Minnesota Department of Health

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

Adopted as Rule: November 2015

Toxicological Summary for: Dimethenamid and Dimethenamid-P

CAS: **87674-68-8 & 163515-14-8**

Synonyms: (*RS*)-2-Chloro-*N*-(2,4-dimethyl-3-thienyl)-*N*-(2-methoxy-1-methylethyl)acetamide, Frontier Herbicide, Dimethenamid-P ((*S*)-isomer)

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

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 600 µg/L

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

$$= \frac{\text{(0.34 mg/kg/d) x (0.5) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 588 rounded to **600 µg/L**

Reference Dose/Concentration:	0.34 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	MDH, 2013
Point of Departure:	149 mg/kg-d (NOAEL, Randall 1996)
Human Equivalent Dose:	149 x 0.23 = 34 mg/kg-d (MDH, 2011)
Total uncertainty factor:	100
Uncertainty factor allocation	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty to ensure that the short-term RfD is protective of potential developmental effects
Critical effect(s):	Liver effects (increased absolute and relative liver weights and change in increased liver enzyme levels)
Co-critical effect(s)	Decreased pup body weights; decreased adult body weight gain; neurological effects (lacrimation, piloerection, excess salivation, decreased motor activity); post implantation loss; liver effects (increase in relative and absolute liver weight and changes in liver enzymes)
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Nervous system, Reproductive system (female)

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 600 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.27 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 701 rounded to 700 µg/L

Reference Dose/Concentration	0.27 mg/kg-d (Sprague Dawley rats)
Source of toxicity value	MDH, 2013
Point of Departure	33.5 mg/kg-d (NOAEL, Ruckman 1990)
Human Equivalent Dose:	33.5 x 0.25 = 8 mg/kg-d (MDH, 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased adult body weight and body weight gain; clinical chemistry changes (increased protein and cholesterol); liver effects (increase absolute and relative liver weight, changes in liver enzyme levels, histological changes)
Co-critical effect(s):	Decrease in body weight and body weight gain in pups and adults; liver effects (increased liver weight, hepatocellular hypertrophy, changes in liver enzyme levels)
Additivity endpoint(s):	Developmental, Hepatic (liver) system

The Subchronic nHRL must be protective of the acute and short-term exposures that occur within the acute and short-term periods and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 600 µg/L. Additivity endpoints: Developmental, Liver system, Nervous system, Reproductive system (female)

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = 300 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.06 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043L/kg-d)}}$$

= 279 rounded to **300 µg/L**

Reference Dose/Concentration:	0.06 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	MDH, 2013
Point of Departure:	7 mg/kg-d (NOAEL, Ruckman 1990)
Human Equivalent Dose:	7 x 0.26 = 1.8 mg/kg-d (MDH, 2011)
Total uncertainty factor:	30
Uncertainty factor allocation	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decrease in body weight gain; liver effects (increased relative liver weight, bile duct hyperplasia)
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification:	Class C “possible human carcinogen” nonlinear approach recommended (EPA 1992)

Slope factor: None
Source of slope factor: None
Tumor site(s): Ovarian and liver (benign liver tumors)

The chronic RfD (0.06 mg/kg-d) is protective for cancer risk.

Volatile: Yes (moderate)

Summary of Guidance Value History:
The 2013 chronic (Health Based Value) HBV of 300 µg/L was 7.5 times higher than the 1999 chronic HBV of 40 µg/L as the result of: 1) the identification of dimethenamid as a nonlinear carcinogen and removal of the 10-fold Group C carcinogen uncertainty factor; 2) the derivation of human equivalent doses; and 3) rounding to one significant digit. The 2013 HBVs were adopted into rule as HRLs in November 2015.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No	No	Yes	Yes	Yes
Effects?	No	No	Yes[1]	Yes[2]	Yes[3]

Note: 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. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:

[1]Developmental effects are listed as a co-critical effect for the short-term and subchronic durations. Decreased pup body weight was observed in reproductive and developmental animal studies at doses 100 times higher than the short-term RfD (0.34 mg/kg-day).

[2]Reproductive effects are listed as a co-critical effect for the short-term duration. A decrease in the number of implantations was observed in a 2-generation reproductive study at a dose 25 times higher than the short-term RfD (0.34 mg/kg-d) and an increase in post implantation loss was observed in the same study at a dose 100 times higher than the short-term RfD. Isolated instances of late abortions occurred in a rabbit developmental study at a dose 200 times higher than the short-term RfD.

[3]Nervous system effects are listed as a co-critical effect for the short-term duration. A range of neurological effects were reported in acute and developmental studies in rats. The effects included lethargy, excessive salivation, increased lacrimation (increased tear production), increase bristling of hair, and decreased motor activity. The effects occurred at doses starting at 130 times higher than the short-term RfD (0.34 mg/kg-d).

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