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

Adopted as Rule: August 2018

Toxicological Summary for: Clothianidin

CAS: **210880-92-5 (Former CAS # 205510-53-8)**

Synonyms: CGA-322704, *(E)*-*N*-[(2-chloro-5-thiazolyl)methyl]-*N'*-methyl-*N''*-nitroguanidine, (*E*)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine

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

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 200 µg/L

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

$$= \frac{\text{(0.093 mg/kg-d) x (0.5*) x (1000 µg/mg)}}{\text{(0.285* L/kg-d)}}$$

= 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 = 2.8 mg/kg-d/30 = 0.093 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	12 mg/kg-d (NOAEL, Freshwater 2000)
Dose Adjustment Factor (DAF):	0.23 (MDH 2011)
Human Equivalent Dose (HED):	POD x DAF = 12 mg/kg/d x 0.23 = 2.8 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Decreased pup body weight gain
Co-critical effect(s):	Decreased body weight gain in pregnant adult rats
Additivity endpoint(s):	Developmental

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

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

$$= \frac{\text{(0.093}^{\#}\text{ mg/kg-d) x (0.2*) x (1000 µg/mg)}}{}$$

(0.070** L/kg-d)

= 266 rounded to 300 µg/L

#The calculated Subchronic RfD (0.28 mg/kg-d) is higher than the Short-term RfD (0.093 mg/kg-d), which is based on developmental effects. The Subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the Short-term RfD is used in place of the calculated Subchronic RfD.

*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 Subchronic nHRL must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 200 µg/L. Additivity endpoints: Developmental

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

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

$$= \frac{\text{(0.077 mg/kg-d) x (0.2*) x (1000 µg/mg)}}{\text{(0.044**L/kg-d)}}$$

= 350 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 = 2.3 mg/kg-d/30 = 0.077 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	8.9 mg/kg-d (BMDL, Biegel 2000b)
Dose Adjustment Factor:	0.26 (MDH 2011)
Human Equivalent Dose (HED):	POD x DAF = 8.9 x 0.26 = 2.3 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Ovarian interstitial gland hyperplasia
Co-critical effect(s):	Decreased pup body weight gain, decreased body weight gain in pregnant adult rats
Additivity endpoint(s):	Developmental, Female reproductive system

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 200 µg/L. Additivity endpoints: Developmental

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification: Not likely to be carcinogenic (US EPA 2009)
Slope factor: Not Applicable
Source of slope factor: Not Applicable
Tumor site(s): Not Applicable

Volatile: No

Summary of Guidance Value History:
A pesticide rapid risk assessment was derived in 2014 and resulted in a value of 200 µg/L. The 2016 toxicological summary of Clothianidin contained the first HBVs calculated for Clothianidin by MDH. In 2016 MDH updated the intake rate values used to derive guidance values. Due to rounding to one significant digit the updated intake rates resulted in a revised calculated Subchronic nHBV of 300 µg/L, therefore it was set to the Short-term nHBV of 200 µg/L. Incorporation of updated intake rates did not result in any change to the Chronic nHBV value. The 2016 guidance was adopted as rule 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	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:
[1] Endocrine effects such as increased relative testes weights occurred in male rats at 600 times the short-term reference dose. Reduced relative uterine and ovarian weights in female rats occurred at doses 500 times higher than the short-term reference dose. Thyroid follicular cysts occurred in female rats at doses 600 times higher than the chronic reference dose. Male mice had seminiferous tubule atrophy at levels 1000 times higher than the short-term reference dose. In a toxicity study designed to study thyroid changes, after Clothianidin exposure in rats, there were no changes in triiodothyronine, thyroxine, and TSH levels.

[2] Although two toxicity studies specifically focused on immunotoxicity did not detect any changes in spleen activity up to 700 times the short-term reference dose, and no adverse effects on humoral or T-cell mediated immunity at levels up to 5,000 times the short-term reference dose, immunological effects were observed in other toxicity studies. These included thymus atrophy and reduced relative thymus weights in mice and rats at levels between 500-1,300 times higher than the short-term reference dose. Changes in spleen weight and spleen atrophy were observed in various toxicity studies in rats and mice at dosing levels 300 to 1,300 times higher than the short-term reference dose. Beagles were most sensitive to Clothianidin in relation to changes in white blood cell, lymphocyte, eosinophil,

neutrophil, monocyte, and platelet counts, often occurring at 200 times higher than the short-term reference dose.

[3] The short-term reference dose is based on decreased pup body weights. At doses 600 times higher than the short-term reference dose, a delay in vaginal patency was observed, and at doses 100 times higher than the short-term reference dose, a delay in preputial separation was noted. Both of these observations could be related to the decrease in pup body weight. Fetal abnormalities occurred at levels 400 to 1,300 times higher than the short-term reference dose.

[4] The chronic reference dose is based on increased ovarian interstitial gland hyperplasia. Changes in uterine and ovary weights were noted at levels beginning at 300 times higher than the short-term reference dose. Changes in testes weight and sperm motility were observed at doses beginning at 500 times higher the short-term reference dose. Changes in metabolism in the testes was seen in rats beginning at 5 times higher than the short-term reference dose. In rabbits, there was an increased incidence of abortion and premature deliveries at levels 400 times higher than the short-term reference dose. Conversely, other studies noted no changes in the estrus cycle up to 600 times the short-term reference dose and no changes in reproductive effects up to 400 times the short-term reference dose.

[5] Neurotoxic effects were most prominent in mice, occurring at levels 40 to 500 times higher than the short-term reference dose. Tremors, convulsions, and reduced motor and locomotor activity in rats were noticed at levels 300 times the short-term reference dose. Increased secretion of tears was observed in rats at 1,300 times higher than the short-term reference dose. In a developmental neurotoxicity study designed specifically to assess neurotoxic parameters in rat pups, reduced response to loud noise, motor activity, time spent in movement, and increased brain thickness occurred at doses 800 times higher than the short-term reference dose.

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