Minnesota Department of Health

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

Adopted as Rule: November 2015

Toxicological Summary for: Pentachlorophenol (PCP)

CAS: **87-86-5**

Synonyms: Santophen, Pentachlorol, Chlorophen, Chlon, Dowicide 7, Pentacon, Penwar, Sinituho, Penta

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

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

$$= \frac{\text{(0.0040 mg/kg/d) x (0.5) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 6.9 rounded to **7 µg/L**

Reference Dose/Concentration:	0.0040 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	MDH 2013
Point of Departure (POD):	5 mg/kd-d (LOAEL) Schwetz et al. 1974
Human Equivalent Dose (HED):	5 x 0.23 = 1.2 mg/kg-d (MDH 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics ; 10 for intraspecies variability; 3 for extrapolation from a minimal LOAEL to a NOAEL; 3 for database uncertainty to address need for additional studies regarding potential thyroid effects on neurodevelopment
Critical effect(s):	Delayed skull ossification
Co-critical effect(s):	Reduction in serum levels of T_4 in pregnant animals
Additivity endpoint(s):	Developmental; Thyroid (E)

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

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

$$= \frac{\text{(0.0040 mg/kg/d) x (0.5) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 6.9 rounded to **7 µg/L**

Reference Dose/Concentration	0.0040 mg/kg-d (Sprague Dawley rats)
Source of toxicity value	MDH 2013
Point of Departure (POD)	5 mg/kd-d (LOAEL) Schwetz et al. 1974

Human Equivalent Dose (HED):	5 x 0.23 = 1.2 mg/kg-d (MDH 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics ; 10 for intraspecies variability; 3 for extrapolation from a minimal LOAEL to a NOAEL; 3 for database uncertainty to address need for additional studies regarding potential thyroid effects on neurodevelopment
Critical effect(s):	Delayed skull ossification
Co-critical effect(s):	Reduction in serum levels of T_4 in pregnant and adult animals, pre-weanling, pre-pubertal and pubertal animals; decreased serum T_3/T_4 ratio
Additivity endpoint(s):	Developmental (E); Thyroid (E)

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

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

$$= \frac{(0.0031) \times (0.2) \times (1000\ \mu g/mg)}{(0.077\ L/kg\text{-}d)}$$

= 8.05 rounded to 8 µg/L

Reference Dose/Concentration	0.0031 mg/kg-d (Beagle Dogs)
Source of toxicity value	MDH 2013
Point of Departure (POD)	1.5 mg/kd-d (LOAEL) Mecler et al. 1996 aci (U.S. Environmental Protection Agency-Iris, 2010)
Human Equivalent Dose (HED):	1.5 x 0.62 = 0.93 mg/kg-d (MDH 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics; 10 for intraspecies variability; 10 for extrapolation from a LOAEL to a NOAEL
Critical effect(s):	Increased liver weight accompanied by histological changes; increased thyroid weights
Co-critical effect(s):	Decreased T_4 concentrations in pregnant and adult animals, pre-weanling, pre-pubertal and pubertal animals; decreased induction of T_4 upon stimulation with TSH in adult females; increased scrotal circumference during pubertal development; seminiferous tubule atrophy at puberty; decreased sperm density in the body of the epididymides at puberty, suppression of serum antibody response to antigen
Additivity endpoint(s):	Developmental (E); Hepatic (liver) system; Immune system; Male reproductive system; Thyroid (E)

The Subchronic nHRL must be protective of the acute and short-term exposures that occur within the acute and short-term periods and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 7 µg/L. Health Endpoints: Developmental (E), Hepatic (liver) system, Immune system, Male Reproductive system, Thyroid (E).

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

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

$$= \frac{\text{(0.0031 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043L/kg-d)}}$$

= 14.4 rounded to **10 µg/L**

Reference Dose/Concentration	0.0031 mg/kg-d (Beagle Dogs)
Source of toxicity value	MDH 2013
Point of Departure (POD)	1.5 mg/kd-d (LOAEL) Mecler et al. 1996 aci (U.S. Environmental Protection Agency-Iris, 2010)
Human Equivalent Dose (HED):	1.5 x 0.62 = 0.93 mg/kg-d (MDH 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics; 10 for intraspecies variability; 10 for extrapolation from a LOAEL to a NOAEL
Critical effect(s):	Increased liver weight accompanied by histological changes; increased thyroid weights
Co-critical effect(s):	Decreased T_4 concentrations in pregnant and adult animals, pre-weanling, pre-pubertal and pubertal animals; decreased induction of T_4 upon stimulation with TSH in adult females; increased scrotal circumference during pubertal development; seminiferous tubule atrophy at puberty; decreased sperm density in the body of the epididymides at puberty, suppression of serum antibody response to antigen
Additivity endpoint(s):	Developmental (E); Hepatic (liver) system; Immune system; Male reproductive system; Thyroid (E)

The Chronic nHRL must be protective of the acute and short-term exposures that occur within the acute, short-term, and subchronic periods and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 7 µg/L. Health Endpoints: Developmental (E), Hepatic (liver) system, Immune system, Male Reproductive system, Thyroid (E).

Cancer Health Risk Limit (cHRL) = 0.3 µg/L

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

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(4E\text{-}1 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (4E\text{ -}1 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (4E\text{-}1 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 0.257 rounded to **0.3 µg/L**

Cancer classification:	Likely to be carcinogenic to humans (U.S. Environmental Protection Agency- IRIS, 2010)
Slope factor:	0.4 $(mg/kg\text{-}d)^{-1}$ (laboratory animal, NTP 1989)

Source of slope factor: EPA IRIS 2010
Tumor site(s): Liver tumors, adrenal gland tumors (pheochromocytomas)

Volatile: Yes (Low)

Summary of Guidance Value History:
The 2008 Health Risk Limit (HRL) for pentachlorophenol (1 µg/L) was set at the EPA Office of Water Maximum Contaminant Level (MCL). An earlier HRL (3 µg/L) promulgated in 1993 was based on cancer. New Health-Based Values (HBVs), including noncancer values, were drafted in 2013. These values were adopted into rule as HRLs n November 2015. The 2015 cancer HRL is approximately 3-fold lower than the 2008 HRL due to: 1) revised cancer slope factor, 2) application of age-dependent adjustment factors to address early life sensitivity, 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?	Yes	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] Endocrine effects are listed as a co-critical for all durations. Reductions of thyroxine (T4), decreased triiodothyronine/thyroxine (T3/T4) ratios, decreased response to stimulation with thyroid stimulating hormone (TSH), and increase in thyroid weights were reported in laboratory animals.

[2.] Immunological effects were reported in short-term and subchronic studies in both mice and rats. In one study, male rats showed lymphocyte effects and suppression of antibody responses when exposed to PCP at levels 16.5 times the short-term RfD. However, another study reported no effects on lymphocytes or leukocytes in male rats exposed to doses over 15,000 times higher than the RfD. One study in mice reported non-statistically significant decreases in lymphocytes at a HED 3,500 higher than the RfD. Immune effects of technical grade PCP (but not for analytical grade), including reduced host-resistance to viral infection, reduced T-cell activity and reduced macrophage activity were reported in adult male mice at approximately 325 times the short-term RfD; however, immune effects at this level were considered to be related to impurities. Analytical grade PCP (>99% purity) caused reduced thymus weight in female mice at doses over 700 times higher than the RfD. Suppression of antibody responses were observed at dose levels similar to the subchronic point of departure and have been identified as a co-critical effect.

[3.] Skeletal malformations are listed as critical effects for the acute and short-term durations. Delayed skull ossification was observed in rats. In addition, a range of skeletal malformations such as lumbar spurs, abnormal sternebrae, abnormal vertebrae, and decreased distance from crown to rump were observed starting at doses almost 900-fold higher than the RfD.

[4.] Male reproductive system effects are identified as co-critical. At a dose 1,700 times higher than the short-term Rfd, the incidence of fetal resorptions was 100% and at 3,300 times the short-term RfD, the

sex ratio was skewed to 100% males. Distended lumina of the uterus, the presence of macrophages in the uterus, and increased uterine weight as well as increased time to vaginal patency were observed in the female rat offspring at doses 4,600 times higher than the short-term RfD.

[5.] Neurotoxicity testing was performed as part of a chronic study in mice. Although the mice showed dose-related increases in motor activity and startle response, they showed no treatment-related effects in pinna, corneal or righting reflexes, visual placement, grip strength or rota-rod testing. These effects were examined beginning at doses 1,900 times higher than the chronic RfD.

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