Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Adopted as Rule: September 30, 2013

Toxicological Summary for Carbon Tetrachloride:
CAS: 56-23-5

Synonyms: Tetrachloromethane, Carbona, Carbon chloride, Carbon tet, Methane tetrachloride, Perchloromethane, benzinoform, 1,1,1,1-Tetrachloromethane, Benzinoform, Freon 10, Halon 104, Tetraform, Tetrasol

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

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

$$= \frac{\text{(0.18 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= **124** rounded to **100 µg/L**

Reference Dose / Concentration:	0.18 mg/kg-d (F344N rats)
Source of toxicity value:	MDH, 2012
Point of Departure:	25 mg/kg-d (NOAEL), Developmental study (Narotsky, et al., 1997b)
Human Equivalent Dose Adjustment:	5.3 mg/kg-d [25 x 0.21] (MDH, 2011)
Total uncertainty factor:	30
UF allocation:	3 for interspecies variability (toxicodynamics); 10 for intraspecies variability
Critical effect(s):	Increased litter resorptions
Co-critical effect(s):	Regenerative hepatocyte proliferation
Additivity endpoint(s):	Developmental system; Hepatic (liver) system

Short-term Non-Cancer Health Risk Limit ($nHRL_{short\text{-}term}$) = 3 µg/L

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

$$= \frac{\text{(0.0037 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= **2.6** rounded to **3 µg/L**

Reference Dose / Concentration:	0.0037 mg/kg-d (F344N rats)

Source of toxicity value:	MDH 2012
Point of Departure:	5 mg/kg-d (minimal LOAEL), 10-day immunotoxicity gavage study (Smialowicz et al, 1991)
Human Equivalent Dose Adjustment:	1.1 mg/kg-d [5 x 0.21] (MDH, 2011)
Total uncertainty factor:	300
UF allocation:	3 for interspecies variability (toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty – no multi-generation study to adequately assess reproductive effects; 3 for minimal LOAEL to NOAEL extrapolation
Critical effect(s):	Minimal vacuolar degeneration in the liver
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Subchronic Non-Cancer Health Risk Limit ($nHRL_{subchronic}$) = $nHRLshort_{-term}$ = 3 µg/L

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

$$= \frac{\text{(0.0098 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= **25** rounded to 30 µg/L

Reference Dose / Concentration:	0.0098 mg/kg-d (SD rats)
Source of toxicity value:	MDH 2012
Point of Departure:	3.9 mg/kg-d ($BMDL_{adj}$); 12-week gavage study (Bruckner, et al., 1986)
Human Equivalent Dose Adjustment:	0.98 mg/kg-d [3.9 x 0.25] (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies variability (toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty – no multi-generation study to adequately assess reproductive effects
Critical effect(s):	Increased serum liver enzyme levels, liver lesions
Co-critical effect(s):	Increased liver enzyme levels, liver lesions, increased liver weight, alterations of liver histopathology, increased bilirubin, decreased serum glucose, increased spleen and thymus weights
Additivity endpoint(s):	Hepatic (liver) system, Immune system

The Subchronic nHRL must be protective of the short-term exposures that occur within the short-term period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 3 µg/L. Additivity Endpoints: Hepatic (liver) system

Chronic Non-Cancer Health Risk Limit ($nHRL_{chronic}$) = $nHRLshort_{-term}$ = 3µg/L

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

$$= \frac{\text{(0.0033 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= **15.3** rounded to 20 µg/L

Reference Dose / Concentration:	0.0033 mg/kg-d (laboratory animal)
Source of toxicity value:	MDH 2012 (same as US EPA 2010)
Point of Departure:	3.9 mg/kg-d ($BMDL_{adj}$); 12-week gavage study (Bruckner, et al., 1986)
Human Equivalent Dose Adjustment:	0.98 mg/kg-d [3.9 x 0.25] (MDH, 2011)
Total uncertainty factor:	300
UF allocation:	3 for interspecies variability (toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty – no multi-generation study to adequately assess reproductive effects; 3 for extrapolation from subchronic to chronic duration
Critical effect(s):	Increased serum liver enzyme levels, liver lesions
Co-critical effect(s):	Increased liver enzyme levels, liver lesions, increased liver weight, alterations of liver histopathology, increased bilirubin, decreased serum glucose, increased spleen and thymus weights
Additivity endpoint(s):	Hepatic (liver) system, Immune system

The chronic nHRL must be protective of the short-term exposures that occur within the short-term period and therefore, the chronic nHRL is set equal to the short-term nHRL of 3 µg/L.
Additivity Endpoints: Hepatic (liver) system

Cancer Health Risk Limit (cHRL) = 1 µg/L

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

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(0.07 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.07 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.07 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= **1.46** rounded to **1 µg/L**

Cancer classification:	*Likely to be carcinogenic to humans* (US EPA IRIS 2010)
Slope factor:	0.07 (laboratory animal; 2-year cancer inhalation study (Nagano et al 2007b as cited by US EPA ISIS 2010)
Source of slope factor:	(US EPA IRIS 2010)
Tumor site(s):	Liver, Adrenal Glands

Volatile: Yes (high)

Summary of changes since 1993/1994 HRL promulgation:

A cancer HRL of 3 µg/L was promulgated in 1993. In 2010, a revised cancer Health-Base Value (HBV) of 1 µg/L was derived. This value is 3 times lower than the 1993 cancer HRL (3 µg/L) as the result of: 1) utilizing more recent intake rates which incorporate higher intake rates during early life; 2) application of age-dependent early-life cancer sensitivity adjustment factors; 3) the use of a new slope factor derived by EPA IRIS 2010; and 4) rounding to one significant digit. In 2010, Acute, Short-term, Subchronic and Chronic HBVs of 200, 3, 3, and 3 µg/L were derived. MDH reevaluated the non-cancer HBVs in 2012 to incorporate HED methodology. The resulting Acute HBV (100 µg/L) was 2-fold lower than the 2010 value. The Short-term, Subchronic and Chronic (non-cancer) HBVs (3 µg/L) were unchanged. HBV values derived in 2010 and updated in 2012 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	Yes	Yes	Yes	Yes
Effects?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

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] In a developmental study in rats, the researchers suggested that the all-or-none nature of the observed full-litter resorptions point to a maternally mediated response and produced evidence that the response is associated with reduced levels of progesterone and luteinizing hormone (LH) in the dams during dosing with carbon tetrachloride. (Narotsky et al., 1997a, 1995 cited in US EPA 2010).

Greim et al. (2009) hypothesized modes of action (MOA) for the induction of mouse pheochromocytomas that included endocrine disturbance, impairment of mitochondrial function, uncoupling of oxidative phosphorylation, hepatoxicity, and nephrotoxicity leading to impaired calcium homeostasis, but provided no support for any of these hypothesized MOAs.(cited in US EPA 2010)

[2]Results of available studies indicate that carbon tetrachloride produces adverse effects on T-cell-dependent immunity at administered doses (beginning at 50 mg/kg-day) that are hepatotoxic. However, it is important to note that immunological effects were, at least in part, secondary to hepatotoxicity and the process of hepatic repair.

[3,4]The critical study selected for the acute HRL is a developmental study that reported increased litter resorptions beginning at a Human Equivalent Dose of 10.5 mg/kg-day. No adequate oral reproductive toxicity studies were conducted for carbon tetrachloride. Developmental effects (decreased fetal body weight and delayed ossification) and reproductive effects (testicular atrophy, testicular degeneration, and reduced fertility) were reported in inhalation studies at doses higher than those that produced liver and kidney toxicity.

[5]No oral animal toxicity studies reported neurotoxicity following exposure to carbon tetrachloride. Human reports of exposure to high doses of carbon tetrachloride by inhalation or ingestion mentioned headaches, drowsiness, comas, or seizures. In acute inhalation studies, animals exposed to high doses (4600-1200 ppm) of carbon tetrachloride experienced stupor, incoordination, and unconsciousness.

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