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**Chemical Name: Chloroform**

**CAS: 67-66-3**

**Synonyms: Trichloroform, Trichloromethane**

**Acute Non-Cancer Health Risk Limit (nHRL<sub>acute</sub>) = Not Derived (Insufficient data)<sup>1</sup>**

<sup>1</sup> 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 (HRL<sub>short-term</sub>) = 30 ug/L**

$$\begin{aligned} &= \frac{\text{(Reference Dose, mg/kg/d)} \times \text{(Relative Source Contribution)} \times \text{(Conversion Factor)}}{\text{(Short-term, L/kg/d)}} \\ &= \frac{(0.05 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.289 \text{ L/kg-d)}} \\ &= 34.6 \text{ rounded to } \mathbf{30 \text{ ug/L}} \end{aligned}$$

Toxicity value:	0.05 mg/kg-d (laboratory animal)
Source of toxicity value:	MDH 2007
Point of Departure:	50 mg/kg-d (LOAEL, Munson et al. 1982)
Human Equivalent Dose Adjustment:	(inadequate information)
Total uncertainty factor:	1000
UF allocation:	10 interspecies, 10 intraspecies, 10 LOAEL-to-NOAEL
Critical effect(s):	Suppression of the humoral immune system (antigen forming cells)
Co-critical effect(s):	Increased relative liver weight with fatty changes to the liver, decreased body weight gain in pups
Additivity endpoint(s):	Immune System, Hepatic (Liver) System, Developmental (body weight gain)
Secondary effect(s):	None

**Subchronic Non-Cancer Health Risk Limit (nHRL<sub>subchronic</sub>) = HRL<sub>short-term</sub> = 30 ug/L**

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

$$= \frac{(0.05 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.077 \text{ L/kg-d})}$$

$$= 129.8 \text{ rounded to } 100 \text{ ug/L}$$

Toxicity value:	0.05 mg/kg-d (laboratory animal)
Source of toxicity value:	MDH 2007
Point of Departure:	50 mg/kg-d (LOAEL) (Munson et al. 1982)
Human Equivalent Dose Adjustment:	(inadequate information)
Total uncertainty factor:	1000
UF allocation:	10 interspecies, 10 intraspecies, 10 LOAEL-to-NOAEL
Critical effect(s):	Suppression of the humoral immune system (antigen forming cells)
Co-critical effect(s):	Increased relative liver weight with fatty changes to the liver, increased epididymal weights and degeneration of epididymal duct epithelium
Additivity endpoint(s):	Immune System, Hepatic (Liver) System, Male Reproductive system.
Secondary effect(s):	None

**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 30 ug/L. Additivity Endpoints: Developmental (body weight gain), Immune system, Hepatic (Liver) system, Male Reproductive system.**

**Chronic Non-Cancer Health Risk Limit (nHRL<sub>chronic</sub>) = HRL<sub>short-term</sub> = 30 ug/L**

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

$$= \frac{(0.01 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.043 \text{ L/kg-d})}$$

$$= 46.5 \text{ rounded to } 50 \text{ ug/L}$$

Toxicity value:	0.01 mg/kg-d (laboratory animal)
Source of toxicity value:	IRIS, 2001
Point of Departure:	1.2 mg/kg-d (BMDL, Heywood et al., 1979)
Human Equivalent Dose Adjustment:	(inadequate information)
Total uncertainty factor:	100
UF allocation:	10 interspecies and 10 intraspecies
Critical effect(s):	Elevated SGPT (ALT) levels and fatty cysts in the liver

Co-critical effect(s): None  
 Additivity endpoint(s): Hepatic (Liver) System  
 Secondary effect(s): None

**The Chronic nHRL must be protective of the short-term exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 30 ug/L. Additivity Endpoints: Developmental (body weight gain), Immune system, Hepatic (Liver) system, Male Reproductive system.**

**Cancer Health Risk Limit (cHRL) = Not Applicable<sup>1</sup>**

Cancer classification: likely to be carcinogenic to humans by all routes of exposure under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues and not likely to be carcinogenic to humans by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration.  
 Slope factor: not available (nonlinear approach recommended, EPA 2001)  
 Source of slope factor: Not available  
 Tumor site(s): kidney, liver

<sup>1</sup>Chloroform is a nonlinear carcinogen, and the RfD and subsequent chronic noncancer HRL of 30 ug/L is considered to be protective against cancer.

**Volatile: Yes (highly volatile)**

**Summary of changes since 1993/1994 HRL promulgation:**

The nHRL values for short-term, subchronic, and chronic are all equal to 30 ug/L and are one half the 1993/1994 HRL value of 60 ug/L that was based on the endpoint of cancer and used an EPA cancer slope factor derived in 1992. In 2001, EPA issued an updated IRIS entry for chloroform along with a toxicological review document. In this document it states that EPA now considers chloroform to be a carcinogen with a nonlinear threshold mode of action, therefore a cancer slope factor is no longer applicable to this chemical and the RfD approach will be protective of carcinogenic effects. The nHRL values are a result of: 1) use of algorithms to address multiple duration exposure scenarios; 2) utilizing more recent duration-specific lifetime intake rates; and 3) rounding to one significant digit.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No	Yes	Yes	Yes	Yes
Effects?	--	Yes <sup>1</sup>	Yes <sup>2</sup>	No <sup>3</sup>	Yes <sup>4</sup>

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.

-- indicates that no specific tests for that effect were conducted, and that effect was not observed as a secondary effect in any other study used in the HRL evaluation.

## Comments on extent of testing or effects:

- <sup>1</sup> 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 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) caused changes in cell-mediated immunity in female mice at 90 days.
- <sup>2</sup> 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 subchronic critical study LOAEL. The liver and epididymal effects have been identified as subchronic co-critical effects. In one study, doses about 3-fold higher than the short-term and subchronic critical study 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).
- <sup>3</sup> A single 2 generation study has been conducted. Changes in the epididymis were noted at levels similar to 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.
- <sup>4</sup> Neurotoxic effects of changes in operant behavior occur at doses at least 2-fold higher than the subchronic and 8-fold higher than the chronic critical study LOAEL. Very high acute doses ( $\geq$  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 effects expected from anesthetics.

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