Adopted as Rule: August 2018

Toxicological Summary for: Acetochlor OXA

CAS: **184992-44-4**
Synonyms: Acetochlor Oxanilate Metabolite

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

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 100 µg/L

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

$$= \frac{\text{(0.081 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 142 rounded to **100 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 = 80.8/1000 = 0.081 mg/kg-d (laboratory rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	367.2 mg/kg-d (LOAEL, MRID 45300506, aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.22 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 367.2 mg/kg-d x 0.22 = 80.8 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for extrapolation from a LOAEL to NOAEL, and 3 for database uncertainty (lack of multigenerational reproductive study)
Critical effect(s):	Decreased thyroid stimulating hormone (TSH)
Co-critical effect(s):	Decreased body weight gain, decreased total triiodothyronine (tT3), increased relative thyroid weight
Additivity endpoint(s):	Thyroid (E)

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 100 µg/L

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

$$= \frac{\text{(0.062 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 177 rounded to 200 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 = 18.5/300 = 0.062 mg/kg-d (rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	77.2 mg/kg-d (NOAEL, MRID 45313805 and 45300506, aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.24 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 77.2 mg/kg-d x 0.24 = 18.5 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 multigenerational reproductive study, lack of studies in a second species (based on parent compound, dog appears to be more sensitive), lack of thyroid and motor activity effects studies [sensitive endpoints for parent compound, acetochlor])
Critical effect(s):	Decreased body weight and body weight gain, decreased food utilization
Co-critical effect(s):	Decreased thyroid stimulating hormone (TSH)
Additivity endpoint(s):	Thyroid (E)

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 100 µg/L. Additivity endpoints: Thyroid (E)

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = 90 µg/L

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

$$= \frac{\text{(0.019 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044 L/kg-d)}^{**}}$$

= 86.4 rounded to **90 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 = 18.5/1000 = 0.019 mg/kg-d (lab rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	77.2 mg/kg-d (NOAEL, MRIDs 45313805 & 45300506, aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.24 (body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 77.2 mg/kg-d x 0.24 = 18.5 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 multigenerational reproductive study, lack of studies in a second species (based on parent compound, dog appears to be more sensitive), lack of studies showing thyroid and motor activity effects [sensitive endpoints for parent compound, acetochlor])
Critical effect(s):	Decreased body weight and body weight gain, decreased food utilization
Co-critical effect(s):	Decreased thyroid stimulating hormone (TSH)
Additivity endpoint(s):	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 noncancer Health-Based Value (HBV) of 50 µg/L. In 2009, MDH derived short-term, subchronic, and chronic noncancer HBVs of 200, 200, and 100 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 100, 100, and 90 µg/L, respectively. The short-term, subchronic, and chronic values were lower 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. The 2017 guidance was adopted into rules 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	Yes	No	No
Effects observed?	Yes[1]	-	No[2]	-[3]	-[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 ESA 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 OXA regarding altered thyroid hormone levels.

[2] A single developmental study has been conducted. No adverse developmental effects were reported at the highest dose tested. An increase in maternal mortality was observed in this study. Based on data for the parent, acetochlor, the 2-generation study reported significantly lower NOAEL/LOAEL value than the developmental study indicating that the standard developmental study protocol is not a sensitive test.

[3] Male reproductive toxicity was a critical effect for the parent, acetochlor. The database uncertainty factor was, in part, applied to address the absence of a 2-generational reproductive study.

[4] A dose-dependent increase in motor activity in males was observed in a 90 day study, however, this parameter was highly variable and only reached statistical significance ($p<0.01$) at the highest dose level. Researchers reported, but did not substantiate, that observations were within the range of historical controls. The nervous system has been identified as a chronic critical effect for the parent, acetochlor. The uncertainty factor for database deficiency is applied to 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 Oxanilate Metabolite. Study Type: §82-1a, 90-Day Oral Toxicity Study in Rats. Work Assignment No. 3-02-144 D (MRIDs 45313805 and 45300506). Prepared for Health Effects Division Office of Pesticide Programs.*

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