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

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Toxicological Summary for: 4-Hydroxychlorothalonil

CAS: **28343-61-5**
Synonyms: 2,4,5-Trichloro-6-Hydroxybenzene-1,3-Dicarbonitrile; 4-Hydroxy-2,5,6-Trichloroisophthalonitrile; Hydroxy Chlorothalonil; Hydroxy-2,5,6-Trichloro-1,3-Benzenedicarbonitrile; SDS-3701; 4-Hydroxy metabolite; metabolite R182281; 2,4,5-trichloro-6-hydroxybenzene-1,3-dicarbonitrile (IUPAC)

Acute Non-Cancer Risk Assessment Advice ($nRAA_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Risk Assessment Advice ($nRAA_{Short\text{-}term}$) = 2 µg/L

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

$$= \frac{\text{(0.0012 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 2.06 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 = 0.345/300 = 0.0012 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2022
Point of Departure (POD):	1.5 mg/kg-d (administered dose NOAEL, unpublished one-generation rat study from 1982 cited in EPA 1999)
Dose Adjustment Factor (DAF):	0.23 Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.5 mg/kg-d x 0.23 = 0.345 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty due to a lack of sufficiently detailed reporting
Critical effect(s):	Decreased body weight of pups at weaning
Co-critical effect(s):	Reduced body weight of pups (age not specified)
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Risk Assessment Advice ($nRAA_{Subchronic}$) = 2 µg/L

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

$$= \frac{(0.0012 \text{ mg/kg-d})^{\#} \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 3.24 rounded to 3 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.

The calculated Subchronic RfD (0.0019 mg/kg-d) is higher than the Short-term RfD (0.0012 mg/kg-d), which is based on developmental effects. The Subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the Short-term RfD is used in place of the calculated Subchronic RfD when deriving subchronic water guidance.

The Subchronic nRAA must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic nRAA is set equal to the Short-term nRAA of 2 µg/L. Additivity endpoints: Developmental

Chronic Non-Cancer Risk Assessment Advice ($nRAA_{Chronic}$) = 2 µg/L

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

$$= \frac{(0.0012 \text{ mg/kg-d})^{\#} \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 5.33 rounded to 5 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.

The calculated Chronic RfD (0.0026 mg/kg-d) is higher than the Short-term RfD (0.0012 mg/kg-d), which is based on developmental effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure, including short-term and subchronic effects (MDH 2008, page 34). Therefore, the Short-term RfD is used in place of the calculated Chronic RfD when deriving chronic water guidance.

The Chronic nRAA must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic nRAA is set equal to the Short-term and Subchronic nRAA of 2 µg/L. Additivity endpoints: Developmental

Cancer Risk Assessment Advice (cRAA) = Not Applicable

Volatile: No (parent Chlorothalonil)

Summary of Guidance Value History:

MDH derived a pesticide rapid assessment for 4-hydroxychlorothalonil of 50 µg/L and a cancer pesticide rapid assessment of 6 µg/L in 2021 that were both set to the Chlorothalonil (parent) non-cancer and cancer pesticide rapid assessments. The new MDH RAAs are based on the evaluation of 4-hydroxychlorothalonil-specific toxicity data rather than the parent (chlorothalonil).

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	No	Yes	Yes	No
Effects observed?	No[1]	No[1]	Yes[2]	No[3]	-[1,4]

Comments on extent of testing or effects:

[1] A database uncertainty factor of "10" was applied due to the lack of details in the reports on endocrine, immunologic, and neurotoxicity effects.

[2] The short-term RfD is based on developmental toxicity in rat pups (reduced body weight). Early resorptions and total litter resorptions were observed in pregnant rats at doses 3,000 times higher than the short-term RfD. Reduced fetal weight and an increased incidence of a 14th rudimentary rib were also reported at this 4-hydroxychlorothalonil dose. Abortions in rabbits were reported at levels 100 times higher than the short-term RfD and in the presence of severe maternal toxicity.

[3] In one- and three-generation rat studies, no reproductive effects were reported at 4-hydroxychlorothalonil levels 1,300 times higher than the short-term RfD. However, litter resorptions in pregnant rats occurred at levels 3,000 times higher than the short-term RfD and abortions occurred in rabbits at levels 100 times higher than the short-term RfD in the presence of severe maternal toxicity.

[4] In a 2-yr toxicity/carcinogenicity study in rats, hemorrhaging of the central nervous system tissues and an overall reduction in brain weight was reported at a dose of 4-hydroxychlorothalonil 5,000 times higher than the short-term RfD.

Resources Consulted During Review:

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U.S. EPA. (2019) Exposure Factors Handbook. Retrieved from https://www.epa.gov/expobox/about-exposure-factors-handbook#about

U.S. EPA. (2021). Chlorothalonil: Revised Human Health Draft Risk Assessment for Registration Review (Memo).