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

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Toxicological Summary for: Isoxaflutole

CAS: 141112-29-0

Synonyms: (5-Cyclopropylisoxazol-4-yl)(2-(methylsulfonyl)-4-(trifluoromethyl)phenyl)methanone; Merlin; Balance; RPA 201772

Acute Non-Cancer Health-Based Value (nHBV) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health-Based Value (nHBV) = 20 µg/L

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

$$= \frac{\text{(0.014 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 24 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.

Reference Dose:	HED/Total UF = 4.12/300 = 0.014 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2024
Point of Departure (POD):	29.4 mg/kg-d (administered dose LOAEL, Esdaile & Dange 1994 aci JMPR 2013)
Dose Adjustment Factor (DAF):	Body weight scaling, default [US EPA 2011 and MDH 2017]
Human Equivalent Dose (HED):	POD x DAF = 29.4 mg/kg-d x 0.14 = 4.12 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 to extrapolate from a LOAEL to NOAEL, and 3 for database uncertainty to account for the lack of adequate developmental and reproductive studies
Critical effect(s):	Decreased serum total bilirubin and creatinine
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Subchronic Non-Cancer Health-Based Value (nHBV) = 10 µg/L

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

$$= \frac{\text{(0.0037 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 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.

Reference Dose:	HED/Total UF = 0.370/100 = 0.0037 mg/kg-d (Crl:CDBR VAF/Plus rats)
Source of toxicity value:	Determined by MDH in 2024
Point of Departure (POD):	1.54 mg/kg-d (administered dose $BMDL_{10\%}$)
Dose Adjustment Factor (DAF):	Body weight scaling, default [US EPA 2011 and MDH 2017]
Human Equivalent Dose (HED):	POD x DAF = 1.54 mg/kg-d x 0.24 = 0.370 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty to account for the lack of adequate developmental and reproductive studies
Critical effect(s):	Increased incidence of centrilobular liver hypertrophy in F0 males
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Chronic Non-Cancer Health-Based Value (nHBV) = 7 µg/L

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

$$= \frac{\text{(0.0016 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 7.1 rounded to **7 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.

Reference Dose:	HED/Total UF = 0.158/100 = 0.0016 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2024
Point of Departure (POD):	1.05 mg/kg-d (administered dose $BMDL_{10\%}$, EPA 1996a)
Dose Adjustment Factor (DAF):	Body weight scaling, default [US EPA 2011 and MDH 2017]
Human Equivalent Dose (HED):	POD x DAF = 1.05 mg/kg-d x 0.15 = 0.158 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty to account for the lack of adequate developmental and reproductive studies
Critical effect(s):	Increased incidence of individual hepatocyte necrosis in male mice
Co-critical effect(s):	Increased liver weights in F0 (both sexes) and F1 (males) generations, increased incidence of centrilobular liver hypertrophy in F1 (both sexes) and F0 (females), increased incidence of hepatic vacuolation in F1 males, periacinar hepatocytic fatty vacuolation and decreased body weight gain in female mice
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	Likely to be a human carcinogen (EPA, 2011)
Tumor site(s):	Liver, thyroid (animal specific)

Statement for non-linear carcinogens:

MDH has determined that isoxaflutole is a nonlinear carcinogen given both its lack of genotoxicity and that the liver effects observed in shorter duration animal studies are known to progress to the types of liver tumors observed in longer duration studies. The chronic RfD is considered protective against the key events observed in shorter duration studies and liver cancer.

Volatile: No

Summary of Guidance Value History:

A noncancer health-based value (nHBV) of 10 µg/L was first derived for isoxaflutole in 2003. A cancer HBV (cHBV) was not derived at that time because the value calculated using the available slope factor would have been higher than the noncancer HBV. In 2014, MDH developed a cancer pesticide rapid assessment of 9 µg/L and a noncancer rapid assessment of 7 µg/L. The noncancer pesticide rapid assessment guidance was lower than the 2003 HBV due to the use of the rapid assessment's conservative framework that includes the use of the infant intake rate, an RSC of 0.5, and an updated RfD. Short-term, subchronic, and chronic nHBVs of 20, 10, 7 µg/L were derived in 2024. The 2024 chronic nHBV of 7 µg/L is the same as the 2014 noncancer pesticide rapid assessment value despite using: 1) MDH's most recent risk assessment methodology; 2) BMD modeling; and 3) a different health endpoint (hepatic) based on a better understanding of isoxaflutole toxicity. A cancer HBV was not derived in 2024 because MDH determined that isoxaflutole is a nonlinear carcinogen and the chronic nHBV will be protective for carcinogenesis.

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]	No[2]	Yes [3]	Yes [4]	Yes[5]

Comments on extent of testing or effects:

[1] Decreased thyroid hormone levels in rats, increased follicular epithelium size in dogs, and increased incidence of thyroid amyloidosis in mice occurred starting at doses more than 70000 times higher than the chronic reference dose.

Mice had increased relative adrenal gland weights following chronic exposure to doses 6000 times higher than the chronic reference dose.

[2] A short-term dietary study in rats evaluating antibody response to sheep red blood cells did not find any significant changes in treated animals from control group.

[3] Several studies in rats and rabbits reported various developmental effects, including increased incidence of visceral malformations, skeletal anomalies, ocular effects (i.e. chronic keratitis, inflammation, retinal vitreous bleeding), decreased fetal and pup viability, and decreased fetal and pup body weights following exposure to doses more than 100- to 1000-fold the short-term

reference dose. Due to metabolic differences with humans, these species are especially sensitive to the mode of action by which isoxaflutole and other pesticides of the same class (HPPD inhibitors) cause developmental and ocular effects and are poor models for humans. Mice are thought to be a more representative developmental model for humans for pesticides of this class; similar developmental effects seen in mouse studies were observed at significantly higher doses than rats or rabbits following exposure to HPPD inhibitors. A database uncertainty factor of 3 has been applied to account for the lack of adequate developmental studies using isoxaflutole in a test species with similar metabolic capacity as humans.

Neurodevelopmental effects including decreased pup brain weights and swimming ability were observed in a rat exposed *in utero* to doses 4100 times greater than the short-term reference dose.

[4] Multiple rat and rabbit studies reported reproductive effects including increased incidence of post-implantation loss, late resorptions, total resorptions, decreased live births and pup viability, increased gestation duration, and delayed sexual maturation following exposure to doses 100- to 1000-fold higher than the short-term reference dose. These species are especially sensitive to the mode of action by which isoxaflutole and other pesticides of the same class cause developmental and reproductive effects. Mice and dogs are thought to be a more representative reproductive toxicity model for humans for pesticides of this class. A database uncertainty factor of 3 has been applied to account for the lack of adequate reproductive studies in species with similar metabolic capacity as humans.

Additionally, effects on reproductive organs including increased weights (i.e. testes, uterus and cervix) in rats, and changes to germ cells (i.e. reduced copora lutea, reduced spermatogenesis, increased multinuclear cells in the testes) in dogs were reported following long term exposure to doses over 1000- to 100,000 fold greater than the short-term reference dose.

[5] An acute neurotoxicity study in rats reported inconsistent changes in neuromuscular related endpoints (e.g., foot splay) in males starting at doses more than 8500 times greater than the short-term reference dose. A developmental neurotoxicity study in rats reported decreased absolute brain weights and decreased swimming ability in pups exposed in utero to doses more than 4100 times the short-term reference dose. In a 90-day rat neurotoxicity study, mean hind limb grip strength was decreased in males starting at doses greater than 3700 times the chronic reference dose and at doses over 112000 times greater, males also had significantly decreased forelimb grip strength. Additionally, a chronic rat study reported increased incidence of axonal and myelin degeneration of the sciatic nerve and nerve granulomas in males at doses greater than 3400 and abnormal gates in males at doses 83000 times the chronic reference dose.

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