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

Adopted as Rule: November 2023

Toxicological Summary for: Imidacloprid

CAS: **138261-41-3**

Synonyms: N-[1-[(6-chloropyridin-3-yl)methyl]-4,5-dihydroimidazol-2-yl]nitramide; 1-((6-chloro-3-pyridinyl)methyl)-N-nitro-2-imidazolidinimine; [N-(6-chloropyridin-3-ylmethyl)-2-nitroiminoimidazolidine]; *(E)* -1-(6-Chloro-3-pyridinylmethyl)-*N*-nitroimidazolidin-2-ylideneamine; NTN; 2-Imidazolidinimine

Acute Non-Cancer Health Risk Limits ($nHRL_{Acute}$) = 100 µg/L

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

$$= \frac{\text{(0.15 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 103 rounded to **100 µg/L**

[*]Relative Source Contribution: MDH 2008, Section IV.E.1. MDH deviated from the default RSC of 0.5 based on assessments from California EPA (2006) and U.S. EPA (2017) indicating that infant dietary exposures and infant exposures from residential pesticide treatments, including pet treatments, are high enough to warrant allocation of only 20% of the RfD to drinking water.

[**]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 = 4.4/30 = 0.15 mg/kg-d (Beagle dogs)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	8 mg/kg-d (administered dose NOAEL, Ruf 1990 cited in California EPA 2006)
Dose Adjustment Factor (DAF):	0.55, Body weight scaling based on dog body weights at start of study (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 8 mg/kg-d x 0.55 = 4.4 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Tremors
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Short-term Non-Cancer Health Risk Limits ($nHRL_{Short\text{-}term}$) = 2 µg/L

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

$$= \frac{\text{(0.0036 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 2.48 rounded to **2 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1. MDH deviated from the default RSC of 0.5 based on assessments from California EPA (2006) and U.S. EPA (2017) indicating that infant dietary exposures and infant exposures from residential pesticide treatments, including pet treatments, are high enough to warrant allocation of only 20% of the RfD to drinking water.

**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 = 0.107/30 = 0.0036 mg/kg-d (BALB/c mice)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	0.820 mg/kg-d (administered dose $BMDL_{1SD}$, Badgujar 2013)
Dose Adjustment Factor (DAF):	0.13, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 0.820 mg/kg-d x 0.13 = 0.107 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 delayed-type hypersensitivity response
Co-critical effect(s):	None
Additivity endpoint(s):	Immune system

Subchronic Non-Cancer Health Risk Limits ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 2 µg/L

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

$$= \frac{\text{(0.0036 mg/kg-d)}^{***} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 9.72 rounded to 10 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.

***The calculated Subchronic RfD (0.073 mg/kg-d) is higher than the Short-term RfD (0.0036 mg/kg-d), which is based on immune 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.

The Subchronic nHRL must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 2 µg/L. Additivity endpoints: Immune system

Chronic Non-Cancer Health Risk Limits ($nHRL_{Chronic}$) = $nHRL_{Short\text{-}term}$ = 2 µg/L

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

$$= \frac{\text{(0.0036 mg/kg-d)}^{***} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 16 rounded to 20 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.

***The calculated Chronic RfD (0.019 mg/kg-d) is higher than the Short-term RfD (0.0036 mg/kg-d), which is based on immune effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure, including subchronic and short-term effects (MDH 2008, page 34). Therefore, the Short-term RfD is used in place of the calculated Chronic RfD.

The Chronic HRL must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic HRL is set equal to the Short-term HRL of 2 µg/L. Additivity endpoints: Immune system

Cancer Health Risk Limits (cHRL) = "Not Applicable"

Cancer classification:	Evidence of non-carcinogenicity for humans (U.S. EPA 2017a)
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 2014, MDH derived a pesticide rapid assessment value for imidacloprid (90 µg/L) based on a US EPA risk assessment from 2010 (US EPA 2010) and the thyroid as a critical health endpoint. The 2019 HBVs for short-term, subchronic, and chronic durations (this assessment) are lower than the pesticide rapid assessment due to the incorporation of a toxicologically more sensitive health endpoint that occurred in a shorter-duration study than the chronic thyroid effects. The 2019 MDH risk assessment methodology includes BMD modeling for the delayed-type hypersensitivity response in mice. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in a change in the short-term duration water guidance value from 3 µg/L to 2 µg/L. As in the 2019 MDH risk assessment, the subchronic and chronic guidance

values were set to equal the short-term guidance value (2 µg/L). In November 2023, the guidance values were adopted into Minnesota Rules, 4717.7860, as Health Risk Limits (HRLs).

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] At an imidacloprid exposure 1,000 times higher than the short-term RfD, reduced ovarian weight was associated with increased ovarian lipid peroxidation, decreased ovarian antioxidant activity, and changes in ovarian hormones and ovarian morphology in the female rat 90-days after exposure. At a dose 2,500 times higher than the short-term RfD, male rats had increased adrenal weight, increased adrenal cholesterol, and increased hypothalamic and pituitary acetylcholinesterase activity. Changes in male hormones were observed in two lower quality, single dose studies in both rat pups and adults at doses 25 – 70 times higher than the short-term RfD. Thyroid lesions were observed in male rats after 2 years of exposure at doses 300 times higher than the short-term RfD. Thyroid changes occurred in female beagles at doses 4,000 times higher than the short-term RfD.

[2] The short-term RfD is based on immunotoxicity (decreased delayed-type hypersensitivity response) in female mice in a 28-day immunotoxicity study. In the same study, a five-fold higher dose resulted in reduced T-cell stimulation and a reduction in the number of lymphocytes. In a longer-duration study, the spleen weight in mice was reduced at a dose 17,000 times higher than the short-term RfD. Immunotoxicity was also observed in other study animals. Rat pups had a reduced hemagglutination titer and phagocytic index at a dose 150 times higher, and had a delayed-type hypersensitivity response at imidacloprid levels 400 times higher than the short-term RfD. At levels 1,000 times higher than the short-term RfD, rat pups had a decreased number of white blood cells. Beagles after a one-month exposure, had atrophy of the bone marrow, involution of the thymus, and a drop in serum α-1 globulin M at a dose 7,000 times higher than the short-term RfD.

[3] Skeletal abnormalities were observed in both rat and rabbit fetuses at doses 6,000 and 9,000 times higher than the short-term RfD, respectively. Reduced body weight in rat pups occurred at doses 2,000 to 6,000 times higher than the short-term RfD. Some of these pups also had morphometric changes in the brain, learning delays, or changes in motor activity. A lower quality, single dose study using a commercial formulation in mice reported changes in neuronal branching and neuronal density in the brain at doses 25 times higher than the short-term RfD.

[4] Maternal death, abortion, total resorption, and post-implantation loss were only observed in rabbits; and at imidacloprid doses 10,000 times higher than the short-term RfD. Despite no apparent change in reproductive outcomes, female rats had reduced ovarian weight along with changes in ovarian morphology, and increased lipid peroxidation and decreased anti-oxidant activity in the ovaries at doses 1,000 times higher than the short-term RfD. Male rats, at doses 70 to 500 times higher than the short-term RfD, had reduced seminal vesicle and testicular weight, testicular atrophy, reduced sperm concentration, reduced sperm mobility and viability, increased sperm abnormalities, and changes in male reproductive hormones. Conversely, increased testicular weight was noted in rats after one-year of exposure at imidacloprid levels 8,000 times higher than the short-term RfD, and increased ovarian weight was noted after two-years exposure at levels 10,000 times higher than the short-term RfD. Testicular degeneration was observed in the beagle at imidacloprid doses 7,500 times higher than the short-term RfD.

[5] The acute duration RfD is based on tremors in beagles after imidacloprid exposure. This occurred at imidacloprid concentrations 3,500 times higher than the short-term RfD. In the rat, tremors (at 1,000 times higher than the short-term RfD), occurred in addition to uncoordinated gait, reduced motor and locomotor activity, reduced hindlimb grip strength, and the absence of response to human touch or a tail pinch at levels 5,000 to 10,000 times higher than the short-term RfD. Rat fetuses, at maternal doses 3,000 times higher than the short-term RfD, had changes in brain thickness. Rat pups had a delay in learning and a decrease in memory consolidation at imidacloprid levels 2,000 times higher than the short-term RfD, and adults were affected at levels 100 to 500 times higher than the short-term RfD in the same study. Chemical changes in the brain were measured in female rat at levels 60 times higher than the short-term RfD. Tremors in mice occurred at levels 4,000 times higher than the short-term RfD. A lower quality, single dose study using a commercial formulation found that male mice had changes in brain thickness at levels 25 times higher than the short-term RfD.

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