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

Adopted as Rule: November 2023

Toxicological Summary for: Tetrachloroethylene

CAS: 127-18-4
Synonyms: Perchloroethene; Perchloroethylene; PERC; PCE

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

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = 7 µg/L

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

$$= \frac{\text{(0.0026 mg/kg/d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 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 Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Subchronic}$ = 7 µg/L

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

$$= \frac{\text{(0.0026 mg/kg/d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 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 nHRL must be protective of the shorter duration exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Subchronic nHRL of 7 µg/L. Additivity endpoint: Nervous system.

Cancer Health Risk Limit (cHRL) = 4 µg/L

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

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(0.025 \times 10^{*} \times 0.155\ \text{L/kg-d}^{**} \times 2) + (0.025 \times 3^{*} \times 0.040\ \text{L/kg-d}^{**} \times 14) + (0.025 \times 1^{*} \times 0.042\ \text{L/kg-d}^{**} \times 54)] / 70}$$

= **4 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 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. In November 2023, the guidance values were adopted into Minnesota Rules, 4717.7860, as Health Risk Limits (HRLs).

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

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