Health-Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
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Toxicological Summary for: Chlorothalonil

CAS: **1897-45-6**
Synonyms: Tetrachloroisophthalonitrile; 1,3-Dicyanotetrachlorobenzene; 2,4,5,6-tetrachlorobenzene-1,3-dicarbonitrile (IUPAC)

Acute Non-Cancer Health-Based Value (nHBVAcute) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health-Based Value ($nHBV_{Short\text{-}term}$) = 20 µg/L

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

$$= \frac{\text{(0.014 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 24.1 rounded to **20 µg/L**

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

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 1.35/100 = 0.014 mg/kg-d (Crl:CD®BR VF/Plus Rat)
Source of toxicity value:	Determined by MDH in 2022
Point of Departure (POD):	6.13 mg/kg-d (administered dose $BMDL_{BMR5\%}$, Myers 1995)
Dose Adjustment Factor (DAF):	0.22 Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 6.13 mg/kg-d x 0.22 = 1.35 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty due to suggestive testicular effects reported in other animal studies and human epidemiology studies that have not been thoroughly assessed
Critical effect(s):	Forestomach roughening and thickening in F1 pups
Co-critical effect(s):	None
Additivity endpoint(s):	Gastrointestinal system

Subchronic Non-Cancer Health-Based Value ($nHBV_{Subchronic}$) = 2 µg/L

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

$$= \frac{\text{(0.00067 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 1.8 rounded to **2 µg/L**

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

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.067/100 = 0.00067 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2022
Point of Departure (POD):	0.293 mg/kg-d (administered dose $BMDL_{BMR5\%}$, Spencer-Briggs 1994)
Dose Adjustment Factor (DAF):	0.23 Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 0.293 mg/kg-d x 0.23 = 0.067 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty due to suggestive testicular effects reported in other animal studies and human epidemiology studies that have not been thoroughly assessed
Critical effect(s):	Epithelial hyperplasia and hyperkeratosis at the limiting ridge of the stomach in female rats
Co-critical effect(s):	Epithelial hyperplasia and hyperkeratosis in the nonglandular region of the stomach in female rats
Additivity endpoint(s):	Gastrointestinal system

Chronic Non-Cancer Health-Based Value ($nHBV_{Chronic}$) = 1 µg/L

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

$$= \frac{\text{(0.00029 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 1.29 rounded to **1 µg/L**

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

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.29/1000 = 0.00029 mg/kg-d (Crl:CD(SD)BR mice)
Source of toxicity value:	Determined by MDH in 2022
Point of Departure (POD):	1.9 mg/kg-d (administered dose LOAEL, Spencer-Briggs 1995)
Dose Adjustment Factor (DAF):	0.15 Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.9 mg/kg-d x 0.15 = 0.29 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for using a LOAEL in place of a NOAEL, and 3 for database uncertainty due to suggestive testicular effects reported in other animal studies and human epidemiology studies that have not been thoroughly assessed
Critical effect(s):	Epithelial hyperplasia and hyperkeratosis in the nonglandular and limiting ridge regions of the stomach in male mice
Co-critical effect(s):	Epithelial hyperplasia and hyperkeratosis at the limiting ridge and in the nonglandular regions of the stomach in females, ulceration of the nonglandular region of the stomach, thickened appearance of the forestomach in males, renal uniform cortical scarring, renal karyomegaly in males, and centrilobular hepatocyte enlargement
Additivity endpoint(s):	Gastrointestinal system, Hepatic (liver) system, Renal (kidney) system

Cancer Health-Based Value (cHBV) = 6 µg/L

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

$$\frac{= (1E\text{-}5) \times (1000\ \mu g/mg)}{[(0.017 \times 10^{*} \times 0.155\ L/kg\text{-}d^{**} \times 2) + (0.017 \times 3^{*} \times 0.040\ L/kg\text{-}d^{**} \times 14) + (0.017 \times 1^{*} \times 0.042\ L/kg\text{-}d^{**} \times 54)] / 70}$$

= 5.84 rounded to **6 µg/L**

*ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.

**Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Cancer classification:	Likely to be a human carcinogen by all routes of exposure (EPA 2021); Possibly carcinogenic to humans (IARC 1999)
Slope factor (SF):	0.017 mg/kg-d^{-1} (Combined renal and forestomach tumors from the male rat, Wilson and Killeen 1989)

Source of cancer slope factor (SF): (California EPA 2012)
Tumor site(s): Forestomach, Kidney, Liver, Thyroid

Volatile: No

Summary of Guidance Value History:

Guidance for chlorothalonil was first developed by MDH in 1993/1994 with a cancer HRL = 30 µg/L. In 2014, MDH developed a cancer pesticide rapid assessment of 6 µg/L and a noncancer rapid assessment of 50 µg/L. The cancer guidance was lower in the pesticide rapid assessment than the 1993/1994 HRL due to the use of a newer slope factor (California EPA 2012). In 2022 MDH conducted an in-depth full review of chlorothalonil. The cancer guidance in the full review (6 µg/L) and the pesticide rapid assessment cancer value are the same because the slope factor and equation used are identical. The 2022 full review noncancer guidance (short-term, subchronic, and chronic) are lower than the 2014 noncancer rapid assessment as a result of using: 1) updated intake rates; 2) BMD modeling; and 3) selection of a more sensitive health endpoint (gastrointestinal).

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?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	No[2]	Yes[3]	Yes[4]	No[5]

Comments on extent of testing or effects:

[1] A provocative but limited study in mice reported changes in the enzymes that make estradiol and progesterone at chlorothalonil levels equal to the short-term RfD, but 19 times higher than the subchronic RfD, and 45 times higher than the chronic RfD. At levels 460 times higher than the short-term RfD, chlorothalonil affected the maturation of ovarian follicles. Fertility in this study was not tested. In rats, increased pituitary gland weight was reported at levels 2,000 times higher than the short-term RfD and a decrease in T4 was reported at levels 3,000 times higher than the short-term RfD. Parathyroid hyperplasia was reported in rats beginning at levels 800 times higher than the short-term RfD. In beagles, increased thyroid weight occurred at chlorothalonil doses 16,000 times higher than the short-term RfD. Also at this dose an enlargement in adrenal cells was reported. In another beagle study, the absolute weight of the adrenal gland and its width were increased at chlorothalonil levels 22,000 times higher than the short-term RfD. Other animal studies also reported adrenal gland

enlargement and hyperplasia. In mice these changes occurred at levels 80 times higher than the short-term RfD. Testicular weight decrease occurred in male rats at levels 13,000 times higher than the short-term RfD while ovarian masses were observed in female rats at levels 1,300 times higher than the short-term RfD.

[2] EPA reported no effects from an immunologic study in laboratory animals. However, in a chronic toxicity study in female rats, a complete involution of the thymus occurred at levels 700 times higher than the short-term RfD.

[3] Early pregnancy resorptions occurred in both rats and mice at levels 7,000 and 4,000 times higher, respectively, than the short-term RfD. Reduced fetal and pup body weights were commonly reported in mouse and rat studies. Fetal mouse and rat pups were both reported to have reduced body weights at chlorothalonil levels beginning at 4,000 and 2,000 times higher, respectively, than the short-term RfD. In the rat, this was accompanied by reduced pup viability at 4,000 times higher than the short-term RfD. Skeletal variations were reported in fetal rats at levels 3,000 times higher than the short-term RfD. Delayed vaginal patency and preputial separation, most likely due to reduced body weights, were reported in developing rats at levels 4,000 times higher than the short-term RfD. In rabbits, reduced fetal bodyweights and skeletal variations were common at doses 700 times higher than the short-term RfD. Fetal malformations were also reported at levels 700 times higher than the short-term RfD. Abortions in rabbits occurred at chlorothalonil levels 300 times higher than the short-term RfD.

[4] The only reproductive effect reported from a sponsored study was reduced uterine weight in one rabbit study at a level of chlorothalonil 100 times higher than the RfD. A recent non-sponsored study in mice reported reduced sperm motility at the same level as the short-term RfD, but at levels 19 times higher than the subchronic RfD, and 45 times higher than the chronic RfD. At a chlorothalonil exposure 100 times higher than the short-term RfD were a reduction in sperm number and slower sperm maturation. The same laboratory reported the hormone and ovarian effects mentioned in the endocrine section, above. Adverse sperm effects have been reported in human epidemiology studies from exposure to chlorinated chemicals. Unfortunately, most of the animal studies in the chlorothalonil database did not test for sperm effects. This resulted in a data base uncertainty factor of "3" added to the chlorothalonil reference doses. Other reproductive effects in rats and mice include a decrease in the number of live fetuses at levels 4,000 times higher than the short-term RfD, and post-implantation loss and early resorptions at levels 4,000 times higher in mice and 7,000 times higher than the short-term RfD in rats.

[5] An acute neurotoxicity study in rats detected no effects at a chlorothalonil dose up to 33,000 times higher than the short-term RfD. In a subchronic neurotoxicity study, no effects were reported in rats up to 4,000 times higher than the short-term RfD. A decrease in brain weight was observed at a level 6,000 times higher than the short-term RfD in rats.

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