Adopted as Rule: August 2018

Toxicological Summary for: Thiamethoxam

CAS: **153719-23-4**

Synonyms: CGA 293343, 4H-1,3,5-Oxadiazin-4-imine, 3-[(2-chloro-5-thiazolyl)methyl] tetrahydro-5-methyl-N-nitro-, 3-((2-Chloro-5-thiazolyl)methyl)tetrahydro-5-methyl-N-nitro-4H-1,3,5-oxadiazin-4-imine

IUPAC name: 3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine

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

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 400 µg/L

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

$$= \frac{\text{(0.25 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 439 rounded to **400 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 = 7.6 mg/kg-d/30 = 0.25 mg/kg-d (Wistar rat)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	34.5 mg/kg-d (NOAEL, Brammer 2007)
Dose Adjustment Factor (DAF):	0.22 (MDH 2011)
Human Equivalent Dose (HED):	POD x DAF = 34.5 mg/kg-d x 0.22 = 7.6 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Reduced pup body weight
Co-critical effect(s):	Hepatocyte hypertrophy, maternal death during pregnancy accompanied by hemorrhage of the uterus, bloody discharge in the perineal area, decreased number

	of animals with live fetuses, decreased fetal body weight, and increased fetal skeletal anomalies (fused sternebrae)
Additivity endpoint(s):	Developmental, Female Reproductive system, Hepatic (liver) system

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = 200 µg/L

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

$$= \frac{\text{(0.057 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 163 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 = 1.7 mg/kg-d/30 = 0.057 mg/kg-d (Beagles)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	4.05 mg/kg-d (NOAEL, Altmann 1998)
Dose Adjustment Factor (DAF):	0.43 (MDH 2011)
Human Equivalent Dose (HED):	POD x DAF = 4.05 mg/kg-d x 0.43 = 1.7 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Seminiferous tubule atrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Male Reproductive system

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Subchronic}$ = 200 µg/L

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

$$= \frac{\text{(0.057 mg/kg-d***) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044 L/kg-d)}^{**}}$$

= 259 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

***The calculated chronic RfD (0.43 mg/kg-d) is higher than the subchronic RfD (0.057 mg/kg-d), which is based on male reproductive effects. The chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure, including subchronic effects (MDH 2008). Therefore, the chronic RfD is set to the subchronic RfD. See the subchronic information above for details about the reference dose.

The Chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic duration; and therefore, the Chronic nHRL is set equal to the Subchronic nHRL of 200 µg/L. Additivity endpoints: Male Reproductive system

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification:	Not likely to be carcinogenic to humans
Slope factor (SF):	Not Applicable
Source of cancer SF:	Not Applicable
Tumor site(s):	Not Applicable

Volatile: No

Summary of Guidance Value History:
A pesticide rapid assessment of 20 µg/L was completed for thiamethoxam in 2014 by MDH. The 2016 nHBVs of 200 µg/L were higher than the pesticide rapid assessment due to the conservative method used for rapid assessments (MDH 2014). The 2016 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?	No	No	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

[1] A comprehensive toxicity study, specific for endocrine effects after Thiamethoxam exposure, has not been completed; however, endocrine effects were observed in other studies. Endocrine effects included changes to the adrenal cortex and thyroid. In short-term and subchronic durations, adrenal gland changes occurred in male and female rats at Thiamethoxam levels 400 to 700 times higher than the corresponding duration's reference dose. Thyroid gland changes occurred in rats between 200-700 times higher than the short-term reference dose.

[2] Immunological effects observed in Thiamethoxam studies include changes in the thymus, spleen, and white blood cells. Changes to the thymus in rats were varied, with a range of changes between 250 to 1,400 times higher than the reference dose in short-term and subchronic durations. Conversely, one report observed no changes to the thymus at levels up to 690 times higher than the short-term

reference dose. Changes to the spleen, in rat, were observed between levels of Thiamethoxam 700 to 1,400 times higher than the subchronic reference dose. Beagles were a more sensitive species, with thymus and spleen changes occurring at levels 72 times higher than the short-term reference dose. White blood cell changes occurred at levels around 400 times higher than the subchronic reference dose.

[3] The short-term reference dose is based on the developmental effect of reduced pup body weight, an effect that occurred in multiple studies. Reductions in fetal body weights and skeletal abnormalities occurred at levels 700 times higher than the short-term reference dose in rats and 300 times higher than the short-term reference dose in rabbits.

[4] The subchronic reference dose is based on adverse reproductive effects occurring in adult male beagles. There were no reproductive effects in pregnant rats exposed to levels of Thiamethoxam up to 700 times higher than the short-term reference dose. Pregnant rabbits were more sensitive, demonstrating reproductive effects at levels 300 times higher than the short-term reference dose. Adult female mice experienced reproductive changes at levels up to 1,400 times higher than the subchronic reference dose, and male mice at levels over 3,000 times higher than the subchronic reference dose. Studies in adult rats varied, with reports of no adverse reproductive events at Thiamethoxam levels 500 times higher than the subchronic reference dose, to changes in sperm concentrations at levels 16 times higher than the subchronic reference dose.

[5] Thiamethoxam exposure in rodents produced transient neurotoxicity at high doses over 250-500 times greater than the short-term and subchronic reference doses. Altered activity and changes in the brain were noted in these studies. The mouse was more sensitive than the rat, with adverse effects in the mouse (reduced locomotor activity, convulsions, prostration) occurring at Thiamethoxam levels 250 times higher than the short-term reference dose. The rat experienced adverse effects from Thiamethoxam levels beginning at levels 450 times higher than the short-term reference dose. There were no adverse effects on pups when pregnant rats were exposed to Thiamethoxam at levels up to 300 times higher than the short-term reference dose.

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