

Adopted as Rule: November 2023

Toxicological Summary for: Metolachlor and s-Metolachlor

CAS: 51218-45-2 and 87392-12-9

Synonyms: Metolachlor: 2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(1-methoxypropan-2-yl)acetamide)

s-Metolachlor: 2-Chloro-N-(2-ethyl-6-methylphenyl)-N-[(2S)-1-methoxypropan-2-yl]acetamide

Acute Non-Cancer Health Risk Limit (nHRL_{Acute}) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Risk Limit (nHRL_{Short-term}) = 300 µg/L

$$\begin{aligned} & \frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Short-term Intake Rate, L/kg-d})} \\ &= \frac{(0.19 \text{ mg/kg-d}) \times (0.5)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}} \\ &= 327 \text{ rounded to } \mathbf{300 \text{ µg/L}} \end{aligned}$$

*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 = 5.72/30 = 0.19 mg/kg-d (laboratory rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	26 mg/kg-d (NOAEL, MRID 00080897 (Smith, 1981 (Ciba-Geigy)) aci (EPA, 1995))
Dose Adjustment Factor (DAF):	0.22 (Body weight scaling, default) (EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 26 mg/kg-d x 0.22 = 5.72 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased body weight in pups
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Risk Limit (nHRL_{Subchronic}) = nHRL_{Short-term} = 300 µg/L

$$\begin{aligned} & \frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Subchronic Intake Rate, L/kg-d})} \\ &= \frac{(0.19 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}} \end{aligned}$$

= 513 rounded to 500 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 = 5.72/30 = 0.19 mg/kg-d (beagle dog)
Source of toxicity value: Determined by MDH in 2017
Point of Departure (POD): 9.7 mg/kg-d (NOAEL, MRID 409807 (Hazelette, 1989) aci (USEPA, 1995))
Dose Adjustment Factor (DAF): 0.59 (Body weight scaling, default) (EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED): POD x DAF = 9.7 mg/kg-d x 0.59 = 5.72 mg/kg-d
Total uncertainty factor (UF): 30
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s): Decreased body weight gain in adults
Co-critical effect(s): Decreased body weight in pups
Additivity endpoint(s): Developmental

The Subchronic nHRL must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 300 µg/L. Additivity endpoints: Developmental

Chronic Non-Cancer Health Risk Limit (nHRL_{Chronic}) = nHRL_{Short-term} = 300 µg/L

$$\begin{aligned} & \frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Chronic Intake Rate, L/kg-d})} \\ &= \frac{(0.19 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}} \\ &= 844 \text{ rounded to } 800 \text{ µg/L} \end{aligned}$$

*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 = 5.72/30 = 0.19 mg/kg-d (beagle dog)
Source of toxicity value: Determined by MDH in 2017
Point of Departure (POD): 9.7 mg/kg-d (NOAEL, MRID 409807 (Hazelette, 1989) aci (EPA, 1995)) (subchronic exposure)
Dose Adjustment Factor (DAF): 0.59 (Body weight scaling, default) (EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED): POD x DAF = 9.7 mg/kg-d x 0.59 = 5.72 mg/kg-d
Total uncertainty factor (UF): 30

Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability (subchronic-to-chronic uncertainty factor not selected as toxicity did not increase with longer durations of related studies)

Critical effect(s): Decreased body weight gain in adults

Co-critical effect(s): Decreased body weight in pups

Additivity endpoint(s): Developmental

The Chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 300 µg/L. Additivity endpoints: Developmental

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification: Group C (possible human carcinogen) (EPA, 2006)

Slope factor (SF): Non-linear approach recommended by US EPA
0.0092 (mg/kg-d)⁻¹ (EPA, 1995) (EPA, 2002) (EPA, 2006)

Source of cancer slope factor (SF): US EPA, 2006

Tumor site(s): liver tumors in rats

Statement for non-linear carcinogens:

At this time, MDH's non-cancer health-based guidance values are considered to be protective for possible cancer risks associated with metolachlor in drinking water. Neither the International Agency for Research on Cancer (IARC) nor the National Toxicology Program (NTP) have classified metolachlor as a carcinogen. Metolachlor has been identified as a nonlinear carcinogen by the US Environmental Protection Agency (EPA). Three long-term animal studies have been conducted with metolachlor, and tumors were reported in only one of these studies at the highest dose level tested (over 200 times higher than the MDH Chronic RfD). Additionally, as part of the 2008 HRL revision, the MDH Group C review committee evaluated the weight of evidence regarding the carcinogenicity and determined that no Group C uncertainty factor was needed and agreed that the data do not support derivation of a cancer specific value. (MDH, 2008)

Volatile: No

Summary of Guidance Value History:

A noncancer chronic Health Risk Limit (HRL) of 100 µg/L was promulgated in 1993. Acute, Short-term, Subchronic, and Chronic Health-Based Values (HBV) of 400, 400, 300, and 300 µg/L were derived in 2009 and promulgated as HRLs in 2011. In 2017, MDH re-evaluated the non-cancer HRLs, resulting in the removal of the acute HRL, an updated short-term HBV of 300 µg/L, and updated subchronic and chronic HBVs set to the short-term HBV of 300 µg/L. The short-term, subchronic, and chronic values were updated and the acute guidance removed as a result of 1) using MDH's most recent risk assessment methodology and 2) rounding to one significant digit. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	No	Yes	Yes	No
Effects observed?	Yes ¹	-	Yes ²	Yes ³	- ⁴

Comments on extent of testing or effects:

¹ Serum levels of testosterone, estradiol, and other hormones were altered in rats after pubertal exposure (PND 23-53) at levels 60 times higher than the short-term RfD. Increased relative thyroid weights were observed in F1 males in a multigenerational study in rats. A related compound, Acetochlor, caused thyroid effects in laboratory studies.

² The short-term reference dose is based on developmental effects (decreased body weight in pups) observed in the critical study.

³ Decreased implantations, increased resorptions, decreased litter size, and increased post-implantation loss has been observed at doses ~1,000 higher than the short-term reference dose.

⁴ Neurotoxicity of metolachlor has not been studied. However, a related compound, acetochlor, causes neurological effects.

Resources Consulted During Review:

Australian Natural Resource Management Ministerial Council; Environmental Protection and Heritage Council; and National Health and Medical Research Council (2008). "Australian Guidelines for Water Recycling. Augmentation of Drinking Water Supplies." from <https://www.waterquality.gov.au/sites/default/files/documents/water-recycling-guidelines-augmentation-drinking-22.pdf>

Barr, D. B., Anath, C.V., Lashley, S., Smulian, J.C., Ledoux, T.A., Hore, P., Robson, M.G. (2010). "Pesticide concentrations in maternal and umbilical cord sera and their relation to birth outcomes in a population of pregnant women and newborns in New Jersey." Science of the Total Environment(408): 790-795.

ChemFinder. Retrieved 2/28/2017, from <http://www.cambridgesoft.com/services/documentation/sdk/chemfinder>

Coleman, S., Linderman, R., Hodgson, E., Rose, R.L. (2000). "Comparative metabolism of chloroacetamide herbicides and selected metabolites in human and rat liver microsomes." Environmental Health Perspectives **108**(12): 1151-1157.

Federal Register 40 CFR Part 180 (2006). "S-metolachlor Pesticide Tolerance [EPA-HQ-OPP-2006-0292; FRL-8090-2]." **71**(168): 51505-51510.

Health Canada (1986). "Guidelines for Canadian Drinking Water Quality - Guideline Technical Document for Metolachlor." from <https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-metolachlor.html>

Mathias, F. T., Romano, R.M., Sleiman, H.K., de Oliveira, C.A., Romano, M.A. (2012). "Herbicide Metolachlor Causes Changes in Reproductive Endocrinology of Male Wistar Rats." Internation Scholarly Research Notices **2012**.

Minnesota Department of Health (MDH) (2008). "Statement of Need and Reasonableness (SONAR), July 11, 2008. Support document relating to Health Risk Limits for Groundwater Rules". from <https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2>

Minnesota Department of Health (MDH) (2017). "MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017)." from <https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf>

New York State Department of Health (Dr. Kenneth Bogdan) (2003). Human Health Fact Sheet for Metolachlor: Ambient Water Quality Value for Protection of Human Health and Sources of Potable Water.

Personal Correspondence with Steve Snyderman (EPA) on 8/8/2017. Status of Metolachlor Re-registration.

Syracuse Research PhysProp Database.

U.S. Environmental Protection Agency (EPA). " Regional Screening Levels (RSLs) Table." <https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables-november-2017>

U.S. Environmental Protection Agency (EPA) (1988). "Integrated Risk Information System: Chemical Assessment Summary for Metolachlor." from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0074_summary.pdf

U.S. Environmental Protection Agency (EPA) (1991). Memorandum: Review additional discussion on Metolachlor's carcinogenicity potential, a chronic dog study with additional data and additional metabolism data. Data Evaluation Records (DERs) for Metolachlor metabolism in the rat and Metolachlor 13/52 week oral toxicity study in dogs.

U.S. Environmental Protection Agency (EPA) (1993a). Data Evaluation Record. Metolachlor: Rat chronic toxicity/carcinogenicity study and subchronic dog study - re-review of data.

U.S. Environmental Protection Agency (EPA) (1993b). Data Evaluation Record. Metolachlor: Re-review of chronic dog study, 2-generation reproduction study, and rabbit developmental toxicity (teratology) study.

U.S. Environmental Protection Agency (EPA) (1995). "Metolachlor Reregistration Eligibility Decision." from <https://archive.epa.gov/pesticides/reregistration/web/pdf/0001.pdf>

U.S. Environmental Protection Agency (EPA) (1997). Health Effects Assessment Summary Table (HEAST).

U.S. Environmental Protection Agency (EPA) (2002). Metolachlor: Revised HED Science Assessment for Tolerance Reassessment Eligibility Decision (RED). PC Code 108801. (May 23, 2002).

U.S. Environmental Protection Agency (EPA) (2002). "Report on the Food Quality Protection Act (FWPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Metolachlor (6/17/2002)." from

https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/tred_PC-108801_1-Oct-02.pdf

U.S. Environmental Protection Agency (EPA) (2002). Revised Toxicology Chapter for Metolachlor/s-Metolachlor (May 13, 2002).

U.S. Environmental Protection Agency (EPA) (2006). S-metolachlor: Human Health Risk Assessment for Proposed Section 18 Uses on Cilantro, Collards, Kale, and Mustard Greens; Section 3 use on Pumpkin and Tolerance of Winter Squash without US Registration. PC Code 108800 s-metolachlor and 108801 Metolachlor (7/13/2006).

U.S. Environmental Protection Agency (EPA) (2007). Fifth Report of the Cancer Assessment Review Committee.

U.S. Environmental Protection Agency (EPA) (2008). Regulatory Determinations Support Document for Selected Contaminants from the Second Drinking Water Contaminant Candidate List (CCL2): Chapter 12 Metolachlor. https://www.epa.gov/sites/production/files/2014-09/documents/report_ccl2-reg2_supportdocument_full.pdf

U.S. Environmental Protection Agency (EPA) (2011). "Recommended Use of Body Weight^{3/4} as the Default Method in Derivation of the Oral Reference Dose. Office of the Science Advisor." from <https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose>

U.S. Environmental Protection Agency (EPA) (2012). "Office of Drinking Water. 2012 Edition of the Drinking Water Standards and Health Advisories." from <https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100N01H.TXT>

U.S. Environmental Protection Agency (EPA) (2019). "Exposure Factors Handbook Chapter 3 Update 2019." from <https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3>

U.S. Geological Survey - Health-Based Screening Levels. from <https://cida.usgs.gov/hbsl/apex/f?p=104:1>

World Health Organization (WHO) (1996 (updated 2003)). "Metolachlor in Drinking Water: Background document for development of WHO Guidelines for Drinking Water."

World Health Organization (WHO) (2011). "Guidelines for Drinking-Water Quality." from http://apps.who.int/iris/bitstream/10665/44584/1/9789241548151_eng.pdf