Toxicological Summary for: Fomesafen

CAS: 72178-02-0
Synonyms: IUPAC 5-{2-chloro-4-(trifluoromethyl)phenoxy}-N-methanesulfonyl-2-nitrobenzamide; 5-{2-chloro-α-α-α-trifluoro-4-tolyloxy}-N-methylsulphonyl-2-nitro benzamide; PP021

Acute Noncancer Health-Based Value (nHBVAcute) = Not Derived

Short-term Noncancer Health-Based Value (nHBVShort-term) = 200 µg/L

\[
(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})
\]

\[
(\text{Short-term Intake Rate, L/kg-d})
\]

\[
(0.12 \text{ mg/kg-d}) \times (0.5) \times (1000 \text{ µg/mg})
\]

\[
(0.285 \text{ L/kg-d})^{**}
\]

\[
= 210.5 \text{ rounded to } 200 \text{ µg/L}
\]

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011b, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration: HED/Total UF = 3.50/30 = 0.12 mg/kg-d (Alderley Park Wistar rat)
Source of toxicity value: Determined by MDH in 2020
Point of Departure (POD): 12.5 mg/kg-d (administered dose NOAEL, 2-generation reproductive study, MRID 00144862, US EPA 1984a)
Dose Adjustment Factor (DAF): 0.28 study-specific, Body weight scaling, default (US EPA 2011c and MDH 2017)
Human Equivalent Dose (HED): POD x DAF = 12.5 mg/kg-d x 0.28 = 3.50 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 litter weight gain, decreased pup survival, and reduced number of pups born alive
Co-critical effect(s): Decreased plasma cholesterol and triglycerides, increased liver weight and hepatocyte hypertrophy; reduced IgM antibody and lymph node enlargement
Additivity endpoint(s): Developmental, Hepatic (liver) system, Immune system
Subchronic Noncancer Health-Based Value \( (nHBV_{\text{subchronic}}) = nHBV_{\text{short-term}} = 200 \, \mu g/L \)

\[
(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor}) \\
\times (\text{Subchronic Intake Rate, L/kg-d}) \\
= (0.14 \, \text{mg/kg-d}) \times (0.2)^* \times (1000 \, \mu g/mg) \\
\times (0.070 \, L/kg-d)^** \\
= 400 \, \mu g/L
\]

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011b, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration: HED/Total UF = 14/100 = 0.14 mg/kg-d (beagle)
Source of toxicity value: Determined by MDH in 2020
Point of Departure (POD): 25 mg/kg-d (administered dose LOAEL, 26-week toxicity study, MRID 00103014, US EPA 1981a)
Dose Adjustment Factor (DAF): 0.56, Body weight scaling, default (US EPA 2011c and MDH 2017)
Human Equivalent Dose (HED): POD x DAF = 25 mg/kg-d x 0.56 = 14 mg/kg-d
Total uncertainty factor (UF): 100
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for using a LOAEL in place of a NOAEL because of wide dose spacing
Critical effect(s): Blood changes (decreased hemoglobin, hematocrit, red blood cell count accompanied by an increased number of platelets); Decreased plasma cholesterol and triglycerides
Co-critical effect(s): Reduced litter weight gain and pup survival, and a reduction in the number of pups born alive; Reduced plasma triglycerides and cholesterol, increased liver weight, hepatocyte hypertrophy, liver inflammation, and liver necrosis; Decreased IgM antibody and increased lymph node enlargement
Additivity endpoint(s): Developmental, Hematological (blood) system, Hepatic (liver) system, Immune system

The Subchronic nHBV must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 200 \( \mu g/L \). Additivity endpoints: Developmental, Hepatic (liver) system, Immune system

Chronic Noncancer Health-Based Value \( (nHBV_{\text{chronic}}) = 20 \, \mu g/L \)

\[
(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor}) \\
\times (\text{Chronic Intake Rate, L/kg-d}) \\
= (0.005 \, \text{mg/kg-d}) \times (0.2)^* \times (1000 \, \mu g/mg) \\
\]

Fomesafen - 2
(0.044 L/kg-d)**

= 22.7 rounded to 20 µg/L

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011b, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration: HED/Total UF = 0.15/30 = 0.005 mg/kg-d (CD-1 mouse)
Source of toxicity value: Determined by MDH in 2020
Point of Departure (POD): 0.96 mg/kg-d (administered dose NOAEL, 2-year toxicity study, MRID 00131491, US EPA 1983);
Dose Adjustment Factor (DAF): 0.16 study-specific, Body weight scaling, default (US EPA 2011c and MDH 2017)
Human Equivalent Dose (HED): POD x DAF = 0.96 mg/kg-d x 0.16 = 0.15 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 liver weight, enlarged and discolored liver; the presence of pigmented macrophages and/or Kupffer cells in the liver (inflammation), liver masses, increased serum alkaline phosphatase activity, and increased glutamic pyruvic transaminase activity

Co-critical effect(s): None
Additivity endpoint(s): Hepatic (liver) system

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification: Not likely to be carcinogenic to humans (US EPA 2018)
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 2018, MDH derived a Pesticide Rapid Assessment value of 3 µg/L, which used an infant water intake rate with a chronic RfD and an RSC of 0.5 (MDH Pesticide Rapid Assessment Results Table, updated 2020). The 2020 nHBV is based on MDH’s duration-specific methodology, which matches the RfD and intake rate, resulting in a higher value of 20 µg/L.

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.
<table>
<thead>
<tr>
<th>Tested for specific effect?</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
<th>Reproductive</th>
<th>Neurotoxicity</th>
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<tbody>
<tr>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>

**Comments on extent of testing or effects:**

1 Although, there are no *in vivo* toxicity studies that tested specifically for endocrine changes after fomesafen treatment, the EPA’s Endocrine Disruptor Screening Program tested fomesafen for endocrine activity *in vitro*. Fomesafen was found to have activity in a small fraction of *in vitro* tests (EPA Chemical Dashboard).

2 The short duration co-critical effects of reduced antibody response and lymph node enlargement are based on an immunotoxicity assay in mice.

3 The short-term duration critical study is based on developmental effects in rat pups whose mothers were exposed to fomesafen. The reference dose is based on decreased litter weight gain, decreased pup survival, and a reduction in the number of pups born alive. In another developmental study in rats, post-implantation loss and decreased litter weight occurred at a dose approximately 400 times higher than the short-term reference dose.

4 A reduction in the number of rat pups born alive was a critical effect for the short-term duration study, and is also listed as a developmental effect. Additionally, in a separate experiment, increased post-implantation loss occurred in pregnant rats at a dose approximately 400 times higher than the short-term reference dose. Small uteri was observed in female mice at a dose 300 times higher than the short-term reference dose, and pale uteri occurred at a dose 1,000 times higher than the short-term reference dose.

5 Neurotoxicity was evaluated in an acute toxicity study in rats. Motor activity was briefly reduced beginning at a dose 500 times higher than the short-term duration reference dose. However, a 13-week neurotoxicity study in rats found no neurotoxic effects at levels 400 times higher than the short-term reference dose.

**Resources Consulted During Review:**
Krijt, J. S., P; Sanitrak, J; Chlumska, A; Fakan, F.; (1999). Liver preneoplastic changes in mice treated with the herbicide fomesafen. *Human & Experimental Toxicology, 18*, 338-344.


