

Adopted as Rule: August 2018

Toxicological Summary for: Chloroform

CAS: 67-66-3

Synonyms: Trichloroform, Trichloromethane

Acute Non-Cancer Health Risk Limit (nHRL_{Acute}) = Not Derived (Insufficient Data)¹

¹ Note: the developmental/reproductive endpoints listed for subsequent durations are co-critical effects taken from supportive studies that do not constitute sufficient information to provide the basis for an acute nHRL value.

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

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

$$= \frac{(0.022 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.285 \text{ L/kg-d})^{**}}$$

$$= 15.4 \text{ rounded to } \mathbf{20 \text{ µg/L}}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.022 mg/kg-d (CD-1 Mouse)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	50 mg/kg-d (LOAEL, Munson et al. 1982)
Dose Adjustment Factor (DAF):	0.13 (Body weight scaling, subchronic average female mouse) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 50 mg/kg-d x 0.13 = 6.5 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for extrapolation from a LOAEL to a NOAEL
Critical effect(s):	Suppression of the humoral immune system (antigen forming cells)

Co-critical effect(s): Increased liver weight, liver lesions, decreased body weight gain in pups, increased frequency of incomplete skull ossification in fetuses
 Additivity endpoint(s): Developmental, Hepatic (liver) system, Immune system

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

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

$$= \frac{(0.022 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.070 \text{ L/kg-d})^{**}}$$

$$= 62.9 \text{ rounded to } 60 \text{ µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.

** Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration: HED/Total UF = 0.022 mg/kg-d (CD-1 Mouse)
 Source of toxicity value: Determined by MDH in 2016
 Point of Departure (POD): 50 mg/kg-d (LOAEL, Munson et al. 1982)
 Dose Adjustment Factor (DAF): 0.13 (Body weight scaling, subchronic average female mouse) (USEPA, 2011) (MDH, 2017)
 Human Equivalent Dose (HED): POD x DAF = 50 mg/kg-d x 0.13 = 6.5 mg/kg-d
 Total uncertainty factor (UF): 300
 Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for extrapolation from a LOAEL to a NOAEL
 Critical effect(s): Suppression of the humoral immune system (antigen forming cells)
 Co-critical effect(s): Increased liver weight and liver lesions, increased epididymal weights and degeneration of epididymal ductal epithelium, decreased body weight gain in pups, increased frequency of incomplete skull ossification in fetuses
 Additivity endpoint(s): Developmental, Hepatic (liver) system, Immune system, Male Reproductive system

The Subchronic nHRL must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 20 µg/L. Additivity endpoints: Developmental, Hepatic (liver) system, Immune system.

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

$$\frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Chronic Intake Rate, L/kg-d})}$$
$$= \frac{(0.020 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.044 \text{ L/kg-d})^{**}}$$
$$= 90.9 \text{ rounded to } 90 \text{ µg/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration: HED/Total UF = 0.020 mg/kg-d (Beagle Dogs)
Source of toxicity value: Determined by MDH in 2016
Point of Departure (POD): 1 mg/kg-d (time adjusted BMDL, Heywood et al. 1979)
Dose Adjustment Factor (DAF): 0.61 (Body weight scaling, 2+ year female dog) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED): POD x DAF = 1 mg/kg-d x 0.61 = 0.61 mg/kg-d
Total uncertainty factor (UF): 30
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s): Fatty cysts in the liver
Co-critical effect(s): None
Additivity endpoint(s): Hepatic (liver) system

The Chronic nHRL must be protective of the acute, short-term, and subchronic 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 endpoints: Developmental, Hepatic (liver) system, Immune system.

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification: Not likely to be carcinogenic to humans at doses that do not cause cytotoxicity and cell regeneration (USEPA, 2001)
Slope factor (SF): Not Applicable
Source of cancer slope factor (SF): Not Applicable
Tumor site(s): Hepatic (liver) and Renal (kidney)

Statement for non-linear carcinogens:

Chloroform is a nonlinear carcinogen and the water guidance of 20 µg/L is considered to be protective against cancer. Per USEPA 2001, cancer classification is described as “Likely to be carcinogenic to humans by all routes of exposure under dose conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues [and] not likely to be carcinogenic to humans by all routes of exposure at dose levels that do not cause cytotoxicity and cell regeneration”. (USEPA, 2001)

Volatile: Yes (high)

Summary of Guidance Value History:

A cancer Health Risk Limit (HRL) of 60 µg/L, based on an EPA cancer slope factor derived in 1992, was promulgated in 1993/1994. In 2001, EPA updated its IRIS review, stating that EPA now considers chloroform to be a carcinogen with a nonlinear threshold mode of action, therefore, a cancer slope factor was no longer applicable, and the RfD approach was sufficiently protective. Short-term, subchronic, and chronic noncancer HRLs all equal to 30 µg/L were promulgated in 2009. In 2016, MDH re-evaluated the noncancer HRLs, resulting in new noncancer short-term, subchronic, and chronic values of 20 µg/L. The 2016 noncancer HBVs were lower than the previous HRLs as a result of 1) using MDH’s most recent risk assessment methodology including the application of Human Equivalence Doses and 2) rounding to one significant digit. The 2016 guidance was adopted into rule as HRLs in 2018.

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	Yes	Yes	Yes	Yes
Effects observed?	-	Yes ¹	Yes ²	No ³	Yes ⁴

Comments on extent of testing or effects:

¹ General toxicity studies with immunological endpoints (Munson et al, 1982) are the critical studies for the short term and subchronic durations with a significant decrease in humoral immunity reported at 50 mg/kg-d (administered dose) in male and female mice following 14 and 90 day exposures. Decreased humoral immunity is identified as a critical effect. Higher doses (250 mg/kg-d (administered dose)) caused changes in cell-mediated immunity in female mice at 90 days.

² Developmental studies show that doses that are maternally toxic may also be toxic to the fetus and cause the same types of liver damage as observed in adult animals. In one

reproductive study in which the animals were exposed throughout their entire lifespan, damage to the liver was observed in adult offspring at a dose that was lower than the dose that was toxic after exposure to mature animals. In addition, changes in the epididymis of the male rats were noted at levels similar to the administered subchronic critical study LOAEL. The liver and epididymal effects have been identified as subchronic co-critical effects. In one study, administered doses about 3-fold higher than the short-term and subchronic critical study administered LOAEL caused changes in rib development. These studies were conducted in rats and the effects were observed at doses higher than the chronic critical study LOAEL observed in dogs (the more sensitive species).

³ A single 2 generation study has been conducted. Changes in the epididymis were noted at levels similar to the administered levels in the short-term and subchronic critical study LOAEL, however, reproductive capacity was not affected. The epididymal effects have been identified as subchronic co-critical effects. Reproductive studies have shown changes in development and liver toxicity in offspring without affecting reproduction of the animals.

⁴ Neurotoxic effects of changes in operant behavior occur at administered doses at least 2-fold higher than the subchronic and 8-fold higher than the chronic critical chronic study LOAEL. Very high administered acute doses (> 10-fold and higher than the short-term, subchronic and chronic critical study LOAELs) can cause changes in motor coordination (such as ataxia) and other acute affects expected from anesthetics.

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