2013 Health Risk Limits for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Adopted as Rule: September 30, 2013

Toxicological Summary for 1,2,4-Trichlorobenzene: CAS: 120-82-1

Synonyms: None

Acute Non-Cancer Health Risk Limit ($nHRL_{acute}$) = Not derived (insufficient information)

Short-term Non-Cancer Health Risk Limit ($nHRL_{short\text{-}term}$) = 100 µg/L

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

$$= \frac{\text{(0.17 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 118 rounded to **100 µg/L**

Reference Dose / Concentration:	0.17 mg/kg-d (rats)
Source of toxicity value:	MDH, 2012
Point of Departure:	75 mg/kg-d (NOAEL) – Developmental gavage study (Black et al. 1988). (LOAEL 150 mg/kg-d)
Human Equivalent Dose Adjustment:	17 mg/kg-d (75 x 0.23) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability; 3 for database insufficiencies (limited data suggests that the adrenal gland may be a more sensitive endpoint than the liver – additional short-term studies are warranted)
Critical effect(s):	Mild hepatic lesions, increase in mixed function oxidase, and decreased hematocrit and hemoglobin
Co-critical effect(s):	Adrenal weight gain and vacuolization of the middle zone of the adrenal cortex, decreased corticosterone levels, liver enzyme induction and sight hepatocellular hypertrophy
Additivity endpoint(s):	Hepatic (liver) system; Adrenal (E); Hematological (blood) system

Subchronic Non-Cancer Health Risk Limit ($nHRL_{subchronic}$) = $nHRL_{short\text{-}term}$ = 100 µg/L

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

$$= \frac{\text{(0.070 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 182 rounded to 200 µg/L

Reference Dose / Concentration:	0.070 mg/kg-d (rats)

Reference Dose / Concentration:	0.070 mg/kg-d (rats)
Source of toxicity value:	MDH, 2012
Point of Departure:	8.9 mg/kg-d NOAEL - 2 generation drinking water study in rats (Robinson, et al., 1981). (LOAEL 33 mg/kg-d)
Human Equivalent Dose Adjustment:	2.1 mg/kg-d (8.9 x 0.24) (MDH, 2011)
Total uncertainty factor:	30
UF allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability
Critical effect(s):	Increased adrenal weight
Co-critical effect(s):	Increased liver weight and increased liver enzyme levels; adrenal weight gain and vacuolization of the middle zone of the adrenal cortex, decreased corticosterone levels; increased kidney weights
Additivity endpoint(s):	Hepatic (liver) system; Adrenal (E); Renal (kidney) system

The Subchronic nHRL must be protective of the shorter-term exposures that occur within the subchronic periods and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 100 µg/L (Additivity endpoints: Hepatic (liver) system; Adrenal (E); Hematological (blood) system.

Chronic Non-Cancer Health Risk Limit ($nHRL_{chronic}$) = 100 µg/L

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

$$= \frac{\text{(0.021 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= 98 rounded to **100 µg/L**

Reference Dose / Concentration:	0.021 mg/kg-d (rats)
Source of toxicity value:	MDH, 2012
Point of Departure:	8.9 mg/kg-d NOAEL - 2 generation drinking water study in rats (Robinson, et al., 1981) (LOAEL 33 mg/kg-d)
Human Equivalent Dose Adjustment:	2.1 mg/kg-d (8.9 x 0.24) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability; 3 for use of a subchronic study for the chronic duration - effects and points of departure across duration indicates limited increase in severity of effects)
Critical effect(s):	Increased adrenal weight
Co-critical effect(s):	Increased liver weight and increased liver enzyme levels; adrenal weight gain and vacuolization of the middle zone of the adrenal cortex, decreased corticosterone levels; increased kidney weights and renal mineralization
Additivity endpoint(s):	Hepatic (liver) system; Adrenal (E); Renal (kidney) system

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

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

$$= \frac{(1E\text{-}5) \times (1000\ \mu g/mg)}{[(0.029 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.029 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.029 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 3.54 rounded to **4 µg/L**

Cancer classification: "Likely to be carcinogenic to Humans"
Slope factor: 0.029 $(mg/kg\text{-}day)^{-1}$ based on liver tumors in male mice
Source of slope factor: EPA, NCEA 2009 (provisional peer reviewed slope factor based on the data from the CMA 1994b study)
Tumor site(s): Liver in male and female mice

Volatile: Yes (highly volatile)

Summary of changes since 1993/1994 HRL promulgation:
Short-term, Subchronic and Chronic non-cancer Health-Based Values (HBVs) of 200, 200, and 100 µg/L and a Cancer HBV of 4 µg/L were derived in 2011. MDH reevaluated the non-cancer HBVs in 2012 to incorporate HED methodology. The resulting Short-term and Subchronic HBVs (100 µg/L) were 2-fold lower than the values derived in 2011 and the Chronic HBV (100 µg/L) was unchanged. The HBVs were adopted as HRLs in 2013.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	No	Yes	Yes	Yes[4]
Effects?	Yes[1]	No	Yes[2]	Yes[3]	No

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] Increased adrenal gland weight was identified as the critical effect for the subchronic and chronic durations. This effect was also a co-critical effect for the short-term duration and was seen at a dose (53 mg/kg-d) that was 30% lower than the short-term point of departure of 75 mg/kg-d. However, the adrenal effect was observed in a short-term study that utilized only one dose level, which precludes evaluation of a dose response or identification of a point of departure. A database uncertainty factor was incorporated into the derivation of the short-term RfD to address the lack of adequate short-term studies evaluating effects on the adrenal gland.

Mice dermally exposed to 30% and 60% solutions of 1,2,4-trichlorobenzene experienced increased adrenal gland weight and adrenal amyloidosis. A single intraperitoneal injection of 1,2,4-trichlorobenzene resulted in decreased in T4 levels in rats at a dose 4.5 to 7 times higher than the short-term critical NOAEL of 75 mg/kg-day.

[2] In an oral developmental study, offspring exposed to 1,2,4-trichlorobenzene (and evaluated as embryos) exhibited a decrease in head and crown rump lengths, a decrease in the number of somites, and a

decrease in embryonic protein content at a dose approximately 5 times higher (360 mg/kg-d) than the short-term point of departure of 75 mg/kg-day and more than 10 times higher than the subchronic and chronic point of departure. Also, one 2 generation and 2 additional developmental oral studies have been conducted. No developmental effects were reported at dose levels up to ~54 mg/kg-d in the 2 generation study in rats. No developmental effects were reported in mice at dose levels up to 130 mg/kg-d or in rats exposed at dose levels up to 300 mg/kg-d.

[3] In a reproductive study there was an increased incidence of dead embryos and fewer implantations in offspring exposed to 1,2,4,-TCB on gestation days 9 through 13 at a dose approximately 5 times higher than the short-term point of departure of 75 mg/kg-day and more than 10 times higher than the subchronic and chronic point of departure. Examination of reproductive organs was performed in oral subchronic toxicity studies and histopathological examination was performed in chronic carcinogenicity studies. Results from these studies do not indicate that the reproductive system is a sensitive endpoint.

[4] The 2 generation oral study included assessment of locomotor activity at various intervals up to 90 days in rats exposed to 1,2,4-TCB in drinking water at doses up to ~54 mg/kg-d - no effects were observed.

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