Adopted as Rule: September 30, 2013

Toxicological Summary for 1,2,3-Trichloropropane: CAS: 96-18-4

Synonyms: Glyceryl trichlorohydrin; glycerol trichlorhydrin; allyl trichloride; propane, 1,2,3-trichloro-; trichlorohydrin

Acute Non-Cancer Health Risk Limit ($nHRL_{acute}$) = 7 µg/L

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

$$= \frac{\text{(0.0042 mg/kg/d) x (0.5) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 7.3 rounded to **7 µg/L**

Reference Dose / Concentration:	0.0042 mg/kg-d (mice)
Source of toxicity value:	MDH 2012
Point of Departure:	3.2 mg/kg-d (BMDL, EPA IRIS 2009 based on NTP 1990)
Human Equivalent Dose Adjustment:	0.42 mg/kg-d [3.2 x 0.13] (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 interspecies variability (toxicodynamics); 10 intraspecies variability; 3 database uncertainty based on lack of additional information related to developmental toxicity.
Critical effect(s):	Decreased fetal survival
Co-critical effect(s):	None found
Additivity endpoint(s):	Developmental

Short-Term-Non-Cancer Health Risk Limit ($nHRL_{short\text{-}term}$) = 7 µg/L

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

$$= \frac{\text{(0.0042 mg/kg/d) x (0.5) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 7.3 rounded to **7 µg/L**

Reference Dose / Concentration:	0.0042 mg/kg-d (mice)
Source of toxicity value:	MDH 2012
Point of Departure:	3.2 mg/kg-d ((BMDL, EPA IRIS 2009 based on NTP 1990)
Human Equivalent Dose Adjustment:	0.42 mg/kg-d [3.2 x 0.13] (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies variability (toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty based on lack of additional

	information related to developmental toxicity.
Critical effect(s):	Decreased fetal survival
Co-critical effect(s):	None found
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Risk Limit ($nHRL_{subchronic}$) = $HRL_{short\text{-}term}$ = 7 µg/L

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

$$= \frac{\text{(0.0040 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 10.4 rounded to 10 µg/L

Reference Dose / Concentration:	0.0040 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	5.7 mg/kg-d (LOAEL, NTP 1993; 17-wk, gavage, rats)
Human Equivalent Dose Adjustment:	1.2 mg/kg-d [5.7 x 0.21] (MDH, 2011)
Total uncertainty factor:	300
UF allocation:	3 for interspecies variability (toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty based on lack of additional information related to developmental toxicity; 3 for use of a minimal LOAEL instead of NOAEL.
Critical effect(s):	Significant, dose-related reduction in serum pseudocholinesterase in female rats; considered to be related to early indications of liver toxicity.
Co-critical effect(s):	Significant decrease in fertility, significant decrease in the number of live pups, significant increase in cumulative days to litter; significant decrease in the proportion of males
Additivity endpoint(s):	Hepatic (liver) system, Developmental (reproductive)

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 7 µg/L (Additivity endpoint: Developmental).

Chronic Non-Cancer Health Risk Limit ($nHRL_{chronic}$) = $HRL_{short\text{-}term}$ = 7 µg/L

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

$$= \frac{\text{(0.0026 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= 12 rounded to 10 µg/L

Reference Dose / Concentration:	0.0026 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	1.1 mg/kg-d (BMDL, NTP 1993)

Human Equivalent Dose Adjustment:	0.26 mg/kg-d (1.1 x 0.24) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies variability (toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty based on lack of additional information related to developmental toxicity.
Critical effect(s):	Increased absolute liver weight in male rats.
Co-critical effect(s):	Liver necrosis, renal tubule hyperplasia, pancreatic acinar hyperplasia
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system, Pancreas

The Chronic nHRL must be protective of the shorter-term exposures that occur within the chronic periods and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 7 µg/L (Additivity endpoint: Developmental).

Cancer Health Risk Limit (cHRL) = 0.003 µg/L

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

$$= \frac{(1E\text{-}5) \times (1000\ \mu g/mg)}{[(30 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (30 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (30 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

$$= 0.0034 \text{ rounded to } \mathbf{0.003\ \mu g/L}$$

Cancer classification:	Likely to be carcinogenic to humans (EPA IRIS 2009)
Slope factor:	30 $(mg/kg\text{-}d)^{-1}$ (laboratory animal) (NTP 1993)
Source of slope factor:	EPA IRIS 2009 (for female mice)
Tumor site(s):	Forestomach, liver, Harderian gland, oral cavity, uterus.

Volatile: Yes (moderate)

Summary of changes since 1993/1994 HRL promulgation:
A cancer HRL of 40 µg/L was promulgated in 1993. In 2010, a revised cancer Health-Based Value (HBV) of 0.003 µg/L was derived. The 2010 cancer HBV is over 10,000 times lower than the 1993 HRL. Acute, Short-term, Subchronic and Chronic HBVs of 20, 20, 10, and 10 µg/L were derived in 2010. MDH reevaluated the non-cancer HBVs in 2012 to incorporate HED methodology. The resulting HBVs (7 µg/L for each duration) were 3-fold and 1.5-fold lower than the 2010 values. The HBVs were adopted as HRLs in 2013 and the 1993 HRL was repealed.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Secondary Observations	Secondary Observations	No	Yes[3]	No[4]
Effects?	Yes[1]	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] Secondary observations from histological evaluation of endocrine organs in existing animal studies showed mild changes in thyroid, testes, ovaries and epididymis at doses at nearly 2000 times higher than the acute, short-term, subchronic or chronic RfDs. Effects on increased estrous cycle length were reported in mice at over 900-fold above the acute, short-term subchronic, and chronic RfDs. Rats had increased incidences of preputial and clitoral gland tumors, mammary tumors, and pancreatic tumors and mice had increased incidences of uterine/cervical tumors at doses 300-800 fold higher than the chronic RfD.

[2] Immunotoxicity and immune function were not directly studied. Secondary observations noted in other studies include dose-related plasma cell hyperplasia and mandibular lymph node hyperplasia in female rats at doses at nearly 2000 times higher than the acute, short-term subchronic or chronic RfDs. The immunological significance of these effects is not known because none of these studies evaluated immune function.

[3]A 2-generation reproductive study was conducted in mice which found decreased viability of embryo/fetus, reduced fertility in females, decreased proportion of viable male pups, and effects on estrous cycle. This study is considered the critical study for both the acute and short-term endpoints. The most sensitive effect was decreased fetal/embryo viability occurring at a benchmark dose which was 800-1100 times higher than the subchronic and chronic RfDs.

[4]Neurotoxicity was not tested directly and there is no evidence of effects on neurological function or behavior. However, relative brain weights were significantly increased at doses over 2000-fold higher than the LOAEL for subchronic and chronic RfDs. There were no changes in brain cells or function noted in rats or mice after chronic oral exposure.

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EPA Office of Pesticide Programs http://www.epa.gov/pesticides/reregistration/status.htm

EPA Toxicity and Exposure Assessment for Children's Health (TEACH) http://www.epa.gov/teach/

EPA Voluntary Children's Chemical Evaluation Program
(VCCEP) http://www.epa.gov/oppt/vccep/pubs/chemmain.htm

European Union Pesticides
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