Minnesota Department of Health

Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
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Toxicological Summary for: Pyraclostrobin

CAS**: 175013-18-0**

Synonyms: methyl 2-[1-(4-chlorophenyl)pyrazol-3-yloxymethyl]-N-methoxycarbanilate; Methyl N-(2-(1-(4-chlorophenyl)-1H-pyrazol-3-yloxymethyl)phenyl)-(N-methoxy)carbamate; Cabrio; Headline

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = 300 µg/L

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

$$= \frac{\text{(0.073 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}^{1**}}$$

= 340 rounded to **300 µg/L**

[1]RfD is based on an NOAEL for early post-implantation loss that occur *in utero*, therefore the intake rate for pregnant women is utilized rather than the default infant intake rate as described in the SONAR (page 46). Since the acute duration intake is based on pregnant women, not infants, an RSC of 0.2 is utilized.

[*]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:	(5 x 0.44)/30 = 0.073 mg/kg-d (Himalayan rabbit)
Source of toxicity value:	determined by MDH in 2015
Point of Departure (POD):	5 mg/kg-d (NOAEL, MRID 45118326, 1999 aci (USEPA, 2003b))
Human Equivalent Dose (MDH, 2011):	5 x 0.44 = 2.2 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Increased post-implantation loss
Co-critical effect(s):	None
Additivity endpoint(s):	Development, Female Reproductive system

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 100 µg/L

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

$$= \frac{\text{(0.057 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 100 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:	(7.8 x 0.22)/30 = 0.057 mg/kg-d (Wistar Rat)
Source of toxicity value:	determined by MDH in 2015
Point of Departure (POD):	7.8 mg/kg-d (NOAEL, MRID 45118327 aci (USEPA, 2003d))
Human Equivalent Dose (MDH, 2011):	7.8 x 0.22 = 1.7 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies difference (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased pup body weight and body weight gain, delayed vaginal opening
Co-critical effect(s):	Increased post-implantation loss, decreased live fetuses, increased incidence of absent lumbar vertebrae in fetuses, hyperplasia in the duodenum, and increased relative spleen weight with changes in histopathology
Additivity endpoint(s):	Development, Female Reproductive system, Gastrointestinal system, Spleen

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 100 µg/L

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

$$= \frac{\text{(0.046 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 131 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:	(9.2 x 0.15)/30 = 0.046 mg/kg-d (B6C3F1 Crl BR mouse)
Source of toxicity value:	determined by MDH in 2015
Point of Departure (POD):	9.2 mg/kg-d (NOAEL, MRID 45118320 aci (USEPA, 2001a))
Human Equivalent Dose (MDH, 2011):	9.2 x 0.15 = 1.38 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased body weight, body weight gain and food efficiencies, clinical chemistry changes indicative or protein metabolism, ulceration/erosion of the glandular stomach, increased apoptosis of the mesenteric lymph nodes, and atrophy of the thymus
Co-critical effect(s):	Decreased pup body weight/body weight gain and delayed vaginal opening, increased post-implantation loss, decreased body weight gain and food efficiency in adult animals, duodenum mucosal hypertrophy, increased

	diarrhea, increased liver and spleen weights, changes in liver and spleen histopathology, clinical chemistry changes (e.g., decreased cholesterol, protein), and hematological changes (e.g., increased white blood cells and platelets)
Additivity endpoint(s):	Development, Female Reproductive system, Gastrointestinal system, Hematological (blood) system, Hepatic (liver) system, Immune system, Spleen

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Subchronic}$ = 100 µg/L

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

$$= \frac{\text{(0.033 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044 L/kg-d)}^{**}}$$

= 150 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:	(3.4 x 0.29)/30 = 0.033 mg/kg-d (Wistar Rat)
Source of toxicity value:	determined by MDH in 2015
Point of Departure (POD):	3.4 mg/kg-d (NOAEL, MRID 45118331 aci (USEPA, 2001a))
Human Equivalent Dose (MDH, 2011):	3.4 x 0.29 = 0.99 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies difference (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased body weight and body weight gain, renal effects (i.e., relative organ weight increase, tubular casts and atrophy), liver necrosis, forestomach acanthosis and ulceration
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system, Gastrointestinal system, Hepatic (liver) system

The Chronic nHBV must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Subchronic nHBV of 100 µg/L. Additivity endpoints: Developmental, Female Reproductive system, Gastrointestinal system, Hematological (blood) system, Hepatic (liver) system, Immune system, Spleen

Cancer Health Based Value (cHBV) = Not Derived

Cancer classification:	"Not likely to be Carcinogenic to Humans" (USEPA, 2007c)
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:

Noncancer Acute, Short-term, Subchronic, and Chronic HBVs of 300, 100, 100, and 100 were derived in 2011. In 2016, MDH re-evaluated the available toxicity data, which resulted in no changes to any value.

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?	-[1]	-[2]	Yes [3]	Yes [4]	No[5]

Comments on extent of testing or effects:

[1] No studies assessing endocrine activity have been conducted. However, no significant findings in other relevant toxicity studies which would suggest endocrine activity have been reported.

[2] No immunotoxicity studies *per se* have been conducted. Thymus atrophy and increased apoptosis of mesenteric lymph nodes, changes in spleen weight and histopathology, increased white blood cell counts were reported in oral toxicity studies at HED doses $\geq$ 100-200 fold higher than the short-term, subchronic and chronic RfD. The immune system has been included as an additivity endpoint for the subchronic and chronic HBV.

Decreases in leukocytes, neutrophils and lymphocytes were also reported at HED doses > 400-fold higher than the short-term, subchronic and chronic RfDs.

[3] Decreased pup body weight/body weight gain as well as delayed vaginal opening (possibly related to decreased body weight) and increased incidence of fetal dilated renal pelvis and cervical ribs with cartilage not present were reported in the developmental, one generation and a two generation studies conducted in rats. Increased resorptions/early implantation loss was reported in an oral developmental study conducted in rabbits. These effects were observed at HED doses $\geq$ 60-fold higher than the acute, short-term, subchronic and chronic RfDs.

Developmental effects were identified as critical effects for the acute and short-term durations and co-critical for subchronic and chronic durations.

[4] Several oral studies (a developmental, one generation and a two generation) have been conducted in rats. No clinical signs of systemic or reproductive toxicity were observed. An oral developmental study and maternal toxicity supplemental study were also been conducted in rabbits. Early resorptions/implantation losses were observed at HED doses $\geq$ 60-fold higher than the acute, short-term, subchronic and chronic RfDs. Decreased maternal body weight/body weight gain were also

reported at these dose levels. Female reproductive effects (i.e., increased resorptions) form the basis of the acute RfD.

[5] Decreases in serum cholinesterase (ChE) were reported in females exposed in the 28 day dietary study in rats. A decrease in serum ChE but not erythrocyte or brain ChE was also observed in the 3 month dietary study in rats. Cholinesterase was not affected in the 2 year dietary study in rats suggesting that ChE may be affected following shorter term high doses but not long term low doses.

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