

## 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 Based Value (nHBV<sub>Acute</sub>) = Not Derived (Insufficient Data)**

**Short-term Non-Cancer Health Based Value (nHBV<sub>Short-term</sub>) = 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 Based Value (nHBV<sub>Subchronic</sub>) = nHBV<sub>Short-term</sub> = 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 nHBV must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 300 µg/L. Additivity endpoints: Developmental**

**Chronic Non-Cancer Health Based Value (nHBV<sub>Chronic</sub>) = nHBV<sub>Short-term</sub> = 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 nHBV must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 300 µg/L. Additivity endpoints: Developmental**

**Cancer Health Based Value (cHBV) = 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)<sup>-1</sup> (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 <sup>1</sup>	-	Yes <sup>2</sup>	Yes <sup>3</sup>	- <sup>4</sup>

**Comments on extent of testing or effects:**

<sup>1</sup> 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.

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

<sup>3</sup> 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.

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

**Resources Consulted During Review:**

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