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

Adopted as Rule: August 2018

Toxicological Summary for: Acetochlor ESA

CAS: **187022-11-3**
Synonyms: Acetochlor Ethane Sulfonic Acid

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

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 500 µg/L

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

$$= \frac{\text{(0.29 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 509 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 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 86.2/300 = 0.29 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	374.6 mg/kg-d (LOAEL, MRID 45300503, aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.23 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 374.6 mg/kg-d x 0.23 = 86.2 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for extrapolation from a LOAEL to a NOAEL, and 3 for database uncertainty (lack of developmental or multigenerational reproductive studies)
Critical effect(s):	Increased free thyroxine (T4)
Co-critical effect(s):	Increased thyroid stimulating hormone (TSH)
Additivity endpoint(s):	Thyroid (E)

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = 500 µg/L

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

$$= \frac{\text{(0.19 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 543 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 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 56.4/300 = 0.19 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	225.4 mg/kg-d (NOAEL, MRID 45313801, aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.25 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 225.4 mg/kg-d x 0.25 = 56.4 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 (lack of 2 generation study, lack of sensitive endpoint testing (thyroid), lack of second species (based on parent compound, dog appears to be more sensitive)
Critical effect(s):	Decreased body weight and body weight gain, decreased food utilization
Co-critical effect(s):	Increased thyroid stimulating hormone (TSH), increased free thyroxine (T4), increased free triiodothyronine (T3), increased relative testes weight
Additivity endpoint(s):	Male Reproductive system, Thyroid (E)

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

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

$$= \frac{\text{(0.056 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{}$$

(0.044 L/kg-d)**

= 255 rounded to **300 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 56.4/1000 = 0.056 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	225.4 mg/kg-d (NOAEL, MRID 45313801, aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.25 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 225.4 mg/kg-d x 0.25 = 56.4 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for subchronic to chronic extrapolation, and 10 for database uncertainty (lack of 2 generation study, lack of sensitive endpoint testing (thyroid), lack of second species (based on parent compound, dog appears to be more sensitive)
Critical effect(s):	Decreased body weight and body weight gain, decreased food utilization
Co-critical effect(s):	Increased thyroid stimulating hormone (TSH), increased free thyroxine (T4), increased free triiodothyronine (T3), increased relative testes weight
Additivity endpoint(s):	Male Reproductive system, Thyroid (E)

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification:	Not Classified
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: No

Summary of Guidance Value History:

In 2005, MDH derived a chronic noncancer Health-Based Value (HBV) of 50 µg/L. In 2009, MDH derived short-term, subchronic, and chronic noncancer HBVs of 600, 600, and 300 µg/L, respectively. These HBVs were adopted as Health Risk Limits (HRLs) in 2011. In 2017, MDH re-evaluated the noncancer HRLs, resulting in new noncancer short-term, subchronic, and chronic HBVs of 500, 500, and 300 µg/L, respectively. The short-term and subchronic values were lower and the chronic value is unchanged as a result of 1) using MDH's most recent risk assessment methodology including the application of Human Equivalence Doses (HED) and 2) rounding to one significant digit. This 2017 guidance was adopted into rule as HRLs in 2018.

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

Comments on extent of testing or effects:

[1] Alterations in thyroid hormone levels were reported at the lowest dose tested in a 28-day range-finding study and form the basis of the Short-term HBV. Alterations in thyroid hormone levels have also been reported for acetochlor OXA and the parent, acetochlor. Thyroid mechanism of action studies conducted on the parent, acetochlor, indicate that acetochlor disrupts thyroid-pituitary homeostasis via increased clearance of serum thyroxin (T4). The subchronic study did not include an evaluation of thyroid hormone levels. The subchronic HBV is based on the no adverse effect level (NOAEL) identified in the subchronic study and includes an uncertainty factor for database deficiency to address the need for additional testing on acetochlor ESA regarding altered thyroid hormone levels.

[2] No developmental study has been conducted. Registrant recommended that the OPP consider the alachlor ESA developmental study in rats as evidence that development is not a sensitive endpoint. The developmental study on the parent, acetochlor, identified HED LOAELs of 88-132 mg/kg-d and HED NOAELs of 33-44 mg/kg-d, based on signs of clinical toxicity and decreased weight gain in pregnant animals, increased resorptions and decreased fetal weights. However, the multiple generation study on the parent identified significantly lower HED NOAEL/LOAEL values (4.9/15.6 mg/kg-d), indicating that the standard developmental study protocol is not a sensitive test. A database uncertainty factor was incorporated into the derivation of the RfD, in part, due to the lack of a multigenerational reproductive study.

[3] Male reproductive toxicity (testicular degeneration and decreased testes weight) was a critical effect for the parent, acetochlor. Alterations in testes weights were reported in the short-term range finding study but not in the 90-day study. A database uncertainty factor was incorporated into the derivation of the RfD, in part, due to concerns that additional testing should be conducted.

[4] A functional observation battery for neurotoxicity was conducted and histopathology of the sciatic nerve was assessed in a 90-day study for general toxicity. There were possible signs of neurotoxicity, but none showed dose dependency. Neurological effects were a sensitive endpoint for the parent, acetochlor. A database uncertainty factor was incorporated into the derivation of the subchronic and chronic RfDs, in part, due to concerns that additional testing should be conducted.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry (ATSDR). (2017). Minimal Risk Levels. Retrieved from https://www.atsdr.cdc.gov/mrls/index.asp

California Environmental Protection Agency. (2017). OEHHA Toxicity Criteria Database. Retrieved from https://oehha.ca.gov/chemicals

European Food Safety Authority (EFSA). (2013). Reasoned opinion on the review of the existing maximum residue levels (MRLs) for acetochlor according to Article 12 of Regulation (EC) No 396/2005. *EFSA Journal, 11*(7), 3315-n/a. doi:10.2903/j.efsa.2013.3315

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. Retrieved from http://www.health.state.mn.us/divs/eh/risk/rules/water/hrlsonar08.pdf.

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). Retrieved from http://www.health.state.mn.us/divs/eh/risk/guidance/hedrefguide.pdf

U.S. Environmental Protection Agency (USEPA). (2006a). *Acetochlor Revised HED Chapter of the Tolerance Reassessment Eligibility Decision (TRED) Document*. Retrieved from https://www.regulations.gov/document?D=EPA-HQ-OPP-2005-0227-0024

U.S. Environmental Protection Agency (USEPA). (2006b). *Data Evaluation Record. Acetochlor ESA Metabolite 90 day study. Citation: Lees, D. (2000) R290131: 90 day dietary toxicity study in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire (UK), laboratory report No: CTL.PR1147/REG/REPT May 19, 2000. MRID 45313801 unpublished.*

U.S. Environmental Protection Agency (USEPA). (2006c). *Data Evaluation Record. Acetochlor Ethane Sulfonate Acid Metabolite 4-week Range-finding study. Citation: Lees, D. R290131: 28 day dietary toxicity study in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire (UK),laboratory report No: CTL/KR1350/REG/REPT, MRID 45300503.*

U.S. Environmental Protection Agency (USEPA). (2011a). *Exposure Factors Handbook: 2011 Edition*. Retrieved from https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

U.S. Environmental Protection Agency (USEPA). (2011b). *Recommended Use of Body Weight 3/4 as the Default Method in Derivation of the Oral Reference Dose*. Retrieved from http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf.

U.S. Environmental Protection Agency (USEPA). (2017a). Human Health Benchmarks for Pesticides. Retrieved from https://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home

U.S. Environmental Protection Agency (USEPA). (2017b). Integrated Risk Information System. Retrieved from https://www.epa.gov/iris

U.S. Environmental Protection Agency (USEPA). (2017c). Office of Water Contaminant Candidate List (CCL) and Regulatory Determination. Retrieved from https://www.epa.gov/ccl/contaminant-candidate-list-4-ccl-4-0