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

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

\[
= \frac{(0.069 \text{ mg/kg-d}) \times (0.2)\text{*}}{(0.290 \text{ L/kg-d})^{\text{**}}}
\]

= 47.5 rounded to 50 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 = 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

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Subchronic Non-Cancer Health-Based Value \( (nHBV_{\text{subchronic}}) = nHBV_{\text{short-term}} = 50 \mu g/L \)

\[
(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor}) \\
= \frac{(0.042 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \mu g/mg)}{(0.074 \text{ L/kg-d})^{**}}
\]

= 113 rounded to 100 \( \mu g/L \)

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

<table>
<thead>
<tr>
<th>Reference Dose/Concentration:</th>
<th>HED/Total UF = 4.21/100 = 0.042 mg/kg-d (Beagle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of toxicity value:</td>
<td>Determined by MDH in 2019</td>
</tr>
<tr>
<td>Dose Adjustment Factor (DAF):</td>
<td>0.59 Body weight scaling, default for female beagle in 1-yr toxicity study (US EPA 2011 and MDH 2017)</td>
</tr>
<tr>
<td>Human Equivalent Dose (HED):</td>
<td>POD x DAF = 7.14 mg/kg-d x 0.59 = 4.21 mg/kg-d</td>
</tr>
<tr>
<td>Total uncertainty factor (UF):</td>
<td>100</td>
</tr>
<tr>
<td>Uncertainty factor allocation:</td>
<td>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.</td>
</tr>
</tbody>
</table>

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\textsubscript{Chronic}) = nHBV\textsubscript{Short-term} = 50 µg/L**

\[
\text{Chronic Intake Rate, L/kg-d} = (0.032 \text{ mg/kg-d}) \times (0.2) \times (1000 \text{ µg/mg}) = 142 \text{ rounded to 100 µg/L}
\]

**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 = 32.1/1000 = 0.032 mg/kg-d (B6C3F\textsubscript{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\textsubscript{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.

<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>
</thead>
<tbody>
<tr>
<td>Effects observed?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**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:

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