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

Adopted as Rule: November 2023

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 Risk Limit ($nHRL_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 20 µg/L

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

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

$$= \mathbf{20\ \mu g/L}$$

*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 Risk Limit ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 20 µg/L

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

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

= 78 rounded to 80 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 HRL must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic HRL is set equal to the Short-term nHRL of 20 µg/L. Additivity endpoint: Developmental

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Short\text{-}term}$ = 20 µg/L

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

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

= 80 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)

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

Cancer Health Risk Limit (cHRL) = 3 µg/L

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

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

= 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. 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	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.

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