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

Adopted as Rule: November 2023

Toxicological Summary for: 1,4-Dichlorobenzene

CAS: **106-46-7**

Synonyms: p-Dichlorobenzene, paradichlorobenzene, para-Dichlorobenzene

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

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 50 µg/L

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

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

= 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 Risk Limit ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 50 µg/L

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

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

= 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 nHRL must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 50 µg/L. Additivity endpoints: **Developmental, Hepatic (liver) system, Nervous system**

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Short\text{-}term}$ = 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 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 = 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 nHRL must be protective of the short-term and subchronic exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 50 µg/L. Additivity endpoints: Developmental, Hepatic (liver) system, Nervous system

Cancer Health Risk Limit (cHRL) = 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 nHRLs 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. 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 (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.

National Institutes of Health. (Accessed April 2019). Toxnet: International Toxicity Estimates for Risk (ITER) Database.

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/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

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