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 (nHBVAcute) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health-Based Value (nHBVShort-term) = 20 µg/L

\[
\text{(Reference Dose, mg/kg-d) \times (Relative Source Contribution) \times (Conversion Factor)} \\
\text{(Short-term Intake Rate, L/kg-d)} \\
= \left(\frac{0.029 \text{ mg/kg-d}}{0.290 \text{ L/kg-d}}\right) \times \left(\frac{1000 \text{ µg/mg}}{0.2}\right) \\
= 20 \text{ µg/L}
\]

**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 = 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 BMDL05, developmental toxicity study by Kirk 1995)

Dose Adjustment Factor (DAF): 0.23, body weight scaling, default (US EPA 2011 and MDH 2017)

1,2-Dichloropropane -1
Human Equivalent Dose (HED): $\text{POD} \times \text{DAF} = 12.8 \text{mg/kg-d} \times 0.23 = 2.94 \text{mg/kg-d}$

Total uncertainty factor (UF): 100

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

Critical effect(s): Delayed ossification of the fetal skull

Co-critical effect(s): None

Additivity endpoint(s): Developmental

Subchronic Non-Cancer Health-Based Value ($nHBV_{\text{subchronic}}$) = $nHBV_{\text{short-term}} = 20 \mu g/L$

\[
(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})
\]
\[
(\text{Subchronic Intake Rate, L/kg-d})
\]
\[
= (0.029 \text{mg/kg-d})^{***} \times (0.2)^* \times (1000 \mu g/\mu g) \\
(0.074 \text{L/kg-d})^{**}
\]
\[
= 78 \text{rounded to } 80 \mu g/L
\]


**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 ($nHBV_{\text{chronic}}$) = $nHBV_{\text{short-term}} = 20 \mu g/L$

\[
(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})
\]
\[
(\text{Chronic Intake Rate, L/kg-d})
\]
\[
= (0.018 \text{mg/kg-d}) \times (0.2)^* \times (1000 \mu g/\mu g) \\
(0.045 \text{L/kg-d})^{**}
\]
\[
= 80 \mu g/L
\]


**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 = 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

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

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

\[
= 2.68 \text{ rounded to } 3 \text{ µg/L}
\]

*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)

1,2-Dichloropropane -3
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.

<table>
<thead>
<tr>
<th>Tested for specific effect?</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
<th>Reproductive</th>
<th>Neurotoxicity</th>
</tr>
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<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Effects observed?</td>
<td>−1</td>
<td>−</td>
<td>Yes^2</td>
<td>Yes^3</td>
<td>Yes^4</td>
</tr>
</tbody>
</table>

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.
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:


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](https://oehha.ca.gov/proposition-65/chemicals/12-dichloropropane)


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.


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


