sera and milk from the same mothers and implications for prenatal and postnatal exposures." Environmental Pollution **159**: 169-174.

Kudo, N. (2015). Chapter 6. Metabolism and Pharmacokinetics. Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances. J. C. DeWitt. Switzerland, Humana Press, Springer International Publishing.

Lau C (2017). Personal Communication re: PFBS Pharmacokinetics. H. Goeden.

Lau, C., J. Rumpler, K. P. Das, C. R. Wood, J. E. Schmid, M. J. Strynar and J. F. Wambaugh (2020). "Pharmacokinetic profile of Perfluorobutane Sulfonate and activation of hepatic nuclear receptor target genes in mice." Toxicology **441**: 152522.

Lieder, P., RG York, DC Hakes, SC Chang and J. Butenhoff (2009b). "A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats." Toxicology **259**: 33-45.

Lieder, P., SC Chang, RG York and J. Butenhoff (2009a). "Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats." Toxicology **255**: 45-52.

Ma D, Y. L., Y Liang, T Ruan, J Li, C Zhao, Y Wang, G Jiang, (2021). " A Critical Review on Transplacental Transfer of Per- and Polyfluoroalkyl Substances: Prenatal Exposure Levels, Characteristics, and Mechanisms." Environmental Science and Technology.

Manzano-Salgado, C., M Casas, MJ Lopez-Espinosa, F Ballester, M Basterrechea, JO Grimalt, AM Jimenez, T Kraus, T Schettgen, J Sunyer, M Vrijheid. (2015). "Transfer of perfluoroalkyl substances from mother to fetus in a Spanish birth cohort." Environmental Research **142**: 471-478.

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."

Minnesota Department of Health (MDH) (2009). East Metro Perfluorochemical Biomonitoring Pilot Project.

Minnesota Department of Health (MDH). (2017). "MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017)." from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf.

National Toxicology Program. (2019). "Toxicity studies of perfluoroalkyl sulfonates administered by gavage to Sprague Dawley (Hsd:Sprague Dawley SD) rats (TOX-96)." from https://cebs.niehs.nih.gov/cebs/publication/TOX-96.

Olsen, G., CC Lange, ME Ellefson, DC Mair, TR Church, CL Goldberg, RM Herron, Z Medhdizadehkashi, JB Nobiletti, JA Rios, WK Reagen, LR Zobel. (2012). "Temporal Trends of Perfluoroalkyl Concentrations in American Red Cross Adult Blood Donors, 2000 - 2010 " Environmental Science & Technology **46**: 6330-6338.

Olsen, G., DC Mair, CC Lange, LM Harrington, TR Church, CL Goldberg, RM Herron, H Hanna, JB Nobiletti, JA Rios, WK Reagen, CA Ley. (2017). "Per- and polyfluoroalkyl substances (PFAS) in American Red Cross adult blood donors, 2000-2015." Environmental Research **157**: 87-95.

Olsen, G., SC Chang, PE Noker, GS Gorman, DJ Ehresman, PH Lieder, JL Butenhoff. (2009). "A comparison of the pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys, and humans." Toxicology **256**: 65-74.

Premedica Redfield Report (2000). A Repeated Dose Range-Finding Toxicity Study of T-7485 in Sprague-Dawley Rats. Study Number 132-006.

Premedica Redfield Report (2001). A 28-Day Oral (Gavage) Toxicity Study of T-7485 in Sprague-Dawley Rats. Study Number 132-007.

Rumpler, J., K Das, C Wood, M Strynar, A Lindstrom, J Wambaugh, C Lau. (2016). "Pharmacokinetic Profiles of Perfluorobutane Sulfonate and Activation of Hepatic Genes in Mice." The Toxicologist, Supplement to Toxicological Sciences **150**(1): Abstract #3439.

U.S. Environmental Protection Agency (EPA). (1988). "Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development." from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855.

U.S. Environmental Protection Agency (EPA). (2014). "Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. Risk Assessment Forum. Office of Research and Development. EPA/100/R-14/002F".

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

U.S. Environmental Protection Agency (EPA). (2021). "Human Health Toxicity Values for Perfluorobutane Sulfonic Acid (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3)."

U.S. Environmental Protection Agency (EPA). (2021). Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA (anionic and acid forms) IRIS Assessments. CASRN 335-76-2 (PFDA), CASRN 375-95-1 (PFNA), CASRN 307-24-4 (PFHxA), CASRN 355-46-4 (PFHxS), and CASRN 375-22-4 (PFBA). Supplemental Information—Appendix A.

Wang, B., R Zhang, F Jin, H Lou, Y Mao, W Zhu, W Zhou, P Zhang, J Zhang. (2017). "Perfluoroalkyl substances and endometriosis-related infertility in Chinese women." Environment International **102**: 207-212.

Wang, Y., W Han, C Wang, Y Zhou, R Shi, EC Bonefeld-Jorgensen, Q Yao, T Yuan, Y Gao, J Zhang, Y Tian (2018). "Efficiency of maternal-fetal transfer of perfluoroalkyl and polyfluoroalkyl substances." Environmental Science and Pollution Research **Advance Access** **https://doi.org/10.1007/s11356-018-3686-3**.

Weaver, Y. M., D. J. Ehresman, J. L. Butenhoff and B. Hagenbuch (2010). "Roles of rat renal organic anion transporters in transporting perfluorinated carboxylates with different chain lengths." Toxicol Sci **113**(2): 305-314.

World Health Organization (WHO). (2005). "Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for the Use of Data in Dose/Concentration-Response Assessment. International Programme on Chemical Safety, IPCS Harmonization Project Document No. 2. WHO/IPCS/01.4, 1-96, Geneva, Switzerland".

Xu, Y., T. Fletcher, D. Pineda, C. H. Lindh, C. Nilsson, A. Glynn, C. Vogs, K. Norström, K. Lilja, K. Jakobsson and Y. Li (2020). "Serum Half-Lives for Short- and Long-Chain Perfluoroalkyl Acids

after Ceasing Exposure from Drinking Water Contaminated by Firefighting Foam." Environmental Health Perspectives **128**(7): 77004.

York, R. (2002). Oral (Gavage) Developmental Toxicity Study of Potassium Perfluorobutane Sulfonate (PFBS) in Rats. Argus Research Protocol Number 418-023.

York, R. (2003a). Oral (Gavage) Repeated Dose 90-Day Toxicity Study of Potassium Perfluorobutane Sulfonate (PFBS) in Rats. Argus Research Protocol Number 418-026.

York, R. (2003b). Oral (Gavage) Two-Generation (One Litter per Generation) Reproduction Study of Perfluorobutane Sulfonate (PFBS) in Rats. Argus Research Protocol Number 418-021.

Zhang, T., H Sun, Y Lin, X Qin, Y Zhang, X Geng, K Kannan. (2013). "Distribution of Poly- and Perfluoroalkyl Substances in Matched Samples from Pregnant Women and Carbon Chain Length Related Maternal Transfer." Environmental Science & Technology **47**: 7974-7981.

Web Publication Date: August 2020

Toxicological Summary for: Perfluorohexane sulfonate

CAS: 108427-53-8 (anion)
355-46-4 (acid)
3871-99-6 (potassium salt)
Synonyms: PFHxS; perfluorohexanesulfonic acid; 1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexane-1-sulfonate

Short-term, Subchronic and Chronic* Non-Cancer Health Based Value (nHBV) = 0.047 μg/L**

*Due to the highly bioaccumulative nature of PFHxS within the human body, serum concentrations are the most appropriate dose metric and the standard equation to derive the HBV is not appropriate. Short-term exposures have the potential to stay in the body for an extended period of time. In addition, accumulated maternal PFHxS is transferred to offspring (i.e., placental and breastmilk transfer). A single HBV has therefore been recommended for short-term, subchronic, and chronic durations. The HBV was derived using a toxicokinetic (TK) model previously developed by MDH (Goeden 2019). Model details and results are presented below.

**Relative Source Contribution (RSC): Using the most recent published biomonitoring results (CDC, accessed February 2019) and USEPA's Exposure Decision Tree (USEPA 2000) as outlined in MDH 2008, Section IV.E.1., an RSC of 0.5 (50%) was selected for the peak serum concentration during infancy. The RSC of 0.5 during infancy resulted in chronic (steady-state) serum concentrations at approximately 0.2 of the 'reference' serum concentration.

Intake Rate: In keeping with MDH's peer-reviewed and promulgated methodology, 95th percentile water intake rates (Table 3-1, 3-3 and 3-5, USEPA 2019) or upper percentile breastmilk intake rates (Table 15-1, USEPA 2011) were used. Breastmilk concentrations were calculated by multiplying the maternal serum concentration by a PFHxS breastmilk transfer factor of 1.4%. For the breast-fed infant exposure scenario, a period of exclusive breastfeeding for one year was used as representative of a reasonable maximum exposure scenario. [Note: "exclusively breast-fed" intake rates refers to infants whose sole source of milk comes from human breastmilk, with no other milk substitutes (USEPA 2011, page 15-2).]

A simple equation is typically used to calculate HBVs at the part per billion level with results rounded to one significant digit. However, the toxicokinetic model used to derive the HBV for PFHxS showed that serum concentrations are impacted by changes in water concentrations at the part per trillion level. As a result, the HBV contains two digits.

Reference Dose/Concentration: HED/Total UF = 0.00292/300 = 0.0000097 mg/kg-d (or 9.7 ng/kg-d) (adult Sprague Dawley rats). [The corresponding serum concentration is 32.4/300 = 0.108 μg/mL. Note: this serum concentration is inappropriate to use for individual or clinical assessment.***]
Source of toxicity value: Determined by MDH in 2019
Point of Departure (POD): 32.4 μg/mL (or mg/L) serum concentration (male rats - NTP 2018, MDH modeled $BMDL_{20\%}$)

Dose Adjustment Factor (DAF):	Toxicokinetic Adjustment based on Chemical-Specific Clearance Rate = Volume of Distribution (L/kg) x (Ln2/Half-life, days) = 0.25 L/kg x (0.693/1935 days) = 0.000090 L/kg-day. (Half-life from Li et al 2018)
Human Equivalent Dose (HED):	POD x DAF = 32.4 mg/L x 0.000090 L/kg-d = 0.00292 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty to address concerns regarding early life sensitivity to decreased thyroxine (T4) levels as well as lack of 2 generation or immunotoxicity studies.
Critical effect(s):	decreased free T4
Co-critical effect(s):	decreased free and total T4, triiodothyronine (T3), and changes in cholesterol levels and increased hepatic focal necrosis
Additivity endpoint(s):	Hepatic (Liver) System and Thyroid (E)

***The serum concentration is useful for informing public health policy and interpreting population-based exposure potential. This value is based on population-based parameters and should not be used for clinical assessment or for interpreting serum levels in individuals.

Toxicokinetic Model Description (Goeden 2019):

PFHxS is well absorbed and is not metabolized. Serum concentrations can be calculated from the dose and clearance rate using the following equation.

$$Serum\ Concentration\ \left(\frac{mg}{L}\right) = \frac{Dose\left(\frac{mg}{kg \cdot day}\right)}{Clearance\ Rate\left(\frac{L}{kg \cdot day}\right)}¶$$

Where:

Dose (mg/kg-day) = Water or Breastmilk Intake (L/kg-day) x Water or Breastmilk Concentration (mg/L)
and
Clearance (L/kg-day) = Volume of distribution (L/kg) x (Ln 2/human half-life, days)

Two exposure scenarios were evaluated: 1) an infant fed formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water through life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking contaminated water. In both scenarios the simulated individuals began life with a pre-existing body burden through placental transfer of PFHxS (maternal serum concentration x 70%) based on median cord to maternal serum concentration ratios reported in the literature. The serum concentration of the mother at delivery was assumed to be at steady-state and was calculated by using the equation above with a time-weighted 95th percentile intake from birth to 30 years of age (0.048 L/kg-d). During lactation a 95th percentile water intake rate

of 47 mL/kg-d and a body weight of 65.1 kg ((USEPA 2019), Table 3-3) was used to calculate daily maternal serum concentrations.

Consistent with MDH methodology, 95th percentile water intake and upper percentile breastmilk intake rates were used to simulate a reasonable maximum exposed individual. A PFHxS breastmilk transfer factor of 1.4%, based on average breastmilk to maternal serum concentration ratios reported in the literature, was used to calculate breastmilk concentration. According to the 2016 Breastfeeding Report Card (CDC, 2016), nearly 66 percent of mothers in Minnesota report breastfeeding at six months, dropping to 41% at twelve months. MDH chose to use the breastmilk intake rates for exclusively breastfed infants, as reported in USEPA 2011, for one year for the breast-fed infant scenario.

Daily post-elimination serum concentration was calculated as:

$$Serum\ Conc.\left(\frac{mg}{L}\right) = \left[Prev.\ day\ Serum\ Conc.\left(\frac{mg}{L}\right) + \frac{Today's\ Intake(mg)}{V_d\left(\frac{L}{kg}\right) \times BW(kg)}\right] \times e^{-k}$$

To maintain mass balance, daily maternal serum concentrations and loss-of-chemical via transfer to the infant as well as excretion represented by the clearance rate, were calculated.

Summary of Reasonable Maximum Exposure (RME) Scenario Model Parameters

Model Parameter	Value Used
Volume of distribution (Vd)	0.25 L/kg (average of male (0.287) and female (0.213) nonhuman primate Vd, Sundstrom, 2012)
Vd Age Adjustment Factor	2.1 age 1-30 days decreasing to 1.2 age 5-10 years and 1.0 after age 10 years (Friis-Hansen 1961)
Half-life	1935 days (mean value for all ages, Li et al 2018)
	(5th to 95th percentile range: 1095 – 3358 days)
Elimination rate constant (k)	Calculated from Ln 2/half-life
Placental transfer factor *(% of maternal serum level)*	70% (mean of median paired maternal:cord blood ratios reported in the literature. Range of mean values 43 – 95%.)
	(Mean 95th percentile value 110%, range 69 – 168%.)
Breastmilk transfer factor *(% of maternal serum level)*	1.4% (mean of mean paired maternal serum:breastmilk ratios reported in the literature. Range of mean values 0.8 – 2%.)
	(No 95th percentile values reported in literature.)
Water Intake Rate (L/kg-d)	95th percentile consumers only (default values, MDH 2008) (Table 3-1 (for ages $\geq$ 2 yrs), 3-3 (for lactating women), and 3-5 (for ages < 2yr)) (USEPA 2019)
Breastmilk Intake Rate (L-kg-d)	Upper percentile exclusively breast-fed infants (Table 15-1, USEPA 2011)
Body weight (kg)	Calculated from water intake and breastmilk intake rate tables

A relative source contribution factor (RSC) is incorporated into the derivation of a health-based water guidance value to account for non-water exposures. MDH utilizes the Exposure Decision Tree process presented in USEPA 2000 to derive appropriate RSCs. Determination of an appropriate RSC must recognize the long elimination half-life of PFHxS, such that a person's serum concentration at any given age is not only the result of his or her current or recent exposures within the duration of concern, but also from exposure from years past.

Human biomonitoring data provide a quantitative description of the ongoing widespread exposure, but the serum data are not informative as to the specific pathways and exposure routes. The most recently reported 95th percentile serum concentrations from CDC (February 2019) range from 1.62 μg/L serum for young children to nearly 5 μg/L serum for older children and adults. This suggests that 'background' exposures, <u>when compared to the 'reference' serum concentration</u> (108 μg/L serum) would not represent significant sources of exposure. Using the most recent published biomonitoring results and USEPA's Exposure Decision Tree (USEPA 2000) as outlined in MDH 2008, an RSC of 0.5 (50%) was selected.

As mentioned above, two exposure scenarios were examined: 1) an infant fed formula reconstituted with PFHxS-contaminated water starting at birth and continuing ingestion of contaminated water throughout life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking PFHxS-contaminated water throughout life. For the first scenario, the formula-fed infant, the water concentration that maintains a serum concentration attributable to drinking water at or below an RSC of 50% is 0.099 μg/L (Figure 1).

Figure 1. Exclusively formula-fed infant scenario serum concentrations over a lifetime, based on MDH's RME and an RSC of 50%.
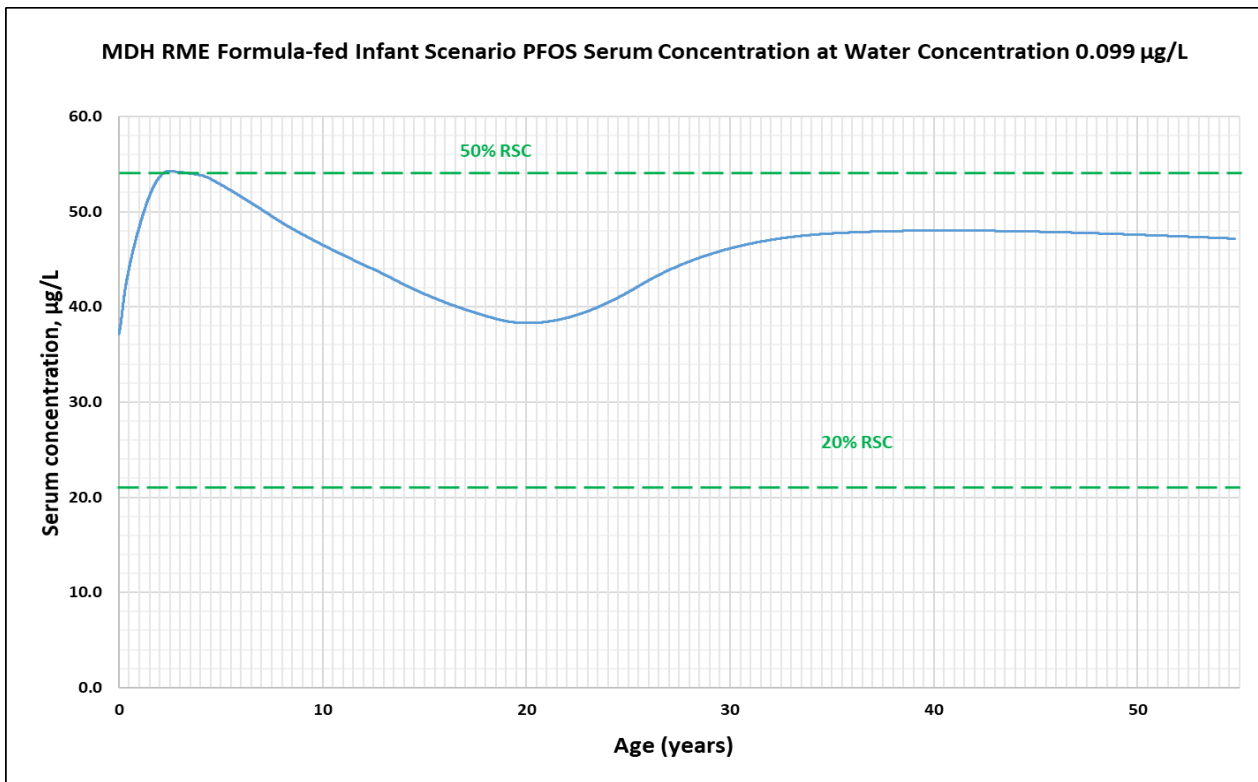
Applying this water concentration (0.099 µg/L) in the context of the breast-fed infant resulted in serum PFHxS concentrations exceeding the 'reference' serum concentration for nearly 2 years, and the 50% RSC threshold for nearly 14 years. See Figure 2.

Figure 2. Breast-fed infant scenario serum concentrations over a lifetime, based on MDH's RME and a water concentration of 0.099 µg/L.
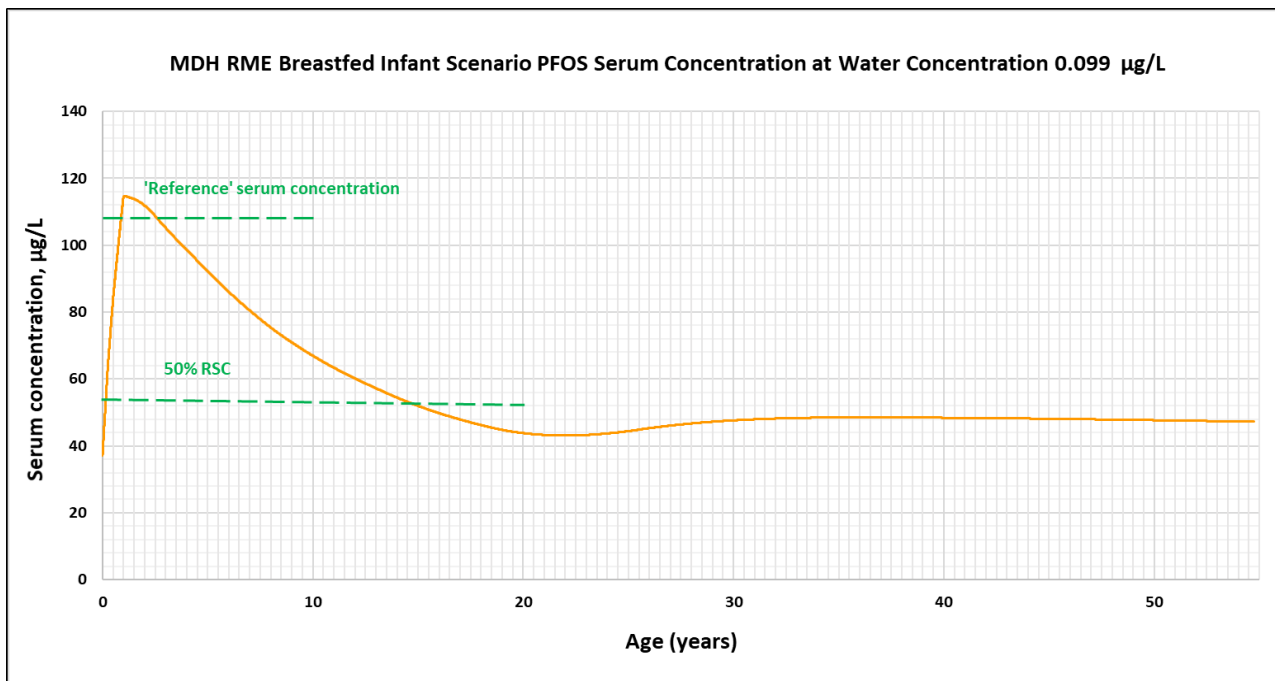
In order to maintain serum concentrations at or below an RSC of 50% for breast-fed infants, the water concentration should not exceed 0.047 µg/L; see Figure 3. This water concentration also produces steady state serum concentrations at approximately 20% of the 'reference' serum concentration.

Figure 3. Exclusively breast-fed infant scenario serum concentrations over a lifetime, based on MDH's RME, and a water concentration of 0.047 μg/L.
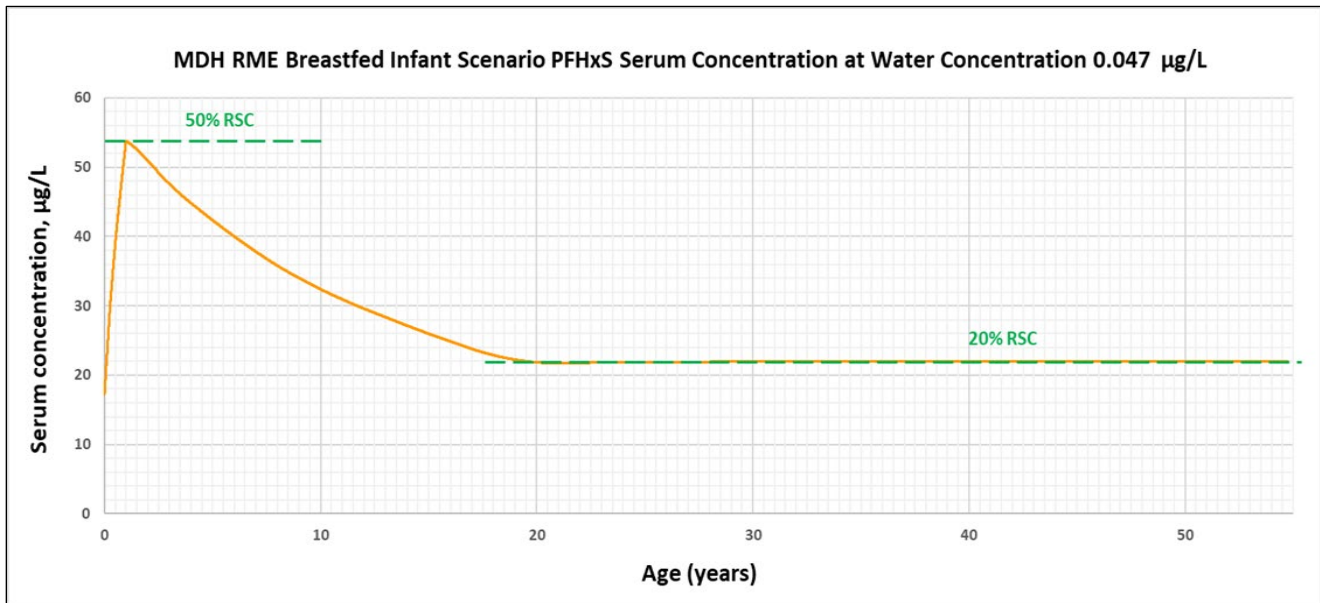
To ensure protection of all segments of the population, the final health-based value for PFHxS is set at 0.047 μg/L.

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not Classified
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (moderate)

Summary of Guidance Value History:

MDH first reviewed PFHxS in 2009 and determined that there was insufficient data to derive a value. In 2013, MDH's Site Assessment and Consultation Unit began using the guidance value for PFOS as a surrogate to assess potential risks from exposure to PFHxS, in the absence of adequate chemical specific data. In 2018 additional toxicokinetic and toxicity information became available. In 2019, MDH derived a noncancer HBV (applicable to short-term, subchronic, and chronic durations) of 0.047 μg/L. In 2020 MDH incorporated updated water intake rates (US EPA 2019). Use of the updated intake rates did not result in changes to the 2018 value.

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?	Yes	No	Yes	Yes	Yes
Effects observed?	Yes[1]	–[2]	No[3]	Yes[4]	No[5]

Comments on extent of testing or effects:

[1] Several human epidemiological studies have evaluated the possible association between serum PFHxS and alterations in thyroid hormone levels. Two studies found an association in women between serum PFHxS and thyroid hormone levels, however, other studies did not find this association. Two general population epidemiology studies have evaluated associations between PFHxS and reproductive hormones, finding no association.

Based on studies in laboratory animals, alterations in serum thyroid hormone levels, in particular thyroxine (T4), appear to be a sensitive effect. The POD is based on decreased serum T4 levels in adult male rats however, decreased serum T4 levels have also been reported in pregnant and lactating rats and pups. Unfortunately, serum PFHxS levels were not measured in pregnant or lactating rats or pups at the NOAEL and LOAEL dose levels, however, study results suggest that pups may be more sensitive than adult nonpregnant animals. A database uncertainty factor (DB UF) has been incorporated into the RfD derivation, in part, due to concerns that early life stages may be more sensitive.

Androgenic effects have also been evaluated in laboratory animals to a limited extent. No changes in adult male reproductive organ weights or sperm parameters were observed at serum levels up to ~600-fold higher than the 'reference' serum concentration. Androgenic activity was also evaluated in pups exposed in utero and through lactation. No significant effects were observed on anogenital distance, nipple retention, or reproductive organ weights at serum levels ~1300-fold higher than the 'reference' serum concentration.

[2] Several epidemiology studies have examined the potential association between PFHxS and suppression of the immune system. Inverse or no associations were observed in these studies. In general, available studies have not found an association between PFHxS and infectious disease resistance or with hypersensitivity outcomes.

Immunotoxicity has not been studied in laboratory animals. A DB UF has been incorporated into the RfD derivation, in part, to address this data gap.

[3] General population epidemiology studies have evaluated potential associations between maternal PFHxS and a variety of birth outcomes. A couple of studies have reported associations with birth weight or neurobehavioral outcome but others found no association.

Reproductive/developmental screening studies in rats and mice have not found treatment related changes in development outcome, including neurobehavioral effects, at serum levels $\geq$ ~900-fold higher than the 'reference' serum concentration. Neurobehavioral outcomes were also evaluated in a study using a single oral exposure to neonatal mice on postnatal day 10. No serum levels were measured and therefore, the results could not be quantitatively incorporated into MDH's assessment. No 2-generation study has been conducted. A DB UF has been incorporated into the RfD derivation, in part, to address this data gap.

[4] In general, epidemiology studies evaluating potential associations between PFHxS and reproductive measures have not found any associations. A small number of studies have reported associations with earlier menopause or time to pregnancy. However, since menstruation, childbirth, and lactation are potential elimination routes for women this could confound the associations.

Laboratory studies in rats did not find changes in reproductive parameters at serum levels $\geq$ ~1600-fold higher than the 'reference' serum concentration. A decrease in the number of pups per litter has been reported in mice, however the dose-response curve was flat and there was no difference in the number of pups born to the implant ratio. The 'reference' serum concentration is ~500-fold lower than the serum concentrations at which this effect occurs in mice, therefore the RfD is protective for this potential effect.

[5] Two epidemiology studies have evaluated association between PFHxS serum levels and self-reported memory loss or periods of confusion. One study reported a decrease in risk at the fifth quintile whereas the second study found no association.

Laboratory animal studies have evaluated neurotoxicity using the functional observation battery (FOB) and motor activity assessment. No effects were observed on adult rats and mice at serum concentrations $\geq$~600-fold higher than the 'reference' serum concentration. Potential neurological effects have also been evaluated in rat pups using these same evaluation tools. No effects were observed at serum concentrations up to ~800-fold higher than the 'reference' serum concentration. A neurotoxicity evaluation following a single oral dose to neonatal animals has also been conducted. See footnote #3 above.

Resources Consulted During Review:

AAP. (2012). (American Academy of Pediatrics) Breastfeeding and the Use of Human Milk. Pediatrics, 129(3).

ATSDR. (2018). Agency for Toxic Substances and Disease Registry. Toxicological Profile for Perfluoroalkyls. Draft for Public Comment. June 2018.
https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=1117&tid=237 .

ATSDR. (2018b). (Agency for Toxic Substances and Disease Registry) Minimal Risk Levels (MRLs) and Environmental Media Evaluation Guides (EMEGs) for PFAS. Retrieved from https://www.atsdr.cdc.gov/pfas/mrl_pfas.html .

Australian Department of Health And Ageing NICNAS. (2005). Existing Chemical Hazard Assessment Report. Potassium Perfluorobutane Sulfonate.

Axelstad, M. (2019). [Personal Communication Re: Numerical Data for Figure 3A-E of Toxicological Science 2018 Publication.].

Beesoon, S., GM Webster, M Shoeib, T Harner, JP Benskin, JW Martin. (2011). Isomer Profiles of Perfluorochemicals in Matched Maternal, Cord, and House Dust Samples: Manufacturing Sources and Transplacental Transfer. Environmental Health Perspectives, 119, 1659-1664.

Bijland, S., PCN Rensen, EJ Pieterman, ACE Mass, JW van der Hoorn, MJ van Erk, KW van Dijk, SC Chang, DJ Ehresman, JL Butenhoff, HMG Princen. (2011). Perfluoroalkyl Sulfonates Cause Alkyl Chain Length-Dependent Hepatic Steatosis and Hypolipidemia Mainly by Impairing Lipoprotein Production in APOE*3-Leiden CETP Mice. Toxicological Sciences, 123(1), 290-303.

Blystone, C. (2019). [Personal Communication. Use of NTP data tables and study protocol (January 2019 email exchange).].

Butenhoff, J., SC Chang, DJ Ehresman, RG York. (2009). Evaluation of potential reproductive and developmental toxicity of potassium perfluorohexanesulfonate in Sprague Dawley rats. Reproductive Toxicology, 27, 331-341.

Cariou, R., B Veyrand, A Yamada, A Berrebi, D Zalko, S Durand, C Pollono, P Marchand, J-C Leblanc, J-P Antignac, B Le Bizec. (2015). Perfluoroalkyl acid (PFAA) levels and profiles in breast milk, maternal and cord serum of French women and their newborns. Environment International, 84, 71-81.

CDC (Center for Disease Control). National Report on Human Exposure to Environmental Chemicals. Biomonitoring Data Tables for Environmental Chemicals. Retrieved February 2019 from https://www.cdc.gov/exposurereport/data_tables.html

CDC. (2016). Centers for Disease Control and Prevention. Breastfeeding Report Card. United States 2016. Retrieved from https://www.cdc.gov/breastfeeding/pdf/2016breastfeedingreportcard.pdf

Chang, S., JL Butenhoff, GA Parker, PS Coder, JD Zitsow, RM Krisko, JA Bjork, KB Wallace, JG Seed. (2018). Reproductive and developmental toxicity of potassiumperfluorohexanesulfonate in CD-1 mice. Reproductive Toxicology, 78, 150-168.

Chen, F., S Yin, BC Kelly, W Liu. (2017). Isomer-Specific Transplacental Transfer of Perfluoroalkyl Acids: Results from a Survey of Paired Maternal, Cord Sera, and Placentas. Environmental Science & Technology, 51, 5756-5763.

Das, K., CR Wood, MT Lin, AA Starkov, C Lay, KB Wallace, JC Corton, BD Abbott. (2017). Perfluoroalkyl acids-induced liver steatosis: Effects on genes controlling lipid homeostasis. Toxicology, 378, 37-52.

Donahue, S., KP Kleinman, MW Gillman, E Oken. (2010). Trends in Birth Weight and Gestational Length Among Singleton Term Births in the United States, 1990-2005. Obstetrics and Gynecology, 115((2 (pt. 1)), 357-364.

ECHA. (2017). (European Chemical Agency) Member State Committee Support Document for Identification of Perfluorohexane-1-sulphonic Acid and Its Salts as Substances of Very High Concern Because of Their VPVB1 (Article 57 E) Properties. Retrieved from https://echa.europa.eu/documents/10162/13638/svhc_msc_support_document_pfhxs_4867_en.pdf/1f48372e-97dd-db9f-4335-8cec7ae55eee

Felter, S., GP Daston, SY Euling, AH Piersma, MS Tassinari. (2015). Assessment of health risks resulting from early-life exposures: Are current chemical toxicity testing protocols and risk assessment methods adequate? Critical Reviews in Toxicology, 45(3), 219-244.

FRANZ. (2017). (Food Standards Australia New Zealand) Hazard Assessment Report - Perfluorooctane Sulfonate (PFOS), Perfluorooctanoic Acid (PFOA), Perfluorohexane Sulfonate (PFHxS). Retrieved from http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-pfas-hbgv.htm

Friis-Hansen, B. (1961). Body Water Compartments in Children: Changes During Growth and Related Changes in Body Composition. Pediatrics, 28(2), 169-181.

Fromme, H., C Mosch, M Morovitz, I Alba-Alejandre, S Boehmer, M Kiranoglu, F Faber, I Hannibal, O Genzel-Boroviczeny, B Koletzko, W Volkel. (2010). Pre- and Postnatal Exposure to Perfluorinated Compounds (PFCs). Environmental Science & Technology, 44, 7123-7129.

Fu, J., Y Gao, T Wang, Y Liang, G Qu, B Yuan, Y Wang, A Zhang, G Jiang. (2016). Occurrence, temporal trends, and half-lives of perfluoroalkyl acids (PFAAs) in occupational workers in China. Scientific Reports, 6:38039.

Goeden, HM., CW Greene, JA Jacobus. (2019). A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. Journal of Exposure Science & Environmental Epidemiology, https://doi.org/10.1038/s41370-018-0110-5 .

Gomis, M., R Vestergren, M MacLeod, JF Mueller, IT Cousins. (2017). Historical human exposure to perfluoroalkyl acids in the United States and Australia reconstructed from biomonitoring data using population-based pharmacokinetic modelling. Environment International, 108, 92-102.

Gutzkow, K., LS Haug, C Thomsen, A Sabaredzovic, G Becher, G Brunborg. (2012). Placental transfer of perfluorinated compounds is selective - A Norwegian Mother and Child sub-cohort study. International Journal of Hygiene and Environmental Health, 215, 216-219.

Harris, M., SL Rifas-Shiman, AM Calafat, X Ye, AM Mora, TF Webster, E Oken, SK Sagiv. (2017). Predictors of Per- and Polyfluoroalkyl Substance (PFAS) Plasma Concentrations in 6–10 Year Old American Children. Environmental Science & Technology, 51(9), 5193-5204.

Hoberman, A., RG York. (2003). Final Report. Argus Research Protocol 418-028. Oral (gavage) combined repeated dose toxicity study of T-7706 with the reproduction/developmental toxicity screening test.

Interstate Technology and Regulatory Council (ITRC). (2018). Regulations, Guidance, and Advisories. Section 4 Tables (Excel). September 15, 2018. Retrieved from https://pfas-1.itrcweb.org/fact-sheets/

Karrman, A., I Ericson, B van Bavel, PO Darnerud, M Aune, A Glynn, S Lignell, G Lindstrom. (2007). Exposure of Perfluorinated Chemicals through Lactation: Levels of Matched Human Milk and Serum and a Temporal Trend, 1996-2004, in Sweden. Environmental Health Perspectives, 115, 226-230.

Kato, K., L-Y Wong, A Chen, C Dunbar, GM Webster, BP Lanphear, AM Calafat. (2014). Changes in Serum Concentrations of Maternal Poly- and Perfluoroalkyl Substances over the Course of Pregnancy and Predictors of Exposure in a Multiethnic Cohort of Cincinnati, Ohio Pregnant Women during 2003-2006. Environmental Science & Technology, 48, 9600-9608.

Kim, S., K Choi, K Ji, J Seo, Y Kho, J Park, S Kim, S Park, I Hwang, J Jeon, H Yang, JP Giesy. (2011a). Trans-Placental Transfer of Thirteen Perfluorinated Compounds and Relations with Fetal Thyroid Hormones. Environmental Science & Technology, 45, 7465-7472.

Kim, S.-K., KT Lee, CS Kang, L Tao, K Kannan, KR Kim, CK Kim, JS Lee, PS Park, YW Yoo, JY Ha, YS Shin, JH Lee. (2011b). Distribution of perfluorochemicals between sera and milk from the same mothers and implications for prenatal and postnatal exposures. Environmental Pollution, 159, 169-174.

Kim, S., SH Heo, DS Lee, IG Hwang, YB Lee, HY Cho. (2016). Gender differences in pharmacokinetics and tissue distribution of 3 perfluoroalkyl and polyfluoroalkyl substances in rats. Food and Chemical Toxicology, 97, 243-255.

Kudo, N. (2015). Chapter 6. Metabolism and Pharmacokinetics. In J. C. DeWitt (Ed.), Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances. Switzerland: Humana Press, Springer International Publishing.

Lee, Y., M-K, Kim, J Bae, J-H Yang. (2013). Concentrations of perfluoroalkyl compounds in maternal and umbilical cord sera and birth outcomes in Korea. Chemosphere, 90, 1603-1609.

Li, Y., T Fletcher, D Mucs, K Scott, CH Lindh, P Tallving, K Jakobsson. (2018). Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occupational and Environmental Medicine, 75, 46-51.

Liu, J., J Li, Y Liu, HM Chan, Y Zhao, Z Cai, Y Wu. (2011). Comparison on gestation and lactation exposure of perfluorinated compounds for newborns. Environment International, 37, 1206-1212.

Manzano-Salgado, C., M Casas, MJ Lopez-Espinosa, F Ballester, M Basterrechea, JO Grimalt, AM Jimenez, T Kraus, T Schettgen, J Sunyer, M Vrijheid. (2015). Transfer of perfluoroalkyl substances from mother to fetus in a Spanish birth cohort. Environmental Research, 142, 471-478.

MDH. (2008). Minnesota Department of Health. Statement of Need and Reasonableness (SONAR) in the Matter of Proposed Rules Relating to Health Risk Limits of Groundwater. https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2.

MDH. (2015). Minnesota Department of Health. Environmental Health & Biomonitoring Advisory Panel June 9, 2015 Meeting Background Materials. Retrieved from https://www.health.state.mn.us/communities/environment/biomonitoring/docs/2015Junematerials.pdf.

Needham, L., P Grandjean, B Heinzow, PJ Jorgensen, F Nielsen, DG Patterson Jr, A Sjodin, WE Turner, P Weihe. (2011). Partition of Environmental Chemicals between Maternal and Fetal Blood and Tissues. Environmental Science & Technology, 45, 1121-1126.

Nelson, J. (2018b). [Personal Communication - Nov 2017 draft manuscript tables regarding MDH MN (East Metro) PFC biomonitoring project data].

New Hampshire Department of Environmental Services. (2019). Summary Report on the Development of Maximum Contaminant Levels and Ambient Groundwater Quality Standards for PFOS, PFOA, PFNA, and PFHxS.

NTP. (2018). National Toxicology Program. TOX-96: Toxicity Report Tables and Curves for Short-term Studies: Perfluorinated Compounds: Sulfonates. Retrieved from https://tools.niehs.nih.gov/cebs3/views/?action=main.dataReview&bin_id=3874 .

Olsen, G., JM Burris, DJ Ehresman, JW Froehlich, AM Seacat, JL Butenhoff, LR Zobel. (2007). Half-life of Serum Elimination of Perfluorooctanesulfonate, Perfluorohexanesulfonate, and Perfluorooctanoate in Retired Fluorochemical Production Workers. Environmental Health Perspectives, 115, 1298-1305.

Ramhøj, L., U Hass, J Boberg, M Scholze, S Christiansen, F Nielsen, M Axelstad. (2018). Perfluorohexane Sulfonate (PFHxS) and a Mixture of Endocrine Disrupters Reduce Thyroxine Levels and Cause Antiandrogenic Effects in Rats. Toxicological Sciences, 163(2), 579-591.

RIVM. (2018). (National Institute for Public Health and the Environment) Mixture exposure to PFAS: A Relative Potency Factor approach. RIVM report 2018-0070. Retrieved from https://rivm.openrepository.com/handle/10029/622164 .

Schecter, A., N Malik-Bass, AM Calafat, K Kato, JA Colacino, TL Gent, LS Hynan, TR Harris, S Malla, L Birnbaum. (2012). Polyfluoroalkyl Compounds in Texas Children from Birth through 12 Years of Age. Environmental Health Perspectives, 120, 590-594.

Sundstrom, M., SC Chang, PE Noker, GS Gorman, JA Hart, DJ Ehresman, A Bergman, JL Butenhoff. (2012). Comparative pharmacokinetics of perfluorohexanesulfonate (PFHxS) in rats, mice, and monkeys. Reproductive Toxicology, 33, 441-451.

USEPA. (2000). US Environmental Protection Agency (EPA). Office of Water. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health. EPA-822-B-00-004. October 2000. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/20003D2R.PDF?Dockey=20003D2R.PDF .

USEPA. (2011). US Environmental Protection Agency - National Center for Environmental Assessment. Exposure Factors Handbook. 2011 Edition. Retrieved from https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252 .

USEPA. (2016). US Environmental Protection Agency - Office of Water. Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS). Retrieved from https://www.epa.gov/sites/production/files/2016-05/documents/pfos_health_advisory_final-plain.pdf.

USEPA. (2018). (US Environmental Protection Agency) Public Comment Draft - Human Health Toxicity Values for Perfluorobutane Sulfonic Acid and Related Compound Potassium Perfluorobutane Sulfonate.

U.S. Environmental Protection Agency (EPA) (2019). Exposure Factors Handbook Chapter 3 Update 2019. https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Verner, M.-A., F Ngueta, ET Jensen, J Fromme, W Volkel, UC Nygaard, B Granum, MP Longnecker. (2016). A Simple Pharmacokinetic Model of Prenatal and Postnatal Exposure to Perfluoroalkyl Substances (PFASs). Environmental Science & Technology, 50, 978-986.

Wang, Y., W Han, C Wang, Y Zhou, R Shi, EC Bonefeld-Jorgensen, Q Yao, T Yuan, Y Gao, J Zhang, Y Tian. (2018). Efficiency of maternal-fetal transfer of perfluoroalkyl and polyfluoroalkyl substances. Environmental Science and Pollution Research, 26(3), 2691-2698.

Weiss, J., PL Andersson, MH Lamoree, PEG Leonards, SPJ van Leeuwen, T Hamers. (2009). Competitive Binding of Poly- and Perfluorinated Compounds to the Thyroid Hormone Transport Protein Transthyretin. Toxicological Sciences, 109(2), 206-216.

Wolf, C., ML Takacs, JE Schmid, C Lau, BD Abbott. (2008). Activation of Mouse and Human Peroxisome Proliferator - Activated Receptor Alpha by Perfluoroalkyl Acids of Different Functional Groups and Chain Lengths. Toxicological Sciences, 106(1), 162-171.

Worley, R., SM Moore, BC Tierney, X Ye, AM Calafat, S Campbell, MB Woudneh, J Fisher. (2017). Per- and polyfluoroalkyl substances in human serum and urine samples from a residentially exposed community. Environment International, 106, 135-143.

Wu, X., DH Bennett, AM Calafat, K Kato, M Stryner, E Andersen, RE Moran, DJ Tancredi, NS Tulve, I Hertz-Picciotto. (2015). Serum concentrations of perfluorinated compounds (PFC) among selected populations of children and adults in California. Environmental Research, 136, 264-273.

Yang, L., J Li, J Lai, H Luan, Z Cai, Y Wang, Y Zhao, Y Wu. (2016a). Placental Transfer of Perfluoroalkyl Substances and Associations with Thyroid Hormones: Bejing Prenatal Exposure Study. Scientific Reports, 6, 21699.

Ye, X., K Kato, LY Wong, T Jia, A Kalathil, J Latremouille, AM Calafat. (2018). Per- and polyfluoroalkyl substances in sera from children 3 to 11 years of age participating in the National Health and Nutrition Examination Survey 2013-2014. International Journal of Hygiene and Environmental Health, 221, 9-16.

Zhang, T., H Sun, Y Lin, X Qin, Y Zhang, X Geng, K Kannan. (2013). Distribution of Poly- and Perfluoroalkyl Substances in Matched Samples from Pregnant Women and Carbon Chain Length Related Maternal Transfer. Environmental Science & Technology, 47, 7974-7981.

Toxicological Summary for: Perfluorohexanoate

CAS: **92612-52-7 (anion)**
     307-24-4 (free acid)
     21615-47-4 (ammonium salt)
     2923-26-4 (sodium salt)

Synonyms: PFHxA; Perfluorohexanoic acid

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

Short-term Non-Cancer Health-Based Value (nHBV$_{Short-term}$) = 0.2 µg/L

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

$$= \frac{(0.00032 \text{ mg/kg-d) x } (0.2)^* \text{ x } (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

= 0.22 rounded to **0.2 µg/L**

*MDH utilizes the EPA Exposure Decision Tree (EPA, 2000) to select appropriate RSCs. For PFHxA, an RSC of 0.2 was used for all exposure durations due to concerns about infant exposures from house dust and diet, potential exposures from the breakdown of precursor chemicals, and uncertainty about infant exposure levels.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.0958/300 = 0.00032 mg/kg-d (laboratory animal – SD rats)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	25.9 mg/kg-d (administered dose BMDL$_{1SD}$, NTP 2019)
Dose Adjustment Factor (DAF):	Chemical and Study-Specific Toxicokinetic Adjustment Half-life$_{MaleRat}$/Half-life$_{Human}$ = 2.87 hrs/ 768 hrs = 0.0037 (based on Dzierlenga et al 2020, for male rats, and Russell et al 2013, for humans)
Human Equivalent Dose (HED):	POD x DAF = 25.9 mg/kg-d x 0.0037 = 0.0958 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (e.g., lack of a 2-generation study, lack of thyroid hormone measurements or neurodevelopmental toxicity in young offspring in a development/reproductive study, and lack of immunotoxicity studies as well as evidence of pup body weight effects near the selected POD)

Critical effect(s):	Decreased total T4
Co-critical effect(s):	Decreased pup body weight
Additivity endpoint(s):	Developmental, Thyroid [E]

Subchronic Non-Cancer Health-Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 0.2 µg/L

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

$$= \frac{(0.00015 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 0.405 \text{ rounded to } 0.4 \text{ µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.045/300 = 0.00015 mg/kg-d (laboratory animal – SD rats)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	22.5 mg/kg-d (administered dose BMDL$_{10\%}$, Loveless et al 2009)
Dose Adjustment Factor (DAF):	Chemical and Study-Specific Toxicokinetic Adjustment Half-life$_{MaleRat}$/Half-life$_{Human}$ = 1.5 hrs/ 768 hrs = 0.0020 (based on Gannon et al 2011, for male rats, and Russell et al 2013, for humans)
Human Equivalent Dose (HED):	POD x DAF = 22.5 mg/kg-d x 0.0020 = 0.045 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (e.g., lack of a 2-generation study, lack of thyroid hormone measurements or neurodevelopmental toxicity in young offspring in a development/reproductive study, and lack of immunotoxicity studies as well as evidence of pup body weight effects near the selected POD)
Critical effect(s):	Nasal epithelium degeneration
Co-critical effect(s):	Decreased bilirubin
Additivity endpoint(s):	Hepatic (liver) system, Respiratory system

The Subchronic nHBV must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 0.2 µg/L. Additivity endpoints: Developmental, Thyroid [E]

Chronic Non-Cancer Health-Based Value (nHBV$_{Chronic}$) = nHBV$_{Short-term}$ = 0.2 µg/L

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

$$= \frac{(0.00015 \text{ mg/kg-d})^{***} \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 0.67 \text{ rounded to } 0.7 \text{ µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

***Reference Dose/Concentration: The calculated Chronic RfD was higher in magnitude than the Subchronic RfD. Therefore, the Chronic RfD is set to the Subchronic RfD, see information above for details on the RfD derivation.

The Chronic nHBV must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 0.2 µg/L. Additivity endpoints: Developmental, Thyroid [E]

Cancer Health-Based Value (cHBV) = Not Applicable

Volatile: Nonvolatile

Summary of Guidance Value History:
There are no previous guidance values for PFHxA. The 2021 derived values represent new guidance.

Additional Information on the MDH TK model (Goeden et al., 2019):
PFHxA water guidance was calculated using MDH's standard equations shown above. The Goeden et al. (2019) toxicokinetic model previously used to calculate guidance for PFOA, PFOS, and PFHxS was evaluated during this review because PFHxA crosses the placenta and is found in breastmilk. The toxicokinetic data that the model requires are quite limited for PFHxA (e.g., no information on breastmilk:maternal serum ratio, limited information on half-life). As a result, the model was not used quantitatively to derive PFHxA water guidance. However, the PFHxA modelling results, using the best available information for model parameters, indicate that water guidance of 0.2 µg/L developed using the standard equation is adequately protective.

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?	Yes	No	Yes	Yes	Yes

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Effects observed?	Yes[1]	–[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1]A significant positive correlation between PFHxA exposure and TGAb (thyroglobin antibodies) and TMAb (thyroid microsomal antibody) was reported in an epidemiological study. Short-term studies in adult laboratory animals identified decreased serum thyroid hormone levels. These effects form the basis of the short-term RfD. A database uncertainty factor (DB UF) was incorporated into the RfD derivation, in part, to address the lack of thyroid evaluations in developing animals. Thyroid cellular hypertrophy in adult animals was also reported, but at doses ~3,000-fold higher than the Subchronic/Chronic RfD.

[2] No immunotoxicity studies have been conducted. Three general toxicity studies reported decreased thymus weight at dose levels ≥5800-fold higher than the Subchronic/Chronic RfD. At slightly higher dose levels atrophy and necrosis in spleen and thymus as well as a depletion of lymph nodes were observed.

[3]Decreases in pup body weight and increased pup mortality have been reported. These effects were observed at levels ~1500-fold higher than the Subchronic/Chronic RfD. A database uncertainty factor (DB UF) was incorporated into the RfD derivation, in part, to address the lack of a two-generation study.

[4] Significant decreases in maternal body weight gain during gestation and complete litter loss were reported at doses >3,000-fold higher than the Subchronic/Chronic RfD. Decreases in sperm count and seminiferous tubule spermatid retention were reported at doses 25,000-fold higher than the Subchronic/Chronic RfD.

[5] Acute studies reported ataxia and abnormal gait at dose levels ~1,000-fold higher than the Subchronic/Chronic RfD. No neurological changes, based on functional observation battery and locomotor activity evaluations, were reported in adult rats following 90 days of exposure at levels up to ~5,000-fold higher than the Subchronic/Chronic RfD.

Resources Consulted During Review:

Anderson, J. K., Luz, A. L., Goodrum, P., & Durda, J. (2019). Perfluorohexanoic acid toxicity, part II: Application of human health toxicity value for risk characterization. *Regul Toxicol Pharmacol, 103*, 10-20. doi:10.1016/j.yrtph.2019.01.020

ATSDR. (2021). *Agency for Toxic Substances and Disease Registry. Toxicological Profile for Perfluoroalkyls.* Retrieved from https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf

Bil W, M. Z., S Fragki, J Lijzen, E Verbruggen, B Bokkers. (2021). Risk Assessment of Per- and Polyfluoroalkyl Substance Mixtures: A Relative Potency Factor Approach. *Environ Toxicol and Chemistry, 40*(3), 859-870. doi:DOI: 10.1002/etc.4835

Bischel, H. N., Macmanus-Spencer, L. A., Zhang, C., & Luthy, R. G. (2011). Strong associations of short-chain perfluoroalkyl acids with serum albumin and investigation of binding mechanisms. *Environ Toxicol Chem, 30*(11), 2423-2430. doi:10.1002/etc.647

Cai, D., QQ Li, C Chu, SZ Wang, YT Tang, AA Appleton, RL Qiu, BY Yang, LW Hu, GH Dong, XW Zeng. (2020). High trans-placental transfer of perfluoroalkyl substances alternatives in the matched

maternal-cord blood serum: Evidence from a birth cohort study. *Science of the Total Environment, 705*, 135885. doi:https://doi.org/10.1016/j.scitotenv.2019.135885

Chengelis, C. P., Kirkpatrick, J. B., Myers, N. R., Shinohara, M., Stetson, P. L., & Sved, D. W. (2009). Comparison of the toxicokinetic behavior of perfluorohexanoic acid (PFHxA) and nonafluorobutane-1-sulfonic acid (PFBS) in cynomolgus monkeys and rats. *Reprod Toxicol, 27*(3-4), 400-406. doi:10.1016/j.reprotox.2009.01.013

Chengelis, C. P., Kirkpatrick, J. B., Radovsky, A., & Shinohara, M. (2009). A 90-day repeated dose oral (gavage) toxicity study of perfluorohexanoic acid (PFHxA) in rats (with functional observational battery and motor activity determinations). *Reprod Toxicol, 27*(3-4), 342-351. doi:10.1016/j.reprotox.2009.01.006

Cordner, A., De La Rosa, V. Y., Schaider, L. A., Rudel, R. A., Richter, L., & Brown, P. (2019). Guideline levels for PFOA and PFOS in drinking water: the role of scientific uncertainty, risk assessment decisions, and social factors. *Journal of Exposure Science & Environmental Epidemiology*. doi:10.1038/s41370-018-0099-9

Dong, G. H., Tung, K. Y., Tsai, C. H., Liu, M. M., Wang, D., Liu, W., . . . Chen, P. C. (2013). Serum polyfluoroalkyl concentrations, asthma outcomes, and immunological markers in a case-control study of Taiwanese children. *Environ Health Perspect, 121*(4), 507-513. doi:10.1289/ehp.1205351

Dzierlenga, A. L., Robinson, V. G., Waidyanatha, S., DeVito, M. J., Eifrid, M. A., Gibbs, S. T., . . . Blystone, C. R. (2020). Toxicokinetics of perfluorohexanoic acid (PFHxA), perfluorooctanoic acid (PFOA) and perfluorodecanoic acid (PFDA) in male and female Hsd:Sprague dawley SD rats following intravenous or gavage administration. *Xenobiotica, 50*(6), 722-732. doi:10.1080/00498254.2019.1683776

European Chemicals Agency. (2019a). *Annex XV Restriction Report, Undecafluorohexanoic acid (PFHxA), its salts and related substances*. Retrieved from https://echa.europa.eu/documents/10162/c4e04484-c989-733d-33ed-0f023e2a200e

European Chemicals Agency. (2019b). *Annex XV Restriction Report, Undecafluorohexanoic acid (PFHxA), its salts and related substances - Appendices and Supporting information*. Retrieved from https://echa.europa.eu/documents/10162/cc64c9fd-0987-854e-7ac7-cdf829b938dc

Fan, H., Ducatman, A., & Zhang, J. (2014). Perfluorocarbons and Gilbert syndrome (phenotype) in the C8 Health Study Population. *Environ Res, 135*, 70-75. doi:10.1016/j.envres.2014.08.011

Friis-Hansen, B. (1961). Body Water Compartments in Children: Changes During Growth and Related Changes in Body Composition. *Pediatrics, 28*(2), 169-181.

Gannon, S. A., Johnson, T., Nabb, D. L., Serex, T. L., Buck, R. C., & Loveless, S. E. (2011). Absorption, distribution, metabolism, and excretion of [1-(1)(4)C]-perfluorohexanoate ([(1)(4)C]-PFHx) in rats and mice. *Toxicology, 283*(1), 55-62. doi:10.1016/j.tox.2011.02.004

Gao K, T. Z., X Liu, J Fu, J Zhang, J Fu, L Wang, A Zhang, Y Liang, M Song, G Jiang,. (2019). Prenatal Exposure to Per- and Polyfluoroalkyl Substances (PFASs) and Association between the Placental Transfer Efficiencies and Dissociation Constant of Serum Proteins–PFAS Complexes. *Environmental Science and Technology, 53*, 6529-6538. doi:DOI: 10.1021/acs.est.9b00715

Goeden, H. M., Greene, C. W., & Jacobus, J. A. (2019). A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. *Journal of Exposure Science & Environmental Epidemiology, https://doi.org/10.1038/s41370-018-0110-5*.

Han, X., Nabb, D. L., Russell, M. H., Kennedy, G. L., & Rickard, R. W. (2012). Renal elimination of perfluorocarboxylates (PFCAs). *Chem Res Toxicol, 25*(1), 35-46. doi:10.1021/tx200363w

HDOH. (2021). *Hawaii Department of Health. Interim Soil and Water Environmental Action Levels (EALs) for Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS).* Retrieved from https://health.hawaii.gov/heer/guidance/ehe-and-eals/

ITRC. (Interstate Technology and Regulatory Council) Regulations, Guidance, and Advisories. Section 4 Tables (Excel). Last Update February 2021. Retrieved from https://pfas-1.itrcweb.org/fact-sheets/

Iwai, H. (2011). Toxicokinetics of ammonium perfluorohexanoate. *Drug Chem Toxicol, 34*(4), 341-346. doi:10.3109/01480545.2011.585162

Iwai, H., & Hoberman, A. M. (2014). Oral (Gavage) Combined Developmental and Perinatal/Postnatal Reproduction Toxicity Study of Ammonium Salt of Perfluorinated Hexanoic Acid in Mice. *Int J Toxicol, 33*(3), 219-237. doi:10.1177/1091581814529449

Iwai, H., Hoberman, A. M., Goodrum, P. E., Mendelsohn, E., & Anderson, J. K. (2019). Addendum to Iwai and Hoberman (2014)-Reassessment of Developmental Toxicity of PFHxA in Mice. *Int J Toxicol, 38*(3), 183-191. doi:10.1177/1091581819837904

Jin H, L. M., J Xie, M Zhao, X Bai, J Wen, T Shen, P Wu,. (2020). Poly- and perfluoroalkyl substance concentrations in human breast milk and their associations with postnatal infant growth. *Science of the Total Environment, 713*, 136417. doi:https://doi.org/10.1016/j.scitotenv.2019.136417

Kang H, K. C., HS Lee, DH Kim, NY Park, S Kim, Y Kho,. (2016). Elevated levels of short carbon-chain PFCAs in breast milk among Korean women: Current status and potential challenges. *Environmental Research, 148*, 351-359. doi:http://dx.doi.org/10.1016/j.envres.2016.04.017

Klaunig, J. E., Shinohara, M., Iwai, H., Chengelis, C. P., Kirkpatrick, J. B., Wang, Z., & Bruner, R. H. (2015). Evaluation of the chronic toxicity and carcinogenicity of perfluorohexanoic acid (PFHxA) in Sprague-Dawley rats. *Toxicol Pathol, 43*(2), 209-220. doi:10.1177/0192623314530532

Li J, D. C., C Chu, Q Li, Y Zhou, L Hu, B Yang, G Dong, X Zeng, D Chen,. (2020). Transplacental Transfer of Per- and Polyfluoroalkyl Substances (PFASs): Differences between Preterm and Full-Term Deliveries and Associations with Placental Transporter mRNA Expression. *Environmental Science and Technology, 54*, 5062-5070. doi:https://dx.doi.org/10.1021/acs.est.0c00829

Li Y., Cheng, Y., Xie, Z., & Zeng, F. (2017). Perfluorinated alkyl substances in serum of the southern Chinese general population and potential impact on thyroid hormones. *Sci Rep, 7*, 43380. doi:10.1038/srep43380

Loveless, S. E., Slezak, B., Serex, T., Lewis, J., Mukerji, P., O'Connor, J. C., . . . Buck, R. C. (2009). Toxicological evaluation of sodium perfluorohexanoate. *Toxicology, 264*(1-2), 32-44. doi:10.1016/j.tox.2009.07.011

Luz, A. L., Anderson, J. K., Goodrum, P., & Durda, J. (2019). Perfluorohexanoic acid toxicity, part I: Development of a chronic human health toxicity value for use in risk assessment. *Regul Toxicol Pharmacol, 103*, 41-55. doi:10.1016/j.yrtph.2019.01.019

Ma D, Y. L., Y Liang, T Ruan, J Li, C Zhao, Y Wang, G Jiang,. (2021). A Critical Review on Transplacental Transfer of Per- and Polyfluoroalkyl Substances: Prenatal Exposure Levels, Characteristics, and Mechanisms. *Environmental Science and Technology*. doi:DOI: 10.1021/acs.est.1c01057

Michigan Science Advisory Workgroup. (2019). *HEALTH-BASED DRINKING WATER VALUE RECOMMENDATIONS FOR PFAS IN MICHIGAN.* Retrieved from

https://www.michigan.gov/documents/pfasresponse/Health-
Based_Drinking_Water_Value_Recommendations_for_PFAS_in_Michigan_Report_659258_7.p
df

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.

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from
https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.p
df

National Toxicology Program (NTP). (2019). 28-Day Evaluation of the Toxicity (C20613) of Perfluorohexanoic acid (PFHXA) (307-24-4) in Harlan Sprague-Dawley Rats Exposed via Gavage. Study tables retrieved from https://cebs.niehs.nih.gov/cebs/publication/TOX-97

Nilsson, H., Karrman, A., Rotander, A., van Bavel, B., Lindstrom, G., & Westberg, H. (2013a). Biotransformation of fluorotelomer compound to perfluorocarboxylates in humans. *Environ Int, 51*, 8-12. doi:10.1016/j.envint.2012.09.001

Nilsson, H., Karrman, A., Rotander, A., van Bavel, B., Lindstrom, G., & Westberg, H. (2013b). Professional ski waxers' exposure to PFAS and aerosol concentrations in gas phase and different particle size fractions. *Environ Sci Process Impacts, 15*(4), 814-822. doi:10.1039/c3em30739e

NOTOX Safety & Environmental Research. (2005). *Repeated Dose 90-Day Oral Toxicity Study with PFHA by Daily Gavage in the Rat Followed by a 28-Day Recovery Period*. Retrieved from

Perez, F., Nadal, M., Navarro-Ortega, A., Fabrega, F., Domingo, J. L., Barcelo, D., & Farre, M. (2013). Accumulation of perfluoroalkyl substances in human tissues. *Environ Int, 59*, 354-362. doi:10.1016/j.envint.2013.06.004

Poothong, S., Thomsen, C., Padilla-Sanchez, J. A., Papadopoulou, E., & Haug, L. S. (2017). Distribution of Novel and Well-Known Poly- and Perfluoroalkyl Substances (PFASs) in Human Serum, Plasma, and Whole Blood. *Environ Sci Technol, 51*(22), 13388-13396. doi:10.1021/acs.est.7b03299

Rice, P. A. (2015). C6-Perfluorinated Compounds: The New Greaseproofing Agents in Food Packaging. *Curr Environ Health Rep, 2*(1), 33-40. doi:10.1007/s40572-014-0039-3

Rice, P. A., Aungst, J., Cooper, J., Bandele, O., & Kabadi, S. V. (2020). Comparative analysis of the toxicological databases for 6:2 fluorotelomer alcohol (6:2 FTOH) and perfluorohexanoic acid (PFHxA). *Food Chem Toxicol, 138*, 111210. doi:10.1016/j.fct.2020.111210

Russell, M. H., Nilsson, H., & Buck, R. C. (2013). Elimination kinetics of perfluorohexanoic acid in humans and comparison with mouse, rat and monkey. *Chemosphere, 93*(10), 2419-2425. doi:10.1016/j.chemosphere.2013.08.060

U.S. Environmental Protection Agency (EPA). Chemistry Dashboard. Retrieved from
https://comptox.epa.gov/dashboard

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

USEPA. (2011). *US Environmental Protection Agency - National Center for Environmental Assessment. Exposure Factors Handbook. 2011 Edition.* Retrieved from
https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2019). *Exposure Factors Handbook Chapter 3 Update 2019*. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

US EPA. (2021). *(US Environmental Protection Agency) Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA (anionic and acid forms) IRIS Assessments. CASRN 335-76-2 (PFDA); CASRN 375-95-1 (PFNA); CASRN 307-24-4 (PFHxA); CASRN 355-46-4 (PFHxS); and CASRN 375-22-4 (PFBA). Supplemental Information—Appendix A. Update.*

WIL Research Laboratories LLC. (2005). *A Combined 28-Day Repeat Dose Oral Toxicity Study with the Reproductive/Developmental Toxicity Screening Test of Perfluorohexanoic acid and 1H, 1H, 2H, 2H-Tridecafluoro-1-octanol in Rats, with recovery*. Retrieved from https://www.agc-chemicals.com/file.jsp?id=file/PFHxA-3.pdf

Wisconsin Department of Health Services. (2020). Recommended Groundwater Standards (Cycle 11). Retrieved from https://www.dhs.wisconsin.gov/water/gws-cycle11.htm

Wolf, C., ML Takacs, JE Schmid, C Lau, BD Abbott. (2008). Activation of Mouse and Human Peroxisome Proliferator - Activated Receptor Alpha by Perfluoroalkyl Acids of Different Functional Groups and Chain Lengths. *Toxicological Sciences, 106*(1), 162-171.

Xu, Y., Fletcher, T., Pineda, D., Lindh, C. H., Nilsson, C., Glynn, A., . . . Li, Y. (2020). Serum Half-Lives for Short- and Long-Chain Perfluoroalkyl Acids after Ceasing Exposure from Drinking Water Contaminated by Firefighting Foam. *Environ Health Perspect, 128*(7), 77004. doi:10.1289/EHP6785

Zhang T, H. S., Y Lin, X Qin, Y Zhang, X Geng, K Kannan,. (2013). Distribution of Poly- and Perfluoroalkyl Substances in Matched Samples from Pregnant Women and Carbon Chain Length Related Maternal Transfer. *Environmental Science and Technology, 47*, 7974-7981. doi:dx.doi.org/10.1021/es400937y

Zheng G, E. S., JC Dempsey, N Uding, V Chu, G Andres, S Sathyanarayana, A Salamova,. (2021). Per- and Polyfluoroalkyl Substances (PFAS) in Breast Milk: Concerning Trends for Current-Use PFAS. *Environmental Science and Technology, 55*(11), 7510-7520. doi:doi: 10.1021/acs.est.0c06978

Zhou, Y., Hu, L. W., Qian, Z. M., Chang, J. J., King, C., Paul, G., . . . Dong, G. H. (2016). Association of perfluoroalkyl substances exposure with reproductive hormone levels in adolescents: By sex status. *Environ Int, 94*, 189-195. doi:10.1016/j.envint.2016.05.018

Toxicological Summary for: Quinoline

CAS: **91-22-5**

Synonyms: Leukol, quinoleine, 1-Azanaphthalene, benzo[b]pyridine

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = Not Derived (Insufficient Data)

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = 4 µg/L

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

$$= \frac{(0.00079 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 3.51 \text{ rounded to } \textbf{4 µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 2.38/3000 = 0.00079 mg/kg-d (F344 rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	8.8 mg/kg-d (LOAEL, Matsumoto, 2018)
Dose Adjustment Factor (DAF):	Body weight scaling, default MDH 2017 and US EPA 2011
Human Equivalent Dose (HED):	POD x DAF = 8.8 mg/kg-d x 0.27 = 2.38 mg/kg-d
Total uncertainty factor (UF):	3000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for LOAEL to NOAEL, and 10 for database uncertainty (lack of reproductive, developmental, immunotoxicity, and neurotoxicity studies)
Critical effect(s):	Increased cellular changes in the liver and kidney including necrosis, increased hematopoiesis in the bone marrow of

both sexes, increased extramedullary hematopoiesis in the spleen of male rats.

Co-critical effect(s): Central degeneration of the liver, increased immature blood cells in the liver and lungs, increased erythropoiesis/hematopoiesis in the bone marrow, spleen, and liver, increased inflammatory infiltration in the lungs, and hemosiderin deposits in the kidney in both male and female mice; increased eosinophilic changes in the respiratory epithelium and increased Kupffer cell mobilization in the liver of female mice.

Additivity endpoint(s): Hematological (blood) system, Hepatic (liver) system, Renal (kidney) system, Respiratory system, Spleen

Cancer Health Based Value cHBV= 0.03 μg/L

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

$$= \frac{(1E\text{-}5) \times (1000\ \mu g/mg)}{[(3 \times 10^* \times 0.155\ L/kg\text{-}d^{**} \times 2) + (3 \times 3^* \times 0.040\ L/kg\text{-}d^{**} \times 14) + (3 \times 1^* \times 0.042\ L/kg\text{-}d^{**} \times 54)] / 70}$$

= 0.033 rounded to **0.03 μg/L**

*ADAF (Age-dependent adjustment factor): MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Cancer classification: Likely to be carcinogenic in humans EPA, 2001
Slope factor (SF): 3 (mg/kg-day)$^{-1}$ (hepatic hemangioendotheliomas or hemangiosarcomas in SD rats, Hirao, 1976)
Source of cancer slope factor (SF): EPA (2001)
Tumor site(s): Liver

Volatile: Yes (low)

Summary of Guidance Value History:
In 2019 MDH derived chronic noncancer and cancer guidance values for quinolone. Quinolone had not been evaluated by MDH previously. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates lowered the cHBV to 0.03 from 0.04 μg/L but did not change the chronic noncancer value.

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	No	No	Yes
Effects observed?	–	–[1]	–	–	No[2]

[1] No studies directly testing immunotoxicity have been conducted, however, one study did note endpoints associated with immune system activation in the liver and respiratory system. While these effects did not indicate immune system toxicity, little information is currently available. The lack of available information on how quinoline may impact the immune system is part of the rationale for selecting a 10-fold database uncertainty factor.

[2] One aspect of neurotoxicity has been investigated in a limited study, which reported that quinoline was not a dopaminergic neurotoxicant. Lack of more complete neurotoxicity testing also contributed to the selection of a database uncertainty factor of 10.

Resources Consulted During Review:

Asakura, S., Sawada, S., Sugihara, T., Daimon, H., & Sagami, F. (1997). Quinoline-induced chromosome aberrations and sister chromatid exchanges in rat liver. *Environ Mol Mutagen, 30*(4), 459-467.

Ashby, J., Mohammed, R., Lefevre, P. A., & Bandara, L. (1989). Quinoline: unscheduled DNA synthesis and mitogenesis data from the rat liver in vivo. *Environ Mol Mutagen, 14*(4), 221-228.

Australian Department of Health - National Industrial Chemicals Notification and Assessment Scheme (NICNAS). (2015). Quinolines: Human health tier II assessment. Retrieved from https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1560#cas-A_91-22-5

Booth, R. G., Castagnoli, N., Jr., & Rollema, H. (1989). Intracerebral microdialysis neurotoxicity studies of quinoline and isoquinoline derivatives related to MPTP/MPP+. *Neurosci Lett, 100*(1-3), 306-312.

California Environmental Protection Agency Office of Environmental Health Hazard Assessment. (1997). *Evidence on the Carcinogenicity of Quinolien and its Strong Acid Salts* Retrieved from https://oehha.ca.gov/proposition-65/chemicals/quinoline-and-its-strong-acid-salts.

Cohen, S. M., Storer, R. D., Criswell, K. A., Doerrer, N. G., Dellarco, V. L., Pegg, D. G., . . . Cook, J. C. (2009). Hemangiosarcoma in rodents: mode-of-action evaluation and human relevance. *Toxicol Sci, 111*(1), 4-18. doi:10.1093/toxsci/kfp131

Cowan, D. A., Damani, L. A., & Gorrod, J. W. (1978). Metabolic N-oxidation of 3-substituted pyridines: identification of products by mass spectrometry. *Biomed Mass Spectrom, 5*(9), 551-556. doi:10.1002/bms.1200050909

European Chemicals Agency (ECHA). (2018). Quinoline - Registration Dossier. Retrieved from https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/14335/7/1

Hamoud, M. A., Ong, T., Petersen, M., & Nath, J. (1989). Effects of quinoline and 8-hydroxyquinoline on mouse bone marrow erythrocytes as measured by the micronucleus assay. *Teratog Carcinog Mutagen, 9*(2), 111-118.

Hasegawa, R., Furukawa, F., Toyoda, K., Sato, H., Imaida, K., & Takahashi, M. (1989). Sequential analysis of quinoline-induced hepatic hemangioendothelioma development in rats. *Carcinogenesis, 10*(4), 711-716.

Health Canada. (2011). *Screening Assessment - Quinoline*. Retrieved from http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=202BA073-1.

Hirao, K., Shinohara, Y., Tsuda, H., Fukushima, S., & Takahashi, M. (1976). Carcinogenic activity of quinoline on rat liver. *Cancer Res, 36*(2 Pt 1), 329.

Iarc Monographs Vol 121 Group. (2018). Carcinogenicity of quinoline, styrene, and styrene-7,8-oxide. *Lancet Oncol*. doi:10.1016/S1470-2045(18)30316-4

International Agency for Research on Cancer (IARC). (2010). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 92: Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures. Retrieved from http://monographs.iarc.fr/ENG/Monographs/vol92/index.php

International Agency for Research on Cancer (IARC). (2018). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 121 (in press). Retrieved from https://monographs.iarc.fr/list-of-classifications-volumes/

LaVoie, E. J., Defauw, J., Fealy, M., Way, B. M., & McQueen, C. A. (1991). Genotoxicity of fluoroquinolines and methylquinolines. *Carcinogenesis, 12*(2), 217-220.

LaVoie, E. J., Dolan, S., Little, P., Wang, C. X., Sugie, S., & Rivenson, A. (1988). Carcinogenicity of quinoline, 4- and 8-methylquinoline and benzoquinolines in newborn mice and rats. *Food Chem Toxicol, 26*(7), 625-629.

LaVoie, E. J., Shigematsu, A., Adams, E. A., Rigotty, J., & Hoffmann, D. (1984). Tumor-initiating activity of quinoline and methylated quinolines on the skin of SENCAR mice. *Cancer Lett, 22*(3), 269-273.

LaVoie, E. J., Shigematsu, A., & Rivenson, A. (1987). The carcinogenicity of quinoline and benzoquinolines in newborn CD-1 mice. *Jpn J Cancer Res, 78*(2), 139-143.

Matsumoto, M., Kano, H., Suzuki, M., Noguchi, T., Umeda, Y., & Fukushima, S. (2018). Carcinogenicity of quinoline by drinking-water administration in rats and mice. *J Toxicol Sci, 43*(2), 113-127. doi:10.2131/jts.43.113

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

Novack, L., & Brodie, B. B. (1950). Quinoline and its transformation products found in urine. *J Biol Chem, 187*(2), 787-792.

Reigh, G., McMahon, H., Ishizaki, M., Ohara, T., Shimane, K., Esumi, Y., . . . Ninomiya, S. (1996). Cytochrome P450 species involved in the metabolism of quinoline. *Carcinogenesis, 17*(9), 1989-1996.

Saeki, K., Takahashi, K., & Kawazoe, Y. (1993). Metabolism of mutagenicity-deprived 3-fluoroquinoline: comparison with mutagenic quinoline. *Biol Pharm Bull, 16*(3), 232-234.

Shinohara, Y., Ogiso, T., Hananouchi, M., Nakanishi, K., Yoshimura, T., & Ito, N. (1977). Effect of various factors on the induction of liver tumors in animals by quinoline. *Gan, 68*(6), 785-796.

Smith, J. N. (1953). Studies in detoxication. 53. The glucuronic acid conjugation of hydroxyquinolines and hydroxpyridines in the rabbit. *Biochem J, 55*(1), 156-160.

Smith, J. N., & Williams, R. T. (1955). Studies in detoxication. 65. The metabolism of quinoline; new metabolites of quinoline, with observations on the metabolism of 3-, 5- and 6-hydroxyquinoline and 2:4-dihydroxyquinoline. *Biochem J, 60*(2), 284-290.

Suzuki, T., Miyata, Y., Saeki, K., Kawazoe, Y., Hayashi, M., & Sofuni, T. (1998). In vivo mutagenesis by the hepatocarcinogen quinoline in the lacZ transgenic mouse: evidence for its in vivo genotoxicity. *Mutat Res, 412*(2), 161-166.

Suzuki, T., Wang, X., Miyata, Y., Saeki, K., Kohara, A., Kawazoe, Y., . . . Sofuni, T. (2000). Hepatocarcinogen quinoline induces G:C to C:G transversions in the cII gene in the liver of lambda/lacZ transgenic mice (MutaMouse). *Mutat Res, 456*(1-2), 73-81.

Tada, M., Takahashi, K., Kawazoe, Y., & Ito, N. (1980). Binding of quinoline to nucleic acid in a subcellular microsomal system. *Chem Biol Interact, 29*(3), 257-266.

Takahashi, K., Kamiya, M., Sengoku, Y., Kohda, K., & Kawazoe, Y. (1988). Deprivation of the mutagenic property of quinoline: inhibition of mutagenic metabolism by fluorine substitution. *Chem Pharm Bull (Tokyo), 36*(11), 4630-4633.

U.S. Environmental Protection Agency - IRIS. (2001). *Toxicological Review of Quinoline (CASRN 91-22-5)*. Washington, D.C. Retrieved from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1004tr.pdf.

U.S. Environmental Protection Agency. (2018). Regional Screening Levels (RSLs) - Generic Tables (May 2018). Retrieved from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2014). Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. Risk Assessment Forum. Office of Research and Development. EPA/100/R-14/002F.

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3.

Uno, F., Tanaka, J., Ueda, M., Nagai, M., Fukumuro, M., Natsume, M., . . . Hayashi, M. (2015). Repeated-dose liver and gastrointestinal tract micronucleus assays for quinoline in rats. *Mutat Res Genet Toxicol Environ Mutagen, 780-781*, 51-55. doi:10.1016/j.mrgentox.2015.01.003

Weyand, E. H., Defauw, J., McQueen, C. A., Meschter, C. L., Meegalla, S. K., & LaVoie, E. J. (1993). Bioassay of quinoline, 5-fluoroquinoline, carbazole, 9-methylcarbazole and 9-ethylcarbazole in newborn mice. *Food Chem Toxicol, 31*(10), 707-715.

World Health Organization (WHO). (2005). Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for the Use of Data in

Dose/Concentration-Response Assessment. International Programme on Chemical Safety, IPCS Harmonization Project Document No. 2. WHO/IPCS/01.4, 1-96, Geneva, Switzerland.

Toxicological Summary for: Tetrachloroethylene

CAS: 127-18-4
Synonyms: Perchloroethene; Perchloroethylene; PERC; PCE

Acute Non-Cancer Health Based Value (nHBV_Acute) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value (nHBV_Short-term) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Based Value (nHBV_Subchronic) = 7 µg/L

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

$$= \frac{(0.0026 \text{ mg/kg/d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 7.0 rounded to **7 µg/L**

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	0.0026 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	2.6 mg/kg-d (EPA calculated the LOAEL based on route-to-route extrapolation of Cavalleri et al. 1994)
Human Equivalent Dose (MDH, 2011):	NA
Total uncertainty factor:	1000
Uncertainty factor allocation:	10 for intraspecies variability, 10 for LOAEL-to-NOAEL because results from residential studies suggest points of departure 3 to 15 times lower than the current LOAEL, and 10 for database uncertainty due to lack of data regarding immune, hematological, and developmental neurotoxicity
Critical effect(s):	Impacts on visual color domain – dyschromatopsia
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = nHBV$_{Subchronic}$ = 7 µg/L

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

$$= \frac{(0.0026 \text{ mg/kg/d}) \text{ x } (0.2)^* \text{ x } (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 11.5 rounded to 10 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	0.0026mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	2.6 mg/kg-d (EPA calculated the LOAEL based on route-to-route extrapolation of Cavalleri et al. 1994)
Human Equivalent Dose (MDH, 2011):	NA
Total uncertainty factor:	1000
Uncertainty factor allocation:	10 for intraspecies variability, 10 for LOAEL-to-NOAEL because results from residential studies suggest points of departure 3 to 15 times lower than the current LOAEL, and 10 for database uncertainty due to lack of data regarding immune and hematological effects and concerns about early life sensitivity
Critical effect(s):	Impacts on visual color domain – dyschromatopsia
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

The Chronic nHBV must be protective of the shorter duration exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Subchronic nHBV of 7 µg/L. Additivity endpoint: Nervous system.

Cancer Health Based Value (cHBV) = 4 µg/L

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

$$= \frac{(1E\text{-}5) \text{ x } (1000 \text{ µg/mg})}{[(0.025 \text{ x } 10^* \text{ x } 0.155 \text{ L/kg-d}^{**} \text{ x 2}) + (0.025 \text{ x } 3^* \text{ x } 0.040 \text{ L/kg-d}^{**} \text{ x 14}) + (0.025 \text{ x } 1^* \text{ x } 0.042 \text{ L/kg-d}^{**} \text{ x 54})] / 70}$$

= 4 µg/L

Cancer classification:	Likely to be carcinogenic in humans by all routes of exposure (EPA, 2012)
Slope factor:	2.49×10^{-2} (laboratory animal) (Japan Industrial Safety Association (JISA), 1993)
Source of slope factor:	Massachusetts Department of Environmental Protection 2014
Tumor site(s):	Leukemia

Volatile: Yes (high)

Summary of Guidance Value History:

The 2014 subchronic and chronic noncancer HBVs (7 µg/L) are new guidance. The 2014 cancer HBV (4 µg/L) is slightly lower than the 2009 Maximum Contaminant Level (MCL) based HRL of 5 µg/L due to: 1) new toxicity data, 2) application of age-dependent early life cancer sensitivity adjustment factors, 3) water intake rates that incorporate higher intakes during early life, and 4) rounding to one significant digit.

In 2021 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	Yes
Effects?	No[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] Few studies in humans or animals have examined altered hormones, and those that did generally found no adverse effects or were inconsistent.

[2] There have been reports indicating potential associations between tetrachloroethylene exposure and immune suppression, allergy/hypersensitivity, and autoimmune disease in humans. Several occupational and environmental studies in humans have reported a statistically significant association with exposure to tetrachloroethylene and leukemia. The most sensitive target for tetrachloroethylene-induced cancer is an immune cell type, mononuclear cell leukemia. Other immune effects, such as increases in white blood cells, lymphocytes, and natural killer cells, have been reported in studies that evaluated dry cleaning worker exposures. Effects on T-cells, natural killer cells, IgE and interleukin-4 suggest a potential for hypersensitivity but limited studies in children do not support associations between tetrachloroethylene and allergy or asthma. However, there have been limited case reports of occupational hypersensitivity. One residential study reported increased incidence of kidney/urinary tract and respiratory infections associated with drinking well water containing tetrachloroethylene. There have been a few occupational case reports and a few case-control studies reporting non-significant associations with sclerosis, an autoimmune disease. There is some evidence suggesting the developing immune system could be susceptible from exposure to tetrachloroethylene. There are very limited data for the evaluation of immune effects in animal studies, but mice exposed via inhalation had

increased susceptibility to respiratory infections and greater mortality from infection. The noncancer immune effects generally occur at high doses greater than 200-fold above the RfD, while the cancer effect of induction of mononuclear cell leukemia is the basis of the cancer HBV.

[3] There is not conclusive evidence from human studies that tetrachloroethylene exposure is linked to developmental effects. Many human studies that have evaluated the association between tetrachloroethylene and developmental effects have confounders and the evaluation of effects is complicated by exposures to solvent mixtures. Most animal studies that evaluated developmental effects did not show specific adverse effects on offspring. Developmental effects have been reported in animal inhalation toxicity studies at high levels of exposure (at 1500 mg/m^3 or higher). The effects include impacts on the developing nervous system (impacts on behavior, impacts on motor activity, and developmental delays) as well as decreased fetal body weight at exposures greater than 4500 mg/m^3 and increased malformations in pups at exposures greater than 1500 mg/m^3.

[4] The evidence of reproductive effects from exposure to tetrachloroethylene is limited from both human and animal studies. Human studies in dry cleaning and laundry workers evaluated reproductive outcomes and showed evidence of impacts on menstrual cycles, altered sperm quality, and longer time to pregnancy in workers exposed to tetrachloroethylene through inhalation. Decreased sperm quality and reduced fertilization of extracted oocytes was also reported in an animal inhalation study at high levels of exposure (12,000 mg/m3).

[5] The nervous system is the most sensitive target following exposure to tetrachloroethylene. The visual and cognitive domains are the most sensitive neurological endpoints and impacts on vision and cognition have been reported in several human occupational and environmental studies. Subtle visual effects including impacts on visual color domain – dyschromatopsia; impacts on visual cognitive domain and reaction times - decrements in visual reproduction, pattern memory, and pattern recognition, were identified as critical endpoints and are the basis of the non-cancer reference dose (0.0026 mg/kg-d) derived in MDH's evaluation of tetrachloroethylene. Acute CNS depression has been reported in children and adults following inhalation and ingestion of high levels of tetrachloroethylene.

References:

Agency for Toxic Substances and Disease Registry (ATSDR) - MRLs. (2009). Minimal Risk Levels for Hazardous Substances (MRLs).

Altmann, L., Neuhann, H. F., Kramer, U., Witten, J., & Jermann, E. (1995). Neurobehavioral and neurophysiological outcome of chronic low-level tetrachloroethene exposure measured in neighborhoods of dry cleaning shops. *Environmental research, 69*(2), 83-89. doi: 10.1006/enrs.1995.1028

Baird, S. J. S., Smith, C. Mark, and Rowan-West, Carol,. (2014a). Tetrachloroethylene (Percloroethylene) Inhalation Unit Risk Value (Massachusetts Department of Environmental Protection (MassDEP) Office of Research and Standards).

Baird, S. J. S., Smith, C. Mark, and Rowan-West, Carol,. (2014b). Tetrachloroethylene (Perchloroethylene) Inhalation Unit Risk Value Appendices, (Massachusetts Department of Environmental Protection (MassDEP) Office of Research and Standards).

Brown Dzubow, R., Makris, S., Siegel Scott, C., & Barone, S., Jr. (2010). Early lifestage exposure and potential developmental susceptibility to tetrachloroethylene. *Birth defects research. Part B, Developmental and reproductive toxicology, 89*(1), 50-65. doi: 10.1002/bdrb.20222

Buben, J. A., & O'Flaherty, E. J. (1985). Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: a dose-effect study. *Toxicology and applied pharmacology, 78*(1), 105-122.

California Environmental Protection Agency - OEHHA Cancer Potency Values. (2005). OEHHA Toxicity Criteria Database.

California Environmental Protection Agency (OEHHA). (2001). Public Health Goal for Tetrachloroethylene in Drinking Water.

California State Water Resources Control Board. (2011). Compilation of Water Quality Goals.

Cavalleri, A., Gobba, F., Paltrinieri, M., Fantuzzi, G., Righi, E., & Aggazzotti, G. (1994). Perchloroethylene exposure can induce colour vision loss. *Neuroscience letters, 179*(1-2), 162-166.

Chiu, W. A., & Ginsberg, G. L. (2011). Development and evaluation of a harmonized physiologically based pharmacokinetic (PBPK) model for perchloroethylene toxicokinetics in mice, rats, and humans. *Toxicology and applied pharmacology, 253*(3), 203-234. doi: 10.1016/j.taap.2011.03.020

Echeverria, D., White, R. F., & Sampaio, C. (1995). A behavioral evaluation of PCE exposure in patients and dry cleaners: a possible relationship between clinical and preclinical effects. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine, 37*(6), 667-680.

Emara, A. M., Abo El-Noor, M. M., Hassan, N. A., & Wagih, A. A. (2010). Immunotoxicity and hematotoxicity induced by tetrachloroethylene in egyptian dry cleaning workers. *Inhalation toxicology, 22*(2), 117-124. doi: 10.3109/08958370902934894

Fredriksson, A., Danielsson, B. R., & Eriksson, P. (1993). Altered behaviour in adult mice orally exposed to tri- and tetrachloroethylene as neonates. *Toxicology letters, 66*(1), 13-19.

Getz, K. D., Janulewicz, P. A., Rowe, S., Weinberg, J. M., Winter, M. R., Martin, B. R., . . . Aschengrau, A. (2012). Prenatal and early childhood exposure to tetrachloroethylene and adult vision. *Environmental health perspectives, 120*(9), 1327-1332. doi: 10.1289/ehp.1103996

Gobba, F., Righi, E., Fantuzzi, G., Predieri, G., Cavazzuti, L., & Aggazzotti, G. (1998). Two-year evolution of perchloroethylene-induced color-vision loss. *Archives of environmental health, 53*(3), 196-198. doi: 10.1080/00039899809605695

Hayes, J. R., Condie, L. W., Jr., & Borzelleca, J. F. (1986). The subchronic toxicity of tetrachloroethylene (perchloroethylene) administered in the drinking water of rats. *Fundamental and applied toxicology : official journal of the Society of Toxicology, 7*(1), 119-125.

Health Canada Guidelines for Canadian Drinking Water Quality. Guidelines for Canadian Drinking Water Quality. from https://www.canada.ca/en/health-canada/services/environmental-workplace-

health/reports-publications/water-quality/guidelines-canadian-drinking-water-quality-summary-table.html

International Agency for Research on Cancer. (2013). *Tetrachloroethylene, Monograph 106*. Retrieved from http://monographs.iarc.fr/ENG/Monographs/vol106/index.php.

International Agency for Research on Cancer (IARC). Complete List of Agents evaluated and their classification. from http://monographs.iarc.fr/ENG/Classification/index.php

Japan Industrial Safety Association (JISA). (1993). Carcinogenicity study of tetrachloroethlene by inhalation in rats and mice. Hadano, Japan.

Marth, E. (1987). Metabolic changes following oral exposure to tetrachloroethylene in subtoxic concentrations. *Archives of toxicology, 60*(4), 293-299.

Marth, E., Stunzner, D., Binder, H., & Mose, J. R. (1985). [Tetrachloroethylene: effect of low concentrations of 1,1,2,2-tetrachloroethylene (perchloroethylene) on organisms in the mouse. I. Laboratory chemical research]. *Zentralblatt fur Bakteriologie, Mikrobiologie und Hygiene. 1. Abt. Originale B, Hygiene, 181*(6), 525-540.

Marth, E., Stunzner, D., Kock, M., & Mose, J. R. (1989). Toxicokinetics of chlorinated hydrocarbons. *Journal of hygiene, epidemiology, microbiology, and immunology, 33*(4 Suppl), 514-520.

Massachussetts Department of Environmental Protection. (2014). *Summary of the Basis of Cancer Risk Values for Tetrachloroethylene*. Retrieved from https://www.mass.gov/doc/summary-of-the-basis-of-cancer-risk-values-for-tetrachloroethylene-january-2014/download.

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2011). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses. from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Cancer Institute (NCI). (1977). *Bioassay of tetrachloroethylene for possible carcinogenicity*. National Insitute of Health Retrieved from http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr013.pdf.

National Toxicology Program (NTP). (1986). *Toxicology and Carcinogenesis Studies of Tetrachloroethylene (Perchloroethylene) in F344/N Rats and B6C3F1 Mice (Inhalation Studies)*.

Schreiber, J. S., Hudnell, H. K., Geller, A. M., House, D. E., Aldous, K. M., Force, M. S., . . . Parker, J. C. (2002). Apartment residents' and day care workers' exposures to tetrachloroethylene and deficits in visual contrast sensitivity. *Environmental health perspectives, 110*(7), 655-664.

Storm, J. E., Mazor, K. A., Aldous, K. M., Blount, B. C., Brodie, S. E., & Serle, J. B. (2011). Visual contrast sensitivity in children exposed to tetrachloroethylene. *Archives of environmental & occupational health, 66*(3), 166-177. doi: 10.1080/19338244.2010.539638

Toxicology Excellence for Risk Assessment - ITER International Toxicity Estimates for Risk (ITER). from http://www.iter.tera.org/

U.S. Environmental Protection Agency. (2019). *Exposure Factors Handbook Chapter 3 Update 2019*. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3.

U.S. Environmental Protection Agency - IRIS. Integrated Risk Information Systems (IRIS) A-Z List of Substances. from http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList

U.S. Environmental Protection Agency - Office of Drinking Water. (2012). 2012 Edition of the Drinking Water Standards and Health Advisories. from http://water.epa.gov/action/advisories/drinking/upload/dwstandards2012.pdf

U.S. Environmental Protection Agency - Office of Research and Development. (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. from https://www.epa.gov/sites/default/files/2013-09/documents/recommended-use-of-bw34.pdf

U.S. Environmental Protection Agency - Regional Screening Tables. Mid-Atlantic Risk Assessment - Regional Screening Table. from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables

U.S. Environmental Protection Agency (EPA). (2003). *Discussion Paper: Neurotoxocity of Tetrachloroethylene (Perchloroethylene)*. Washington, DC.

U.S. Environmental Protection Agency (EPA). (2012). *Toxicological Review of Tetrachloroethylene (Perchloroethylene)*. Washington, DC: Integrated Risk Information System Retrieved from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0106tr.pdf

World Health Organization - Guidelines for Drinking-Water Quality. (2011). from http://whqlibdoc.who.int/publications/2011/9789241548151_eng.pdf

Web Publication Date: August 2020

Toxicological Summary for: Toluene

CAS: **108-88-3**

Synonyms: methyl-Benzene, methylbenzol, monomethyl benzene, phenylmethane, Tol, Toluol, tolu-sol

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

Short-term Non-Cancer Health-Based Value (nHBV$_{Short-term}$) = 70 µg/L

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

$$= \frac{(0.10 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

= 68.9 rounded to **70 µg/L**

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.

[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 3.08/30 = 0.10 mg/kg-d (CD-1 mice)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	22 mg/kg-d (NOAEL; Hsieh, 1989)
Dose Adjustment Factor (DAF):	0.14, Body weight scaling, default (USEPA, 2011b) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 22 mg/kg-d x 0.14 = 3.08 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Immunosuppression
Co-critical effect(s):	behavior changes due to nervous system effects, neurotransmitter level changes in the brain, changes in immune response
Additivity endpoint(s):	Immune system, Nervous system

Subchronic Non-Cancer Health-Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 70 µg/L

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

$$= \frac{(0.18 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ μg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 486 \text{ rounded to } 500 \text{ μg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 54.7/300 = 0.18 mg/kg-d (F344 rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	238 mg/kg-d (BMDL$_{10}$; USEPA, 2005 using NTP, 1990)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (USEPA, 2011b) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 238 mg/kg-d x 0.23 = 54.7 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (concerns regarding lack of evaluation of immunological and neurotoxicity endpoints. Alterations in immune response and in behavior were reported in shorter-term studies at doses lower than the subchronic and chronic PODs.)
Critical effect(s):	Increased liver and kidney weights (with histological changes in higher doses)
Co-critical effect(s):	Increased liver weight, behavior changes due to nervous system effects, neurotransmitter level changes in the brain, changes in immune response and immunosuppression
Additivity endpoint(s):	Hepatic (liver) system, Immune system, Nervous system, Renal (kidney) system

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 70 μg/L. Additivity endpoints: Immune system, Nervous system.

Chronic Non-Cancer Health-Based Value (nHBV$_{Chronic}$) = nHBV$_{Short-term}$ = 70 μg/L

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

$$= \frac{(0.055 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ μg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 244 \text{ rounded to } 200 \text{ μg/L}$$

Reference Dose/Concentration:	HED/Total UF = 54.7/1000 = 0.055 mg/kg-d (F344 Rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	238 mg/kg-d (BMDL; NTP, 1990; subchronic exposure)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (USEPA, 2011b)(MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 238 mg/kg-d x 0.23 = 54.7 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for database uncertainty (For concerns regarding lack of evaluation of immunological and neurotoxicity endpoints. Alterations in immune response and in behavior were reported in shorter-term studies at doses lower than the subchronic and chronic PODs), and 3 for subchronic to chronic extrapolation
Critical effect(s):	Increased liver and kidney weights (with histological changes in higher doses)
Co-critical effect(s):	Increased liver weight, behavior changes due to nervous system effects, neurotransmitter level changes in the brain, changes in immune response and immunosuppression
Additivity endpoint(s):	Hepatic (liver) system, Immune system, Nervous system, Renal (kidney) system

The Chronic nHBV must be protective of the short-term exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 70 μg/L. Additivity endpoints: Immune system, Nervous system.

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	Inadequate information to assess the carcinogenic potential in humans (USEPA, 2005)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (high)

Summary of Guidance Value History:

A non-cancer health risk limit (HRL) of 1000 μg/L was promulgated in 1993/1994. Short-term, subchronic, and chronic health-based values (HBV) of 200 μg/L were derived in 2009 and were promulgated as HRLs in 2011. In 2019, MDH re-evaluated the non-cancer HRLs, resulting in lower

water guidance values of 70 µg/L for the short-term, subchronic, and chronic durations. The changes to existing guidance were the result of 1) using MDH's most recent risk assessment methodology and 2) rounding to one significant digit. In 2020 MDH updated intake rates (US EPA 2019). Use of the updated intake rates did not result in changes to the 2019 values.

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	Yes	Yes	No	Yes
Effects observed?	– [1]	Yes[2]	Yes[3]	– [4]	Yes[5]

Comments on extent of testing or effects:

[1]Endocrine activity of toluene has not been studied. However, increased adrenocorticotropic hormone (ACTH) was observed at the highest dose tested in a short-term drinking water study in mice. The biological significance of this limited data is uncertain.

[2]The short-term reference dose is based on immunosuppression (decreased lymphocyte culture responses and decreased antibody PFC responses) in male mice. The immunological effect of decreased IL-2 production was seen at similar doses in other studies, and was included as co-critical effect for the subchronic and chronic durations. In a single dose study, additional immunological effects were seen at doses approximately 800 times higher than the short-term RfD. A database uncertainty factor was added to the subchronic and chronic RfDs to account for a lack of immunological studies at longer durations.

[3]Neurodevelopmental behavioral effects as well as other developmental effects (fetal body weight and organ weight decreases, kidney pelvis dilation) have been seen at doses 1,000 (fetal body weight and organ weight decreases) and up to 3,000 (kidney pelvis dilation) times higher than the short-term RfD.

[4]Oral exposure multigenerational or reproductive studies have not been conducted. No functional reproductive effects were observed in single dose developmental studies at doses up to 3,000 times the short-term RfD. Increased testicular weights were observed at high doses in a systemic subchronic study, but reproductive performance was not evaluated.

[5]Several short-term and subchronic studies have reported changes in brain neurotransmitter levels, histological changes in the brain, and mild behavioral changes in rodents. Changes in neurotransmitter levels as well as mild behavior changes were observed at similar doses to the critical effects dose ranges, and were included as co-critical effects for the short-term, subchronic, and chronic durations. A database uncertainly factor was added to the subchronic and chronic RfDs to account for a lack of neurological studies at longer durations.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). (2017). *Toxicological Profile for Toluene*. Retrieved from https://www.atsdr.cdc.gov/ToxProfiles/tp56.pdf

Agency for Toxic Substances and Disease Registry (ATSDR). (2019). Minimal Risk Levels (MRLs) List. Retrieved from https://www.atsdr.cdc.gov/mrls/mrllist.asp

Australian Natural Resource Management Ministerial Council; Environmental Protection and Heritage Council; and National Health and Medical Research Council. (2008). Australian Guidelines for Water Recycling. Augmentation of Drinking Water Supplies. Retrieved from https://www.waterquality.gov.au/sites/default/files/documents/water-recycling-guidelines-augmentation-drinking-22.pdf

California Environmental Protection Agency - OEHHA Cancer Potency Values. (2019). OEHHA Toxicity Criteria Database. Retrieved from https://oehha.ca.gov/chemicals

California Environmental Protection Agency (CalEPA). (1999). *Public Health Goal for Toluene in Drinking Water*. Retrieved from https://oehha.ca.gov/water/chemicals/toluene

California State Water Resources Control Board. (2019). Compilation of Water Quality Goals. Retrieved from http://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/

Canada, H. (2014). *Guidelines for Canadian Drinking Water Quality - Guideline Technical Document for Toluene, Ethylbenzene , and Xylenes*. Retrieved from https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-toluene-ethylbenzene-xylenes.html

Hsieh, G., Sharma, RP., Parker, RDR. (1989). Immunotoxicological Evaluation of Toluene Exposure via Drinking Water In Mice. *Env Res, 49*, 93-103.

Hsieh, G., Sharma, RP., Parker, RDR., Coulombe, RA. (1990a). Evaluation of Toluene Exposure via Drinking Water on Levels of Regional Brain Biogenic Monoamines and Their Metabolites in CD-1 Mice. *Ecotox & Env Safety, 20*, 175-184.

Hsieh, G., Parker, RDR., Sharma, RP., Hughes, BJ. (1990b). Subclinical effects of groundwater contaminants: III. Effects of repeated oral exposure to combinations of benzene and toluene on immunologic responses in mice. *Arch Toxicol, 64*, 320-328.

Hsieh, G., Sharma, RP., Parker, RDR. (1990c). Subclinical effects of groundwater contaminants: IV. Effects of repeated oral exposure to combinations of benzene and toluene on regional brain monoamine metabolism in mice. *Arch Toxicol, 64*, 669-676.

Hsieh, G., Sharma, RP., Parker, RDR. (1991). Hypothalmic-pituitary-adrenocortical axis activity and immune function after oral exposure to benzene and toluene. . *Immunopharm, 21*, 23-32.

International Agency for Research on Cancer (IARC). (2019). Complete List of Agents evaluated and their classification. Retrieved from http://monographs.iarc.fr/ENG/Classification/index.php

Kostas, J., Hotchin, J. (1981). Behavioral Effects of Low-Level Perinatal Exposure to Toluene in Mice. *Neurobehav Tox & Teratology, 3*, 467-469.

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from

https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Toxicology Program (NTP). (1990). *Technical Report on the Toxicology and Carcinogenesis Studies of Toluene (CAS NO. 108-88-3) in F344/N Rats and B6C3F1 Mice*. Retrieved from https://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr300399/abstracts/tr371/index.html

Soffritti, M., Belpoggi, F., Padovani, M., Lauriola, M., Esposti, DD., Minardi, F. . (2004). Life-time carcinogenicity bioassays of toluene given by stomach tube to Sprague-Dawley rats. *Eur. J. Oncol., 9*(2), 91-102.

Syracuse Research PhysProp Database. Retrieved from http://www.syrres.com/what-we-do/databaseforms.aspx?id=386

U.S. Environmental Protection Agency (EPA). (2005). *Toxicological Review of Toluene*. Retrieved from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0118tr.pdf

U.S. Environmental Protection Agency (EPA). (2009). *Provisional Peer-Reviewed Subchronic Toxicity Values*. Retrieved from https://cfpub.epa.gov/ncea/pprtv/documents/Toluene.pdf

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2018). *2018 Edition of the Drinking Water Standards and Health Advisories Tables*. Retrieved from https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3 .

Wisconsin Department of Health Services. (2009). *Scientific Support Documentation for Cycle 9 Revisions of NR 140.10. Groundwater Enforcement Standard and Preventative Action Limit Recommendations*.

World Health Organization (WHO). (2008). Guidelines for Drinking Water Quality - Volume 1: Recommendations. Third edition, incorporating first and second addenda. Retrieved from https://www.who.int/water_sanitation_health/publications/gdwq3rev/en/

Yamaguchi, H., Kidachi, Y., Ryoyama, K. (2002). Toluene at Environmentally Relevant Low Levels Disrupts Differentiation of Astrocyte Precursor Cells. . *Arch Env Hlth, 57*(3), 232-

Toxicological Summary for: 1,2,4-Trimethylbenzene; 1,3,5- Trimethylbenzene; and 1,2,3-Trimethylbenzene

CAS: **95-63-6; 108-67-8; 526-73-8**
1,2,4-Trimethylbenzene Synonyms: 1,2,4-TMB; pseudocumene; asymmetrical trimethylbenzene
1,3,5-Trimethylbenzene Synonyms: 1,3,5-TMB; mesitylene; symmetrical trimethylbenzene
1,2,3-Trimethylbenzene Synonyms: 1,2,3-TMB; hemimellitene; hemellitol; pseudocumol

The trimethylbenzene (TMB) isomers, 1,2,4-TMB, 1,2,3-TMB, and 1,3,5-TMB, have similar chemical structures and properties. Toxicological studies in laboratory animals demonstrate similar health effects at similar dose levels and durations (USEPA 2016). Based on these similarities, the Minnesota Department of Health (MDH) used the information provided in the 2016 USEPA IRIS review to derive HBVs for the short-term, subchronic, and chronic durations that are applicable for all three isomers.

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 30 µg/L

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

$$= \frac{(0.042 \text{ mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{(0.290 \text{ L/kg-d)}^{**}}$$

$$= 28.9 \text{ rounded to } \textbf{30 µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 4.2/100 = 0.042 mg/kg-d (Wistar rat)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	22.0 mg/m^3 (MDH calculated continuous inhalation exposure based on Gralewicz et al 1997 for NOAEL of 123 mg/m^3 identified in USEPA, 2016)
Dose Adjustment Factor (DAF):	0.19 mg/kg-d per mg/m^3 (ratio of subchronic oral POD$_{HED}$ (3.5 mg/kg-d) to inhalation POD$_{HEC}$ (18.15 mg/m^3) from (USEPA, 2016). Chemical-Specific PBPK model-based route-to-route extrapolation.)

Human Equivalent Dose (HED):	POD x DAF = 22.0 mg/m^3 x 0.19 mg/kg-d per mg/m^3 = 4.2 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 (lack of a multi-generation developmental/reproductive study and lack of a neurodevelopmental study)
Critical effect(s):	Central nervous system changes (increased open field grooming), decreased pain sensitivity (lowered step down latency and paw lick latency)
Co-critical effect(s):	Central nervous system changes (impaired learning of passive avoidance and deleterious effects on locomotor activity), decreased pain sensitivity (paw lick latency)
Additivity endpoint(s):	Nervous system

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 30 µg/L

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

$$= \frac{(0.035 \text{ mg/kg-d}) \text{ x } (0.2)^* \text{ x } (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

$$= 94.5 \text{ rounded to } 90 \text{ µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 3.5/100 = 0.035 mg/kg-d (Wistar rat)
Source of toxicity value:	USEPA, 2016
Point of Departure (POD):	POD$_{ADJ}$ (0.099 mg/L) weekly average blood concentration resulting from an inhalation POD$_{HEC}$ of 18.15 mg/m^3 (dose metric from Korsak and Rydzynski, 1996 calculated by EPA, Table 2-5, USEPA, 2016)
Dose Adjustment Factor (DAF):	Chemical-Specific PBPK model as calculated by USEPA, 2016 (USEPA, 2016)
Human Equivalent Dose (HED):	3.5 mg/kg-d (PBPK basis as calculated by USEPA, 2016 (page 2-34))
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database

	uncertainty (lack of a multi-generation developmental/reproductive study and lack of a neurodevelopmental study)
Critical effect(s):	Decreased pain sensitivity (paw lick latency)
Co-critical effect(s):	Central nervous system changes (impaired learning of passive avoidance and deleterious effects on locomotor activity), decreased pain sensitivity (paw lick latency)
Additivity endpoint(s):	Nervous system

The Subchronic nHBV must be protective of short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 30 µg/L. Additivity endpoints: Nervous system

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = (nHBV$_{Short-term}$) = 30 µg/L

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

$$= \frac{(0.012 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 53.3 \text{ rounded to } 50 \text{ µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 3.5/300 = 0.012 mg/kg-d (Wistar rat)
Source of toxicity value:	USEPA, 2016
Point of Departure (POD):	POD$_{ADJ}$ (0.099 mg/L) weekly average blood concentration resulting from an inhalation POD$_{HEC}$ of 18.15 mg/m^3 (dose metric from Korsak and Rydzynski, 1996 calculated by EPA, Table 2-5, USEPA, 2016) (subchronic exposure)
Dose Adjustment Factor (DAF):	Chemical-Specific PBPK model as calculated by USEPA, 2016 (USEPA, 2016)
Human Equivalent Dose (HED):	3.5 mg/kg-d (PBPK basis as calculated by USEPA, 2016 (page 2-34))
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for database uncertainty (lack of a multi-generation developmental/reproductive study and lack of a neurodevelopmental study), and 3 for subchronic

	to chronic extrapolation (use of subchronic study and slight potential for an increased severity of effects with increasing duration)
Critical effect(s):	Decreased pain sensitivity (paw lick latency)
Co-critical effect(s):	Central nervous system changes (impaired learning of passive avoidance and deleterious effects on locomotor activity), decreased pain sensitivity (paw lick latency)
Additivity endpoint(s):	Nervous system

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 30 µg/L. Additivity endpoints: Nervous system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not Classified
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (high)

Summary of Guidance Value History:

Short-term, subchronic, and chronic duration health-based values (HBV) of 100 µg/L were derived for 1,3,5-TMB in 2008 and promulgated as health-risk limits (HRL) in 2009. Short-term, subchronic, and chronic duration risk assessment advice (RAA) of 100 µg/L was derived for 1,2,4-TMB in 2010, and was based on the MDH guidance values for 1,3,5-TMB. The derived guidance values for 1,3,5-TMB and 1,2,4-TMB were re-evaluated in 2018. The re-evaluation included one additional TMB isomer, 1,2,3-TMB. All three isomers were evaluated together for the purposes of updating and deriving guidance values. As a result of the 2018 re-evaluation, short-term, subchronic, and chronic HBVs of 30 µg/L were derived for all three TMB isomers (1,2,3-; 1,2,4-; and 1,3,5-). The values are lower than previous MDH guidance as a result of 1) incorporation of more recent toxicological information, 2) route-to-route extrapolation using US EPA PBPK results, and 3) rounding to one significant digit. In 2020 MDH incorporated updated intake rates (US EPA 2019). Using the updated intake rates did not result in changes to the 2018 values.

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	Yes
Effects observed?	-[1]	-[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1]Endocrine activity of the trimethylbenzene isomers has not been tested. There is some evidence that other alkylbenzenes may modulate endocrine function and signaling. Alkylbenzene alterations of hormone concentrations may be tied to alterations in fetal growth and the development of inflammatory responses.

[2]Immunotoxicity was not directly tested with trimethylbenzene isomers. Studies examining nonimmune endpoints reported increases in immune and inflammatory cells and alveolar macrophages in lung lavage fluid. The increased macrophages could potentially indicate immune suppression activity at high doses in laboratory animals.

[3]Limited information is available on the developmental effects of the trimethylbenzene isomers. Decreased fetal body weight in decreased maternal body weight was observed in laboratory animals at doses over 3000 times higher than the reference dose for the short-term duration. The lack of a multigenerational study is addressed with a database uncertainty factor for all three durations.

[4] Limited information is available on the reproductive effects of the trimethylbenzene isomers. Decreased maternal body weight in addition to decreased fetal body weight was observed in laboratory animals at doses over 3000 times higher than the reference dose for the short-term duration. The lack of a multi-generational study is addressed with a database uncertainty factor for all three durations.

[5]The reference doses for the short-term, subchronic, and chronic durations are based on neurotoxicity endpoints (central nervous system disturbances and decreased pain sensitivity) observed in inhalation studies. Co-critical effects are also based on the same nervous system effects at doses up to the non-PBPK adjusted dose associated with the reference dose.

Resources Consulted During Review:

Gralewicz, S., Wiaderna, D., Tomas, T., Rydzynski, K. (1997). Behavioral changes following 4-week inhalation exposure to pseudocumene (1,2,4-trimethylbenzene) in the rat. *Neurotoxicology and Teratology, 19*(4), 327-333.

Gralewicz, S., Wiaderna, D. (2001). Behavioral effects following subacute inhalation exposure to m-xylene or trimethylbenzene in the rat: A comparative study. *Neurotoxicology, 22*(1), 79-89.

Korsak, Z., Rydzynski, K. (1996). Neurotoxic effects of acute and subchronic inhalation exposure to trimethylbenzene isomers (pseudocumene, mesitylene, hemimellitene) in rats.

International Journal of Occupational Medicine and Environmental Health, 9(4), 341-349.

Korsak, Z., Rydzynski, K., Jajte, J. (1997). Respiratory irritative effects of trimethylbenzenes: An experimental animal study. *International Journal of Occupational Medicine and Environmental Health, 10*(3), 303-311.

Maltoni, C., Ciliberti, A., Pinto, C., Soffritti, M., Belpoggi, F., Menarini, L. (1997). Results of long-term experimental carcinogenicity studies of the effects of gasoline, correlated fuels, and major gasoline aromatics on rats. *Annals of the New York Academy of Sciences, 837*(1), 15-52.

McKee, R., Wong, ZA., Schmitt, S., Beatty, P., Swanson, M., Schreiner, CA., Schardein, JL. (1990). The reproductive and developmental toxicity of High Flash Aromatic Naphtha. *Toxicology and Industrial Health, 6*(3-4), 441-460.

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Saillenfait, A., Gallissot, F., Sabate, JP., Morel, G. (2005). Developmental toxicity of two trimethylbenzene isomers, mesitylene and pseudocumene, in rats following inhalation exposure. *Food and Chemical Toxicology, 43*(7), 1055-1063.

U.S. Environmental Protection Agency (EPA). Chemistry Dashboard. Retrieved from https://comptox.epa.gov/dashboard

U.S. Environmental Protection Agency (EPA). Regional Screening Levels (RSLs) - Generic Tables. Retrieved from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables-november-2017

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (EPA). (2014). Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies

Extrapolation. Risk Assessment Forum. Office of Research and Development. EPA/100/R-14/002F.

US Environmental Protection Agency (EPA). (2009). *Provisional Peer-Reviewed Toxicity Value for 1,3,5-Trimethylbenzene (CASRN 108-67-8).* Retrieved from https://hhpprtv.ornl.gov/issue_papers/Trimethylbenzene135.pdf.

US Environmental Protection Agency (EPA). (2010). *Provisional Peer-Reviewed Toxicity Value for 1,2,3-Trimethylbenzene (CASRN 526-73-8).* Retrieved from https://hhpprtv.ornl.gov/issue_papers/Trimethylbenzene123.pdf.

US Environmental Protection Agency (EPA). (2016). IRIS Toxicological Review of Trimethylbenzenes [CASRNs 25551-13-7, 95-63-6, 526-73-8, and 108-67-8]. Retrieved from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1037tr.pdf

US Environmental Protection Agency (EPA). (2016). IRIS Toxicological Review of Trimethylbenzenes [CASRNs 25551-13-7, 95-63-6, 526-73-8, and 108-67-8] - Supplemental Information Retrieved from https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=254525

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3 .

Wiaderna, D., Gralewicz, S., Tomas, T. (1998). Behavioral changes following a four-week inhalation exposure to hemimellitene (1,2,3-trimethylbenzene) in rats. *International Journal of Occupational Medicine and Environmental Health, 11*(4), 319-334.

Wiaderna, D., Gralewicz, S., Tomas, T. (2002). Assessment of long-term neurotoxic effects of exposure to mesitylene (1,3,5-trimethylbenzene) based on the analysis of selected behavioral responses. *International Journal of Occupational Medicine and Environmental Health, 15*(4), 385-392.

World Health Organization (WHO). (2005). Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for the Use of Data in Dose/Concentration-Response Assessment. International Programme on Chemical Safety, IPCS Harmonization Project Document No. 2. WHO/IPCS/01.4, 1-96, Geneva, Switzerland.

Toxicological Summary for: Tris(2-butoxyethyl) Phosphate

CAS: **78-51-3**

Synonyms: TBEP, Tributoxyethyl phosphate

Acute Noncancer Health-Based Value (nHBV$_{Acute}$) = Not Derived (Insufficient Data)

Short-term Noncancer Health-Based Value (nHBV$_{Short-term}$) = 30 µg/L

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

$$= \frac{(0.043 \text{ mg/kg-d}) \text{ x } (0.2)^* \text{ x } (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

= 29.6 rounded to **30 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1. Based on the potential for infants to be exposed at levels equal to a significant fraction of the short-term MDH RfD value from house dust (Fromme, 2014), an RSC of 0.2 has been used.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 4.34 / 100 = 0.043 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	18.08 mg/kg-d (administered dose BMDL$_{10}$, HRI, 1996)
Dose Adjustment Factor (DAF):	0.24 sex averaged body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 18.08 mg/kg-d x 0.24 = 4.34 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 due to a lack of any 2-generational study and additional studies in a second test species
Critical effect(s):	Liver cell vacuolization
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Subchronic Noncancer Health-Based Value (nHBV$_{Subchronic}$) = nHBV$_{Short-term}$ = 30 µg/L

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

$$= \frac{(0.022 \text{ mg/kg-d) x (0.2)}^* \text{ x (1000 µg/mg)}}{(0.074 \text{ L/kg-d)}^{**}}$$

$$= 59.4 \text{ rounded to } 60 \text{ µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 2.23 / 100 = 0.022 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	8.92 mg/kg-d (administered dose BMDL$_{10}$, Reyna & Thake, 1987)
Dose Adjustment Factor (DAF):	Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 8.92 mg/kg-d x 0.25 = 2.23 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 due to a lack of any 2-generational study and additional studies in a second test species
Critical effect(s):	Liver cell vacuolization
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

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 30 µg/L. Additivity endpoints: Hepatic (liver) system

Chronic Noncancer Health-Based Value (nHBV$_{Chronic}$) = 30 µg/L

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

$$= \frac{(0.0074 \text{ mg/kg-d) x (0.2)}^* \text{ x (1000 µg/mg)}}{(0.045 \text{ L/kg-d)}^{**}}$$

$$= 32.8 \text{ rounded to } \mathbf{30 \text{ µg/L}}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 2.23 / 300 = 0.0074 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2020

	Point of Departure (POD):	8.92 mg/kg-d (administered dose $BMDL_{10}$, Reyna & Thake, 1987, subchronic exposure)

Point of Departure (POD): 8.92 mg/kg-d (administered dose $BMDL_{10}$, Reyna & Thake, 1987, subchronic exposure)

Dose Adjustment Factor (DAF): Body weight scaling, default (US EPA 2011 and MDH 2017)

Human Equivalent Dose (HED): POD x DAF = 8.92 mg/kg-d x 0.25 = 2.23 mg/kg-d

Total uncertainty factor (UF): 300

Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty due to a lack of any 2-generational study and additional studies in a second test species, and 3 for use of a subchronic study for chronic guidance

Critical effect(s): Liver cell vacuolization

Co-critical effect(s): None

Additivity endpoint(s): Hepatic (liver) system

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification: Not Classified

Slope factor (SF): Not Applicable

Source of cancer slope factor (SF): Not Applicable

Tumor site(s): Not Applicable

Volatile: No

Summary of Guidance Value History:

In 2020 MDH derived guidance for TBEP. Previously no MDH guidance existed. Later in 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	Yes
Effects observed?	_[1]	_[2]	No[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] No specific animal studies are available. A general toxicity study in rats noted a slight endocrine system organ weight change (thyroid) at a dose approximately 2,000 times higher than the subchronic reference dose. In cell culture studies, a small number of tests have been positive for endocrine activity.

[2] No specific animal studies are available. A general toxicity study in rats noted a slight decrease in spleen weight after five weeks of exposure at a dose over 10,000 times higher than the short-term reference dose. A small reduction in white blood cells has also been reported in two studies at doses over 6,000 times higher than the subchronic reference dose.

[3] Two studies have examined developmental effects in rats, and neither reported developmental effects at doses 1,700 and 8,000 times higher than the short-term reference dose. However, due to the lack of specific developmental studies and the lack of a second test species, a database uncertainty factor was applied.

[4] Male reproductive toxicity in adult rats was reported at a dose 1,700 times higher than the short-term reference dose. A slight increase in testis weight and a slight decrease in ovary weight has been reported at doses over 10,000 times higher than the subchronic reference dose. A database uncertainty factor has been applied due to the overall lack of reproductive studies.

[5] Neurotoxicity has been examined in two dated studies where effects were not seen until approximately 5,000 – 10,000 times higher than the short-term reference dose. Serum cholinesterase decreases have also been observed at doses 1,000 – 10,000 times higher than the subchronic reference dose.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). (2012). *Toxicological Profile for Phosphate Ester Flame Retardants*. Retrieved from https://www.atsdr.cdc.gov/ToxProfiles/tp202.pdf.

Compound Safety Research Institute (Japan). (2012). *Simple Reproductive Test of Tris(2-butoxyethyl) phosphate in rats, SR09201*. Retrieved from https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF78-51-3c.pdf.

Fromme, H., Lahrz, T., Kraft, M., Fembacher, L., Mach, C., Dietrich, S., & Göen, T. (2014). Organophosphate flame retardants and plasticizers in the air and dust in German daycare centers and human biomonitoring in visiting children (LUPE 3). *Environment International*, 158-163.

Hatano Research Institute (HRI) (Japanese Food and Drug Safety Center). (1996). *28 Day Repeat Dose Oral Toxcity Study of Tris(2-butoxyethyl) phosphate in rats*. Retrieved from https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF78-51-3b.pdf.

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Center for Biotechnology Information. PubChem Database. Tris(2-butoxyethyl) phosphate, CID=6540, https://pubchem.ncbi.nlm.nih.gov/compound/6540 (accessed on June 8, 2020)

National Sanitation Foundation (NSF) International. (2012). Tris (2-butoxyethyl) Phosphate CAS # 78-51-3 Oral Risk Assessment Document. Retrieved from https://images.techstreet.com/direct/nsf/tris_phosphate_es.pdf

Reyna, M., & Thake, D. (1987). *Eighteen week feeding study of tributoxyethyl phosphate administered to Sprague-Dawley rats (with cover letter)*. Monsanto Agricultural Company. OTS0530087

U.S. Environmental Protection Agency (EPA). (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Office of Research and Development. Retrieved from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency (EPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency. Chemistry Dashboard. https://comptox.epa.gov/dashboard/DTXSID5021758 (accessed June 08, 2020), Tris(2-butoxyethyl) phosphate

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

Van den Eede, N., Erratico, C., Exarchou, V., Maho, W., Neels, H., & Covaci, A. (2015). In vitro biotransformation of tris(2-butoxyethyl) phosphate (TBOEP) in human liver and serum. *Toxicol Appl Pharmacol, 284*(2), 246-253. doi:10.1016/j.taap.2015.01.021

Volkel, W., Fuchs, V., Wockner, M., & Fromme, H. (2018). Toxicokinetic of tris(2-butoxyethyl) phosphate (TBOEP) in humans following single oral administration. *Arch Toxicol, 92*(2), 651-660. doi:10.1007/s00204-017-2078-7

Wang, Y., Li, W., Martínez-Moral, M. P., Sun, H., & Kannan, K. (2019). Metabolites of organophosphate esters in urine from the United States: Concentrations, temporal variability, and exposure assessment. *Environment international*, 213-221.

World Health Organization - International Programme on Chemical Safety (IPCS). (2000). *Flame Retardants: Tris(2-butoxyethyl) phosphate, tris(2-ethylhexyl) phosphate and tetrakis(hydroxymethyl) phosphonium salts*. Retrieved from https://www.who.int/ipcs/publications/ehc/en/EHC218.pdf.

Toxicological Summary for: Tris - (1,3 - dicholorisopropyl) phosphate

CAS: **13674-87-8**

Synonyms: Tris(1,3-dichloro-2-propyl)phosphate; Tri[2-chloro-1-(chloromethyl)ethyl] phosphate; Fyrol FR 2; TDCPP; TDCP

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = 20 μg/L

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

$$= \frac{(0.0067 \text{ mg/kg/d) x (0.2)}^* \text{ x (1000 μg/mg)}}{(0.074 \text{ L/kg-d)}^{**}}$$

$$= 18 \text{ rounded to } \mathbf{20 \text{ μg/L}}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	0.0067 mg/kg-d (mice)
Source of toxicity value:	MDH, 2013
Point of Departure:	15 mg/kg-d (NOAEL from 3 month dietary study by Kamata et al 1989)
Human Equivalent Dose (MDH, 2011):	15 x 0.13 = 2.0 mg/kg-d (MDH 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (to address no or inadequate information regarding developmental/reproductive function, neurological, immune and endocrine effects)
Critical effect(s):	Increased liver and kidney weights
Co-critical effect(s):	None

Additivity endpoint(s):   Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = 8 µg/L

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

$$= \frac{(0.0019 \text{ mg/kg/d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 8.4 rounded to **8 µg/L**

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	0.0019 mg/kg-d (rats)
Source of toxicity value:	MDH, 2013
Point of Departure:	1.94 mg/kg-d (BMDL$_{10\%}$ calculated by ATSDR 2012 based on renal tubule epithelial hyperplasia reported in Bio/dynamics 1981)
Human Equivalent Dose (MDH, 2011):	1.94 x 0.29 = 0.56 mg/kg-d (MDH 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (to address no or inadequate information regarding developmental/reproductive function, neurological, immune and endocrine effects)
Critical effect(s):	Renal tubule epithelial hyperplasia and seminal vesicle atrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system; Male reproductive system

Cancer Health Based Value (cHBV) = 0.8 µg/L

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

$$= \frac{(1E\text{-}5) \times (1000 \text{ µg/mg})}{[(0.13 \times 10^* \times 0.155 \text{ L/kg-d}^{**} \times 2) + (0.13 \times 3^* \times 0.040 \text{ L/kg-d}^{**} \times 14) + (0.13 \times 1^* \times 0.042 \text{ L/kg-d}^{**} \times 54)] / 70}$$

= 0.764 rounded to **0.8 µg/L**

[*]ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
[**]Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Cancer classification:	Has not been classified by US EPA
	Probable human carcinogen (Consumer Product Safety Commission 2006)
	Identified under Proposition 65 as a chemical known to cause cancer (CalEPA 2012)
Slope factor:	0.13 per mg/kg-d (2 year dietary study in rats, Freudenthal and Henrich 2000)
Source of slope factor:	CalEPA 2012
Tumor site(s):	Liver, kidney and testes

Volatile: **No**

Summary of Guidance Value History:

Guidance values for TDCPP were developed in 2013. In 2021 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in a change in the chronic duration water guidance value from 9 μg/L to 8 μg/L.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	Yes
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] A recent epidemiological study reported significant associations between serum prolactin and free T4 levels and TDCPP levels in household dust. However, study limitations preclude drawing conclusions from these observations. Oral toxicity studies in laboratory animals have mainly been limited to organ weights and histological assessments. Chronic exposure resulted in effects on male reproductive organs and increased thyroid weights at higher doses (> 2,600-fold higher than the chronic RfD). Hormonal measurements, however, were not taken. Studies conducted *in vitro* and in zebrafish demonstrate that TDCPP affects steroidogenesis, acts as an estrogen receptor antagonist and alters thyroid hormone concentrations. A database uncertainty factor has been incorporated into the derivation of the RfD to address the inadequate dataset regarding endocrine activity.

[2] Oral studies of immunological effects have been limited to measurements of thymus and spleen organ weights which do not appear to be sensitive endpoints. However, a 4 day subcutaneous injection study reported changes in immune function. In addition immune effects have been observed following exposure to other triphosphate flame retardants. A database uncertainty factor has been incorporated into the derivation of the RfD to address the inadequate oral toxicity dataset regarding immunological assessment.

[3] Oral mammalian developmental studies are limited. No multigeneration studies have been conducted. Two

developmental studies reported increased incidence of fetal death as dose levels resulting in maternal toxicity. These dose levels were more than 3000-fold higher than the subchronic and chronic RfDs.

[4] Male reproductive organ effects were observed at the lowest dose tested in a 2 year dietary study in rats. These effects, in part, form the basis of the chronic RfD. Oral studies regarding functional reproductive effects are limited. No multigeneration studies have been conducted. Female reproductive effects have not been adequately assessed. Effects on male reproductive ability were not observed in a 12 week study in rabbits. A database uncertainty factor has been incorporated into the derivation of the RfD to address the inadequate dataset regarding reproductive toxicity.

[5] Oral studies regarding neurotoxicity are limited. A 2 year dietary study did not report clinical signs or morphological changes in the brain. Changes in red blood cell cholinesterase were measured but were inconsistent throughout the study. No developmental neurobehavioral effects were reported following *in utero* exposure but data reporting in that particular study were limited. Studies on other structurally related chemicals suggest the need for additional studies. A database uncertainty factor has been incorporated into the derivation of the RfD to address the inadequate dataset regarding neurological assessment.

References:

Agency for Toxic Substances and Disease Registry (ATSDR). (2012). Toxicological Profile for Phosphate Ester Flame Retardants. from http://www.atsdr.cdc.gov/ToxProfiles/tp202.pdf

Australian Government Department of Health and Aging: National Industrial Chemicals Notification and Assessment Scheme (NICNAS). (2001). Triphosphates: Priority Existing Chemical (PEC) Assessment Report No. 17.

Australian Guidelines- Natural Resource Management Ministerial Council; Environmental Protection and Heritage Council; and National Health and Medical Research Council. (2008). Augmentation of Drinking Water Supplies. from http://nepc.gov.au/system/files/resources/5fe5174a-bdec-a194-79ad-86586fd19601/files/wq-agwr-gl-adws-corrected-final-200809_1.pdf

California Environmental Protection Agency (CalEPA) - Office of Environmental Health Hazard Assessment (OEHHA). (2011). Evidence on the Carcinogenicity of Tris(1,3-dichloro-2-propyl)phosphate. from http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/TDCPP070811.pdf

California Environmental Protection Agency (CalEPA) - Office of Environmental Health Hazard Assessment (OEHHA). (2012). Proposition 65. Initial Statement of Reasons. Proposed Amendment to Specific Regulatory Levels Posing No Significant Risk. Tris (1,3-Dichloro-2-Propyl) Phosphate. from https://oehha.ca.gov/media/060112TDCPPISOR.pdf

Consumer Product Safety Commission. (2006). Staff Preliminary Risk Assessment of Flame Retardant (FR) Chemicals in Upholstered Furniture Foam., from https://www.cpsc.gov/content/CPSC-Staff-Preliminary-Risk-Assessment-of-Flame-Retardant-FR-Chemicals-in-Upholstered-Furniture-Foam-December-2006

Dishaw LV, CM Powers, IT Ryde, SC Roberts, FJ Seidler, TA Slotkin, et al. (2011). Is the PentaBDE replacement, tris (1,3-dichloropropyl) phosphate (TDCPP), a developmental neurotoxicant? Studies in PC12 cells. *Toxicology and Applied Pharmacology, 256*, 281-289.

European Commission. (2008). European Union Risk Assessment Report: Tris[2-Chloro-1-(Chloromethyl)ethyl]phosphate (TDCP). CAS No: 13674-87-8. from https://echa.europa.eu/documents/10162/13630/trd_rar_ireland_tccp_en.pdf/315063b0-593d-4703-9519-562c258506e6

Freudenthal RI and RT Henrich. (2000). Chronic Toxicity and Carcinogenic Potential of Tris-(1,3-

Dichloro-2-propyl) Phosphate in Sprague-Dawley Rat. *International Journal of Toxicology, 19*, 119-125.

Kamata E, K Naito, Y Nakaji, Y Ogawa, S Suzuki, T Kaneko, et al. (1989). Acute and subacute toxicity studies of Tris (1,3-dichloro-2-propyl) Phosphate on Mice. *Bull Natl Inst Hyg Sci, 107*, 36-43.

Kawashima K, S Tanaka, S Nakaura, S Nagao, T Endo, K Onoda, et al. (1983). Effect of phosphoric acid tri-esters flame retardants on the prenatal and postnatal developments of the rats. *The Japanese Society of Toxicology, 8*(1), 339.

Liu X, K Ji, & K Choi. (2012). Endocrine disruption potentials of organophosphate flame retardants and related mechanisms in H295R and MVLN cell lines and zebrafish. *Aquatic Toxicology, 114-115*, 173-181.

Luster MI, JH Dean, GA Boorman, DL Archer, L Lauer, LD Lawson, et al. (1981). The Effects of Orthophenylphenol, Tris(2,3-dichloropropyl) Phosphate, and Cyclophosphamide on the Immune System and Host Susceptibility of Mice following Subchronic Exposure. *Tox Appl Tox, 58*, 252-261.

McGee SP, EM Cooper, HM Stapleton, & DC Volz. (2012). Early Zebrafish Embryogenesis Is Susceptible to Developmental TDCPP Exposure. . *Environmental Health Perspectives, 120*, 1585-1591.

Meeker JD and HM Stapleton. (2010). House Dust Concentrations of Organophosphate Flame Retardants in Relation to Hormone Levels and Semen Quality Parameters. *Environmental Health Perspectives, 118*, 318-323.

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2011). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses. from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Research Council (NRC): Subcommittee on Flame-Retardant Chemicals. (2000). Toxicological Risks of Selected Flame-Retardants. Chapter 16. Tris (1,3-dichloropropyl-2) Phosphate., from http://www.nap.edu/catalog.php?record_id=9841

Organization for Economic Co-operation and Development (OECD). (2009). Screening Information Dataset (SIDs) Initial Assessment Profile., from http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?Key=aedbd212-ac9a-4436-8ce6-cf29eabd7cbe&idx=0

Tanaka S, S Nakaura, K Kawashima, S Nagao, T Endo, K Onoda, et al. (1981). Effect of oral administration of tris(1,3-dichloroisopropyl)phosphate to pregnant rats on prenatal and postnatal developments. *Eisei Shikenjo Hokoku, 99*, 50-55.

U.S. Environmental Protection Agency - Office of Research and Development. (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency - Regional Screening Tables. Mid-Atlantic Risk Assessment -

Regional Screening Table. from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables

US Environmental Protection Agency - Office of Water. (2012). 2012 Edition of the Drinking Water Standards and Health Advisories. from http://water.epa.gov/action/advisories/drinking/upload/dwstandards2012.pdf

US Environmental Protection Agency (EPA) Design for the Environment (DfE) Program. (2005a). Flame Retardant Alternatives: Tris(1,3-dichloro-2-propyl) Phosphate Hazard Review. from http://www.epa.gov/dfe/pubs/flameret/altrep-v2/altrept-v2-section3a.pdf

US Environmental Protection Agency (EPA) Design for the Environment (DfE) Program. (2005b). Volume 1. Furniture Flame Retardancy Partnership: Environmental Profiles of Chemical Flame Retardant Alternatives for Low-Density Polyurethane Foam. from https://www.epa.gov/sites/default/files/2013-12/documents/ffr_foam_alternatives_vol1.pdf

US Environmental Protection Agency. (2019). *Exposure Factors Handbook Chapter 3 Update 2019*. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3.

van der Veen I and J de Boer. (2012). Phosphorus flame retardants: Properties, production, environmental occurrence, toxicity and analysis. *Chemosphere, 88*, 1119-1153.

Wang Q, K Liang, J Liu, L Yang, Y Guo, C Liu, et al. (2013). Exposure of zebrafish embryos/larvae to TDCPP alters concentrations of thyroid hormones and transcriptions of genes involved in the hypothalamic-pituitary-thryoid axis. *Aquatic Toxicology, 126*, 207-213.

World Health Organization (WHO). (1998 incorporating corrigenda published November 2004). Environmental Health Criteria 209. Flame Retardants: Tris(chloropropyl) phosphate and Tris(2-chloroethyl) phosphate. from http://apps.who.int/iris/bitstream/10665/42148/1/WHO_EHC_209.pdf

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Toxicological Summary for: Venlafaxine

CAS: **93413-69-5 (free base)**
99300-78-4 (HCl salt, Effexor XR)

Synonyms: Venlafaxine-HCl (Effexor XR); 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol (IUPAC)

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

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 10 ug/L

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

$$= \frac{(0.0054 \text{ mg/kg-d) x (0.8*) x (1000 µg/mg)}}{(0.290 \text{ L/kg-d)**}}$$

$$= 14.9 \text{ rounded to } \textbf{10 µg/L}$$

 * MDH utilizes the U.S. EPA Exposure Decision Tree (U.S. EPA 2000) to select appropriate RSCs, ranging from 0.2 to 0.8. An RSC greater than 0.8 may be warranted for those who have no other route of exposure besides drinking water because of the unlikelihood of exposure from any other sources. However, without additional information a specific value cannot be determined at this time. Therefore, the recommended upper limit default of 0.8 was utilized. For those who take venlafaxine according to prescription the additional drinking water exposure will be negligible. For nursing infants whose mothers are taking venlafaxine, the drinking water exposure from supplemental bottle-feeding will also be negligible.
** Intake Rate: MDH, 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	0.0054 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.54 mg/kg-d (LOAEL, lowest starting dose of 37.5 mg/d from Wyeth Pharmaceuticals, 2014a)
Human Equivalent Dose (MDH, 2011):	n/a
Total uncertainty factor:	100
Uncertainty factor allocation:	10 for intraspecies variability and 10 for use of LOAEL
Critical effect(s):	Developmental (persistent pulmonary hypertension and nervous system effects), gastrointestinal system (nausea, constipation), male reproductive effects (decreased libido, abnormal orgasm, erectile dysfunction, ejaculation failure/disorder), and nervous system effects (effects on serotonin hormone receptor interaction, sweating, abnormal dreams, and dizziness, and neuroendocrine-mediated increases in blood pressure)
Co-critical effect(s):	None

Additivity endpoint(s):	Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = Short-term HBV = 10 µg/L

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

$$= \frac{(0.0054 \text{ mg/kg-d}) \times (0.8^*) \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 58 rounded to 60 µg/L

*Refer to RSC explanation provided for the short-term non-cancer health risk limit.
** Intake Rate: MDH, 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	0.0054 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.54 mg/kg-d (LOAEL, lowest starting dose of 37.5 mg/d and lowest dose tested in a 6-month clinical trial, Cobalt Pharmaceutical Co. 2014, Emslie et al. 2007a, Emslie et al. 2007b)
Human Equivalent Dose (MDH, 2011):	n/a
Total uncertainty factor:	100
Uncertainty factor allocation:	10 for intraspecies variability and 10 for use of LOAEL
Critical effect(s):	Cardiovascular system (neuroendocrine-mediated increases in blood pressure), developmental (persistent pulmonary hypertension and nervous system effects), gastrointestinal system (constipation), male reproductive effects (effects on orgasm, ejaculation failure, decreased libido), and nervous system (effects on serotonin hormone receptor interaction, abnormal dreams, sweating, and neuroendocrine-mediated increases in blood pressure)
Co-critical effect(s):	Nervous system (mydriasis or dilation of pupils)
Additivity endpoint(s):	Cardiovascular system, Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)

The Subchronic nHBV must be protective of the acute, and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 10 µg/L. Additivity endpoints: Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = Short-term HBV = 10 µg/L

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

$$= \frac{\text{(0.0054 mg/kg-d) x (0.8*) x (1000 µg/mg)}}{\text{(0.045 L/kg-d)**}}$$

$$= 96 \text{ rounded to } 100 \text{ µg/L}$$

*Refer to RSC explanation provided for the short-term non-cancer health risk limit.
** Intake Rate: MDH, 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	0.0054 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.54 mg/kg-d (LOAEL, lowest starting dose of 37.5 mg/d, and lowest dose tested in a 6-month clinical trial Cobalt Pharmaceutical Co. 2014, Emslie et al. 2007a, Emslie et al. 2007b)
Human Equivalent Dose (MDH, 2011):	n/a
Total uncertainty factor:	100
Uncertainty factor allocation:	10 for intraspecies variability and 10 for use of LOAEL
Critical effect(s):	Cardiovascular system (neuroendocrine-mediated increases in blood pressure), developmental (persistent pulmonary hypertension in newborns and nervous system effects), gastrointestinal system (constipation), male reproductive effects (effects on orgasm, ejaculation failure, decreased libido), and nervous system (effects on serotonin hormone receptor interaction, abnormal dreams, sweating, and neuroendocrine-mediated increases in blood pressure)
Co-critical effect(s):	Nervous system (mydriasis or dilation of pupils)
Additivity endpoint(s):	Cardiovascular system, Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)

The Chronic nHBV must be protective of the acute, 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 10 µg/L. Additivity endpoints: Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)

Cancer Health Based Value (cHBV) =   Not Applicable

Volatile: No

Summary of Guidance Value History:
There are no previous drinking water guidance values for venlafaxine. All values are new. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	Yes
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]Neuroendocrine effects related to serotonin and norepinephrine are identified as critical effects. Serotonin receptor interactions are the basis for the intended pharmacological action of venlafaxine and many of the adverse effects. Significant neuroendocrine-mediated increases in systolic blood pressure related to norepinephrine have been reported in some clinical trials and are considered as a critical effect. Doses more than 200 times higher than the RfD have been associated with sustained hypertension (defined as supine diastolic blood pressure (SDBP) ≥90 mm Hg and ≥10 mm Hg above baseline for 3 consecutive therapy visits). Other endocrine system effects have been described as "limited" and have generally occurred only at doses greater than those required for antidepressant therapeutic effects. Menstrual disorders in humans have been identified at doses over 200 times higher than the RfD. Inappropriate antidiuretic hormone secretion (SIADH) in the kidney has been reported as an adverse event in dehydrated patients. Rare reports of endocrine effects at therapeutic doses over 200 times higher than the RfD include galactorrhea, goiter, hyper- and hypothyroidism, thyroid nodule, thyroiditis, and increased prolactin.

[2]Venlafaxine has been reported to have only limited effects on the immune system that generally occur at doses greater than those required for therapeutic antidepressant effects (more than 200 times higher than the RfD). Since depression is associated with alterations in immune function, the effects of antidepressants on the immune system have been of interest, primarily from the perspective of restoring immune function in depressed patients. Some reports suggest that antidepressant treatment, including venlafaxine, may have a beneficial anti-inflammatory effect. In laboratory mice, effects on various pro-inflammatory cytokines were reported when mice were exposed to venlafaxine at HED doses more than 150 times higher than the RfD.

[3]Developmental toxicity in humans is identified as a critical endpoint with effects in newborns exposed during the third trimester of pregnancy as a result of maternal antidepressant therapy. Effects on newborns exposed to therapeutic doses during the third trimester can be life-threatening and require hospitalization. Effects may include respiratory distress at birth and/or tachypnea, persistent pulmonary hypertension, cyanosis, apnea, seizures, tremor, irritability, temperature instability, vomiting, hypoglycemia, and changes in muscle tone. Exposure during pregnancy at doses more than 200 times higher than the RfD did not adversely affect behavior or IQ of children at age 3 to 6 years. In laboratory animals, developmental toxicity including decreased fetal size and pup weight, increased stillborn pups, and increased pup deaths during early lactation were reported at doses over 1,400 times higher than the RfD.

[4]Male reproductive toxicity effects in humans are identified as critical effects for all durations. Female reproductive toxicity, including amenorrhea, dysmenorrhea or other menstrual disorders have been reported in humans at doses over 200 times higher than the RfD.

[5]Nervous system effects are identified as critical effects for all durations. Venlafaxine is a neurologically-active drug with intended pharmacological effects on the nervous system.

References:

Archer, D. F., J. V. Pinkerton, C. J. Guico-Pabia, E. Hwang, R. F. Cheng and I. Study (2013). Cardiovascular, cerebrovascular, and hepatic safety of desvenlafaxine for 1 year in women with vasomotor symptoms associated with menopause (reviewed abstract only). *Menopause* 20(1): 47-56.

Basterzi, A. D., K. Yazici, V. Buturak, B. Cimen, A. Yazici, G. Eskandari, et al. (2010). Effects of venlafaxine and fluoxetine on lymphocyte subsets in patients with major depressive disorder: a flow cytometric analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 34(1): 70-75 (abstract reviewed).

Boucher, N., G. Koren and L. Beaulac-Baillargeon (2009). Maternal use of venlafaxine near term: correlation between neonatal effects and plasma concentrations. *Ther Drug Monit* 31(3): 404-409.

Broy, P. and A. Berard (2010). Gestational exposure to antidepressants and the risk of spontaneous abortion: a review. *Curr Drug Deliv* 7(1): 76-92.

Cobalt Pharmaceutical Company (2014). Canada Drug Products Monograph, Venlafaxine XR, March 3, 2014.

Coleman, K. A., V. Y. Xavier, T. L. Palmer, J. V. Meaney, L. M. Radalj and L. M. Canny (2012). An indirect comparison of the efficacy and safety of desvenlafaxine and venlafaxine using placebo as the common comparator (reviewed abstract). *CNS Spectr* 17(3): 131-141.

da-Silva, V. A., S. P. Altenburg, L. R. Malheiros, T. G. Thomaz and C. J. Lindsey (1999). Postnatal development of rats exposed to fluoxetine or venlafaxine during the third week of pregnancy. *Braz J Med Biol Res* 32(1): 93-98.

Denys, D., S. Fluitman, A. Kavelaars, C. Heijnen and H. G. Westenberg (2006). Effects of paroxetine and venlafaxine on immune parameters in patients with obsessive compulsive disorder. *Psychoneuroendocrinology* 31(3): 355-360 (abstract reviewed).

Dubovicky, M., E. Csaszarova, Z. Brnoliakova, E. Ujhazy, J. Navarova and M. Mach (2012). Effect of prenatal administration of venlafaxine on postnatal development of rat offspring. *Interdiscip Toxicol* 5(2): 92-97.

ECHA (European Chemicals Agency). (2014). "CAS 93413-62-8 Search using The Global Portal to Information on Chemical Substances (eChemPortal), hosted by OECD (Organization for Economic Cooperation and Development)." Retrieved 5/23/2014

Emslie, G. J., R. L. Findling, P. P. Yeung, N. R. Kunz and Y. Li (2007a). Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry* 46(4): 479-488.

Emslie, G. J., P. P. Yeung and N. R. Kunz (2007b). Long-term, open-label venlafaxine extended-release treatment in children and adolescents with major depressive disorder. *CNS Spectr* 12(3): 223-233.

Findling, R. L., J. Groark, D. Chiles, S. Ramaker, L. Yang and K. A. Tourian (2014). Safety and tolerability of desvenlafaxine in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol* 24(4): 201-209.

Ghanizadeh, A., R. D. Freeman and M. Berk (2013). Efficacy and adverse effects of venlafaxine in children and adolescents with ADHD: a systematic review of non-controlled and controlled trials. *Rev Recent Clin Trials* 8(1): 2-8.

Hill, L. and K. C. Lee (2013). Pharmacotherapy considerations in patients with HIV and psychiatric disorders: focus on antidepressants and antipsychotics. *Ann Pharmacother* 47(1): 75-89 (abstract reviewed).

HSDB. (2014). "National Library of Medicine HSDB Database: Venlafaxine." Retrieved May 2014, 2014.

Hulisz, D., Lagzdins, M. (2008). Drug-Induced Hypertension. *U.S. Pharmacist* 33(9): HS11-HS20.

Ilett, K. F., L. P. Hackett, L. J. Dusci, M. J. Roberts, J. H. Kristensen, M. Paech, et al. (1998). Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk. *Br J Clin Pharmacol* 45(5): 459-462.

Ilett, K. F., J. H. Kristensen, L. P. Hackett, M. Paech, R. Kohan and J. Rampono (2002). Distribution of venlafaxine and its O-desmethyl metabolite in human milk and their effects in breastfed infants. *Br J Clin Pharmacol* 53(1): 17-22.

Iwata, N., K. A. Tourian, E. Hwang, L. Mele and C. Vialet (2013). Efficacy and safety of desvenlafaxine 25 and 5050% shaded blockmg/day in a randomized, placebo-controlled study of depressed outpatients (abstract reviewed). *J Psychiatr Pract* 19(1): 5-14.

Kamath, J. and V. Handratta (2008). Desvenlafaxine succinate for major depressive disorder: a critical review of the evidence. *Expert Rev Neurother* 8(12): 1787-1797.

Kjaersgaard, M. I., E. T. Parner, M. Vestergaard, M. J. Sorensen, J. Olsen, J. Christensen, et al. (2013). Prenatal antidepressant exposure and risk of spontaneous abortion - a population-based study. *PLoS One* 8(8): e72095.

Lee, K. M. and Y. K. Kim (2006). The role of IL-12 and TGF-beta1 in the pathophysiology of major depressive disorder. *Int Immunopharmacol* 6(8): 1298-1304 (abstract reviewed).

Liebowitz, M. R., K. A. Tourian, E. Hwang, L. Mele and I. Study (2013). A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/day in adult outpatients with major depressive disorder. *BMC Psychiatry* 13: 94.

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2011). "MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses." from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf.

Nakhai-Pour, H. R., P. Broy and A. Berard (2010). Use of antidepressants during pregnancy and the risk of spontaneous abortion (abstract reviewed). *CMAJ* 182(10): 1031-1037.

Nulman, I., G. Koren, J. Rovet, M. Barrera, A. Pulver, D. Streiner, et al. (2012). Neurodevelopment of children following prenatal exposure to venlafaxine, selective serotonin reuptake inhibitors, or untreated maternal depression. *Am J Psychiatry* 169(11): 1165-1174.

Park, P., J. Caballero and H. Omidian (2014). Use of serotonin norepinephrine reuptake inhibitors in the treatment of attention-deficit hyperactivity disorder in pediatrics. *Ann Pharmacother* 48(1): 86-92.

Polen, K. N., S. A. Rasmussen, T. Riehle-Colarusso, J. Reefhuis and S. National Birth Defects Prevention (2013). Association between reported venlafaxine use in early pregnancy and birth defects, national birth defects prevention study, 1997-2007. *Birth Defects Res A Clin Mol Teratol* 97(1): 28-35.

Rampono, J., S. Teoh, L. P. Hackett, R. Kohan and K. F. Ilett (2011). Estimation of desvenlafaxine transfer into milk and infant exposure during its use in lactating women with postnatal depression. *Arch Womens Ment Health* 14(1): 49-53.

Sansone, R. A. and L. A. Sansone (2014). Serotonin norepinephrine reuptake inhibitors: a pharmacological comparison. *Innov Clin Neurosci* 11(3-4): 37-42.

Shea, M. L., L. D. Garfield, S. Teitelbaum, R. Civitelli, B. H. Mulsant, C. F. Reynolds, 3rd, et al. (2013). Serotonin-norepinephrine reuptake inhibitor therapy in late-life depression is associated with increased marker of bone resorption. *Osteoporos Int* 24(5): 1741-1749.

Snyder, S., RA Trenholm, EM Snyder, GM Bruce, RC Pleus, and JDC Hemming, (2008). Toxicological Relevance of EDCs and Pharmaceuticals in Drinking Water. AWWA Research Foundation.

Sopko, M. A., Jr., M. J. Ehret and M. Grgas (2008). Desvenlafaxine: another "me too" drug? *Ann Pharmacother* 42(10): 1439-1446.

Steinhorn, R. H. (2010). Neonatal pulmonary hypertension. *Pediatr Crit Care Med* 11(2 Suppl): S79-84.

Tynan, R. J., J. Weidenhofer, M. Hinwood, M. J. Cairns, T. A. Day and F. R. Walker (2012). A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on LPS stimulated microglia. *Brain Behav Immun* 26(3): 469-479 (abstract reviewed).

U.S. Environmental Protection Agency - Office of Research and Development. (1988). "Recommendations for and Documentation of Biological Values for Use in Risk Assessment." from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855.

U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). "Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose." from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose.

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3

U.S. FDA. (2007). ""U.S. Food and Drug Administration - Center for Drug Evaluation and Research. Risk Assessment and Risk Mitigation Reviews for NDA 21-992 for Pristiq (Desvenlafaxine Succinate).", from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021992s000TOC.cfm.

U.S. FDA. (2008). "U.S. Food and Drug Adminstration - Center for Drug Evaluation and Research. Pharmacology Reviews for NDA 21-992 for Pristiq (Desvenlafaxine Succinate) Extended Release Tablets. from Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.", from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021992s000TOC.cfm.

Uguz, F., M. Sahingoz, S. A. Kose, O. Ozbebit, C. Sengul, Y. Selvi, et al. (2012). Antidepressants and menstruation disorders in women: a cross-sectional study in three centers. *Gen Hosp Psychiatry* 34(5): 529-533.

Vidal, R., E. M. Valdizan, M. T. Vilaro, A. Pazos and E. Castro (2010). Reduced signal transduction by 5-HT4 receptors after long-term venlafaxine treatment in rats. *Br J Pharmacol* 161(3): 695-706.

Vollmar, P., S. Nessler, S. R. Kalluri, H. P. Hartung and B. Hemmer (2009). The antidepressant venlafaxine ameliorates murine experimental autoimmune encephalomyelitis by suppression of pro-inflammatory cytokines. *Int J Neuropsychopharmacol* 12(4): 525-536 (abstract reviewed).

Wyeth Pharmaceuticals Inc. a subsidiary of Pfizer Inc. (2014a). "EFFEXOR XR - Venlafaxine hydrochoride capsule, extended release FDA label." from http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=53c3e7ac-1852-4d70-d2b6-4fca819acf26.

Wyeth Pharmaceuticals Inc. a subsidiary of Pfizer Inc. (2014b). "Pristiq Extended Release (desvenlafaxine succinate) Drug Label." from http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=0f43610c-f290-46ea-d186-4f998ed99fce.

Web Publication Date: August 2020

Toxicological Summary for: Xylenes

CAS: **1330-20-7**

Synonyms: xylene; xylene mixture; o-,m-,p-xylene; xylenes mixed isomers; xylol; dimethylbenzene

Xylenes are a mixture of three isomers: meta-xylene (m-xylene), ortho-xylene (o-xylene), and para-xylene (p-xylene) with the meta-isomer usually being the dominant part of the mixture at 40-70%. The exact composition of the commercial xylene grade depends on the source but a typical mixture will also contain ethylbenzene at 6 - 20% in addition to the three isomers. The environmental fate (transport, partitioning, transformation, and degradation) is expected to be similar for each of the xylene isomers based on the similarities of their physical and chemical properties (ATSDR, 2007). The metabolism of each individual isomer is thought to be similar, and the U.S. Environmental Protection Agency, 2003 IRIS Toxicological Review states that, "although differences in the toxicity of the xylene isomers have been detected, no consistent pattern following oral or inhalation exposure has been identified" (USEPA, 2003).

Acute Non-Cancer Health Based Value (nHBV$_{Acute}$) =700 µg/L

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

$$= \frac{(1.0\ mg/kg\text{-}d) \times (0.2)^{*} \times (1000\ µg/mg)}{(0.290\ L/kg\text{-}d)^{**}}$$

$$= 689\ rounded\ to\ \mathbf{700\ µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 30/30 = 1.0 mg/kg-d (Long Evans Rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	125 mg/kg-d (NOAEL; Dyer, 1988 aci ATSDR 2007)
Dose Adjustment Factor (DAF):	0.24, Body weight scaling, default (MDH, 2017)(USEPA, 2011)
Human Equivalent Dose (HED):	POD x DAF = 125 mg/kg-d x 0.24 = 30 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Altered visual evoked potentials
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = 300 µg/L

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

$$= \frac{(0.38 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

= 262 rounded to **300 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 115/300 = 0.38 mg/kg-d (F344/N Rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	500 mg/kg-d (NOAEL; NTP, 1986 (14 day study))
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (MDH, 2017) (USEPA, 2011)
Human Equivalent Dose (HED):	POD x DAF = 500 mg/kg-d x 0.23 = 115 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (lack of multigenerational reproductive study as well as adequate ototoxicity and neurotoxicity studies. Neurotoxicity was identified as a sensitive endpoint from inhalation studies.)
Critical effect(s):	Decreased body weight gain
Co-critical effect(s):	Altered visual evoked potentials, decreased fetal body weight, increased fetal malformations
Additivity endpoint(s):	Developmental, Nervous System

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = 300 µg/L

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

$$= \frac{(0.12 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 324 rounded to **300 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 34.5/300 = 0.12 mg/kg-d (SD Rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	150 mg/kg-d (NOAEL; Condie, 1988)

Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (MDH, 2017) (USEPA, 2011)
Human Equivalent Dose (HED):	POD x DAF = 150 mg/kg-d x 0.23 = 34.5 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (lack of multigenerational reproductive study as well as adequate ototoxicity and neurotoxicity studies. Neurotoxicity was identified as a sensitive endpoint from inhalation studies.)
Critical effect(s):	Increased kidney weights, minimal chronic nephropathy
Co-critical effect(s):	Altered visual evoked potentials, decreased fetal body weight, decreased adult body weight gain, increased fetal malformations, hyperactivity
Additivity endpoint(s):	Developmental, Nervous system, Renal (kidney) system

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = nHBV$_{Subchronic}$ = 300 µg/L

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

$$= \frac{(0.16 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

$$= 711 \text{ rounded to } 700 \text{ µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 48.3/300 = 0.16 mg/kg-d (F344/N rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	179 mg/kg-d (NOAEL; NTP, 1986 (2 year study))
Dose Adjustment Factor (DAF):	0.27, Body weight scaling, default (MDH, 2017) (USEPA, 2011)
Human Equivalent Dose (HED):	POD x DAF = 179 mg/kg-d x 0.27 = 48.3 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (lack of multigenerational reproductive study as well as adequate ototoxicity and neurotoxicity studies. Neurotoxicity was identified as a sensitive endpoint from inhalation studies.)
Critical effect(s):	Decreased body weight gain

	Co-critical effect(s):	Altered evoked visual potentials, decreased body weight gain, hyperactivity, minimal chronic nephropathy and increased kidney weights
	Additivity endpoint(s):	Nervous system, Renal (kidney) system

The Chronic nHBV must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Subchronic nHBV of 300 µg/L. Additivity endpoints: Developmental, Nervous system, Renal (kidney) system.

Cancer Health Based Value (cHBV) = Not Applicable

	Cancer classification:	Not Classified
	Slope factor (SF):	Not Applicable
	Source of cancer slope factor (SF):	Not Applicable
	Tumor site(s):	Not Applicable

Volatile: Yes (high)

Summary of Guidance Value History:

A non-cancer Health Risk Limit (HRL) of 10,000 µg/L was promulgated in 1993/1994. Acute, short-term, subchronic, and chronic health-based values (HBV) of 800, 300, 300, and 300 µg/L, respectively, were derived in 2010 and were promulgated as HRLs in 2011. In 2019, MDH re-evaluated the non-cancer HRLs, resulting in a lower acute duration value of 700 µg/L and no changes to the values for short-term, subchronic, and chronic durations. The changes to existing guidance were due to 1) using MDH's most recent risk assessment methodology and 2) rounding to one significant digit. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in changes to the 2019 guidance values.

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	Yes	Yes	Yes	Yes
Effects observed?	-	Yes[1]	Yes[2]	Yes[3]	Yes[4]

Comments on extent of testing or effects:

[1]Decreased thymus and spleen weights have been reported in laboratory animals at doses over 1,000 times higher than the current short-term reference dose.

[2]Developmental effects are included as co-critical effects for the short-term, subchronic, and chronic durations. Increased fetal malformations, mostly cleft palate malformations, were observed in laboratory animals in the absence of maternal toxicity at doses less than one fold higher than doses that caused increased kidney weights and mild nephropathy and decrease body weight gain in short-term, subchronic, and chronic duration studies.

[3]Decreased uterine weight and increased resorptions have been reported in laboratory animals at doses approximately 700 times higher than the current short-term reference dose. Other studies in laboratory animals at similar doses reported no adverse reproductive effects.

[4]The acute reference dose is based on neurotoxicity in male rats with observed effects of altered visual evoked potentials. Transient hyperactivity was observed in laboratory animals at doses at or less than one fold difference than doses observed to cause increased kidney weights and mild nephropathy in laboratory animals. Nervous system effects of altered visual evoked potentials and transient hyperactivity were listed as co-critical effects for the short-term, subchronic, and chronic durations. The nervous system was identified as a sensitive endpoint following inhalation exposure.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). (2007). Toxicological Profile for Xylene. Retrieved from http://www.atsdr.cdc.gov/toxprofiles/tp71.pdf

California State Water Resources Control Board. (2019). Water Quality Goals Online Database. Retrieved from https://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/

Condie, L., Hill, J., & Borzelleca, J. (1988). Oral toxicology studies with xylene isomers and mixed xylenes. *Drug Chem Toxicol, 11*(4), 329-354. doi:10.3109/01480548809018107

Dyer, R., Bercegeay, M., & Mayo, L. (1988). Acute exposures to p-xylene and toluene alter visual information processing. *Neurotoxicol Teratol, 10*(2), 147-153. doi:0892-0362(88)90079-7 [pii]

Gagnaire, F., Langlais, C. (2005). Relative ototoxicity of 21 aromatic solvents. *Arch Toxicol, 79*, 346-354.

Government of Canada. (1993). *Priority Substances List Assessment Report: Xylenes*. Retrieved from http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl1-lsp1/xylenes/xylene-eng.pdf.

Health Canada. (2014). *Guidelines for Canadian Drinking Water Quality - Guideline Technical Document for Toluene, Ethylbenzene, and Xylenes*. Retrieved from https://www.canada.ca/content/dam/canada/health-canada/migration/healthy-canadians/publications/healthy-living-vie-saine/water-toluene-eau/alt/water-toluene-eau-eng.pdf

Korsak, Z., Wisniewska-Knypl, J., & Swiercz, R. (1994). Toxic effects of subchronic combined exposure to n-butyl alcohol and m-xylene in rats. *Int J Occup Med Environ Health, 7*(2), 155-166.

Kum, C., Sekkin, S., Kiral, F., & Akar, F. (2007). Effects of xylene and formaldehyde inhalations on renal oxidative stress and some serum biochemical parameters in rats. *Toxicol Ind Health, 23*(2), 115-120.

Marks, T. A., Ledoux, T. A., & Moore, J. A. (1982). Teratogenicity of a commercial xylene mixture in the mouse. *J Toxicol Environ Health, 9*(1), 97-105.

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 https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2017). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017). Retrieved from
https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Toxicology Program. (1986). *NTP Toxicology and Carcinogenesis Studies of Xylenes (Mixed) (60% m-Xylene, 14% p-Xylene, 9% o-Xylene, and 17% Ethylbenzene) (CAS No. 1330-20-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies).* (0888-8051). Retrieved from
https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr327.pdf

Saillenfait, A., Gallissot, F., Morel, G., & Bonnet, P. (2003). Developmental toxicities of ethylbenzene, ortho-, meta-, para-xylene and technical xylene in rats following inhalation exposure. *Food Chem Toxicol, 41*(3), 415-429. doi:S0278691502002314 [pii]

U.S. Environmental Protection Agency (USEPA). (2003). *TOXICOLOGICAL REVIEW OF XYLENES (CAS No. 1330-20-7).* Retrieved from
https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0270tr.pdf.

U.S. Environmental Protection Agency (USEPA). Regional Screening Levels (RSLs) - Generic Tables. Retrieved from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables-november-2017

U.S. Environmental Protection Agency (USEPA). (2009). Provisional Peer-Reviewed Toxicity Values for Xylenes (CASRN 1330-20-7). Retrieved from
https://cfpub.epa.gov/ncea/pprtv/documents/XyleneMixture.pdf

U.S. Environmental Protection Agency (USEPA). (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor. Retrieved from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency (USEPA). (2018). *2018 Edition of the Drinking Water Standards and Health Advisories Tables*. Retrieved from
https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf

U.S. Environmental Protection Agency (EPA). (2019). Exposure Factors Handbook Chapter 3 Update 2019. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3 .

Wolfe, G. (1988a). Subchronic toxicity study in rats with m-xylene. *Rockville, MD, Report by Hazleton Laboratories America, Inc., sponsored by Dynamac Corporation. Project No. 2399–108.*

Wolfe, G. (1988b). Subchronic toxicity study in rats with p-xylene *Report by Hazleton Laboratories America, Inc., sponsored by Dynamac Corporation. Project No. 2399–110.*

World Health Organization (WHO). (2008). Guidelines for Drinking Water Quality Third Edition. Retrieved from https://www.who.int/water_sanitation_health/dwq/fulltext.pdf

APPENDIX F. MMB Correspondence

November 22, 2022

Mr. Thomas Carr
Executive Budget Officer
Minnesota Management and Budget
658 Cedar St., Ste. 400
St. Paul, MN 55155

> ***Re:*** **Proposed Amendments to Rules Governing Health Risk Limits,** *Minnesota Rules,*
> *Parts 4717.7500, .7850, .7860; Revisor's ID Number RD4587*

Dear Mr. Carr:

Minnesota Statutes, section 14.131, requires that an agency engaged in rulemaking consult with the Commissioner of Minnesota Management and Budget "to help evaluate the fiscal impact and fiscal benefits of the proposed rule on units of local government."

Enclosed for your review are copies of the following documents on the above-referenced rule revisions:

1. November 1, 2022, Revisor's draft of the proposed rule; and
2. November 17, 2022, draft SONAR.

If you or any other representative of the Commissioner of Minnesota Management & Budget has questions about the proposed rule revisions, please email me at *josh.skaar@state.mn.us*. If necessary, you can also call me at 651-368-0751.

Sincerely,

/s/ Josh Skaar

Josh Skaar
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Rulemaking Coordinator
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Enclosures: