Toxicological Summary for: Glyphosate

CAS: 1071-83-6 (acid)
38641-94-0 (isopropylamine salt)
40465-76-7 (ethanolamine salt)
34494-04-7 (dimethylamine salt)
114370-14-8 (ammonium salt)
39600-42-5 (potassium salt)

Synonyms: 2-(phosphonomethylamino)acetic acid; N-(phosphonomethyl)glycine

Acute Non-Cancer Health Based Value (\(n\)HBV\textsubscript{Acute}) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value (\(n\)HBV\textsubscript{Short-term}) = 1,000 \(\mu\)g/L

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

\[
= (2.0 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ \(\mu\)g/mg}) \\
(0.285 \text{ L/kg-d})^{**}
\]

\[
= 1,404 \text{ rounded to 1,000 \(\mu\)g/L}
\]

*Relative Source Contribution: MDH 2008, Section IV.E.1. MDH utilizes the US EPA Exposure Decision Tree (US EPA 2000) to select appropriate RSCs. Given the significant potential for non-water sources of exposure, an RSC of 0.2 rather than the default of 0.5 has been selected.

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

Reference Dose/Concentration: HED/Total UF = 61.2/30 = 2.0 mg/kg-d (Wistar rats)
Source of toxicity value: Determined by MDH in 2017
Point of Departure (POD): 278 mg/kg-d [administered dose NOAEL from a 2-generation reproductive study by Moxon 2000 (unpublished Syngenta test report) as cited by JMPR 2006 and also cited as TOX2000-2000 by European Commission 2015]
Dose Adjustment Factor (DAF): 0.22 [Body weight scaling, default (US EPA 2011 and MDH 2017)]
Human Equivalent Dose (HED): POD x DAF = 278 mg/kg-d x 0.22 = 61.2 mg/kg-d
Total uncertainty factor (UF): 30
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s): Decreased pup body weight
Co-critical effect(s): Increased skeletal variations
Additivity endpoint(s): Developmental

**Subchronic Non-Cancer Health Based Value (nHBV_{subchronic}) = 1,000 \mu g/L**

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

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

\[= (0.41 \text{ mg/kg-d}) \times (0.2) \times (1000 \mu g/mg) \times (0.070 L/kg-d)\]

\[= 1,171 \text{ rounded to } 1,000 \mu g/L\]

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

Reference Dose/Concentration: HED/Total UF = 12.3/30 = 0.41 mg/kg-d (Crl:CD(SD)BR rats)
Source of toxicity value: Determined by MDH in 2017
Point of Departure (POD): 55.9 mg/kg-d [administered dose BMDL_{10} derived by MDH using data from a 2-generation reproductive study by Brooker et al. 1992 (unpublished Cheminova test report) as cited in JMPR 2006 and also cited as TOX9552389 by European Commission 2015]
Dose Adjustment Factor (DAF): 0.22 [Body weight scaling, default (US EPA 2011 and MDH 2017)]
Human Equivalent Dose (HED): POD x DAF = 55.9 mg/kg-d x 0.22 = 12.3 mg/kg-d
Total uncertainty factor (UF): 30
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s): Parotid salivary gland histopathology
Co-critical effect(s): None
Additivity endpoint(s): Gastrointestinal system

**Chronic Non-Cancer Health Based Value (nHBV_{chronic}) = 500 \mu g/L**

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

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

\[= (0.12 \text{ mg/kg-d}) \times (0.2) \times (1000 \mu g/mg) \times (0.044 L/kg-d)\]

\[= 545 \text{ rounded to } 500 \mu g/L\]

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81
Reference Dose/Concentration: HED/Total UF = 3.67/30 = 0.12 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value: Determined by MDH in 2017
Point of Departure (POD): 14.1 mg/kg-d [administered dose BMDL10 derived by MDH using data from a 2-year study by Atkinson et al. 1993 (unpublished Cheminova test report) as cited in JMPR 2006 and also cited as MRID496317023 and MRID49631701 by US EPA 2015c, 2016b and also cited as TOX9750499 by European Commission 2015]
Dose Adjustment Factor (DAF): 0.26 [Body weight scaling, default (US EPA 2011 and MDH 2017)]
Human Equivalent Dose (HED): POD x DAF = 14.1 mg/kg-d x 0.26 = 3.67 mg/kg-d
Total uncertainty factor (UF): 30
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s): Parotid salivary gland histopathology
Co-critical effect(s): None
Additivity endpoint(s): Gastrointestinal system

Cancer Health Based Value (cHBV) = Not Applicable***
Cancer classification: “Not Likely to be Carcinogenic to Humans” at doses relevant to human health risk assessment (US EPA 2016)
IARC Group 2A, Probably carcinogenic to humans (IARC 2015)
Proposition 65 carcinogen (OEHHA 2017a)
Slope factor (SF): No US EPA slope factor exists
0.00062 (mg/kg-d)^{-1} (OEHHA 2017)
Source of cancer slope factor (SF): OEHHA, 2017b
Tumor site(s): OEHHA slope factor based on hemangiosarcomas in male mice (IARC 2015 and JMPR 2006, as cited in OEHHA 2017b). [The original study was Atkinson et al. 1993, a Cheminova unpublished test report, as cited in JMPR 2006.]

***Statement for non-linear carcinogens:
The International Agency for Research on Cancer (IARC) concluded that glyphosate is a probable human carcinogen based on “limited evidence” for non-Hodgkin lymphoma (NHL) in humans and “sufficient evidence” based on renal tubule carcinoma, hemangiosarcoma, and pancreatic islet cell adenoma in laboratory animals (IARC, 2015). IARC’s conclusion generated considerable global scientific controversy because many of the tumors noted were not consistently observed across multiple studies, occurred only at very high doses in animals, and have numerous issues around statistical significance for both animal and human data. New information continues to emerge and scientific consensus has not yet been established. IARC evaluates cancer hazards without considering exposure
levels or route of exposure and does not conduct quantitative cancer risk assessments. Other agencies, including ones that develop quantitative cancer risk assessments, such as the US EPA (2016), the European Food Safety Authority (EFSA 2015), the European Joint FAO/WHO Meeting on Pesticides Residues (JMPR 2006, 2016), and the European Chemicals Agency (ECHA 2017), currently conclude that glyphosate is either not classifiable as a carcinogen or that it is unlikely to pose a cancer risk to humans ingesting foods treated with glyphosate. The FIFRA Science Advisory Panel (US EPA 2017) agreed with US EPA’s conclusions that glyphosate is non-genotoxic. The mechanisms for carcinogenicity are likely threshold or nonlinear in nature, and when positive trends were reported for tumors in rats or mice, tumors were generally elevated only at the highest doses tested, which were over 1,000 times higher than the MDH Chronic RfD. This was the case for the study used by California OEHHA to develop a cancer slope factor. MDH did not use this slope factor to develop a cHBV because cancer slope factors are not appropriate for threshold or non-linear carcinogens. MDH will continue to monitor glyphosate and its associated cancer risks, but at this time the non-cancer health-based guidance values are considered protective for possible cancer risks associated with glyphosate in drinking water.

Volatile: No

**Summary of Guidance Value History:**
There are no previous MDH HBVs or HRLs for glyphosate. MDH developed a non-cancer pesticide rapid assessment value of 1,000 µg/L in 2014. The chronic non-cancer HBV is lower than the 2014 pesticide rapid assessment due to differences in risk assessment methodology and incorporation of more recent toxicological information.

**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>
</tr>
</thead>
<tbody>
<tr>
<td>Effects observed?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

1. Glyphosate was evaluated extensively for endocrine effects in in vitro and in vivo studies by the US EPA Endocrine Disruptor Screening Program (EDSP). The US EPA concluded that the overall weight-of-evidence for estrogen, androgen, and thyroid endocrine effects is negative for glyphosate. The European Joint FAO/WHO Meeting on Pesticides Residues (JMPR) also concluded that glyphosate did not demonstrate interactions with estrogen, androgen or thyroid pathways based on results from a range of validated in vitro and in vivo assays. Delayed male puberty was reported in rats in one study at HED doses about 750 times higher than the subchronic RfD, but was not reported in several other
studies. Estrous cycles were affected in one study at HED dose about 1,700 times higher than the subchronic RfD, but this effect was not replicated in other studies.

2 IARC concluded “there is weak evidence that glyphosate may affect the immune system, both humoral and cellular response” based on laboratory animal studies. Glyphosate did not cause immunotoxicity (humoral immunity, thymus weight, or spleen weight) in mice tested at doses up to 100 times higher than the short-term RfD. Thymus weight was decreased in rat at HED 2,000 times higher than the subchronic RfD, but increased in mice at doses almost 4,000 times higher than the subchronic RfD and over 370 times higher than the chronic RfD. Leukocytes were increased in rats at HED doses over 400 times higher than the subchronic RfD and in mice at doses over 4,800 times higher than the chronic RfD. Glyphosate was not a skin sensitizer when tested in guinea pigs.

3 The short-term reference dose and co-critical effects are based on developmental effects (decreased pup body weight and increased skeletal variations). Glyphosate has an affinity for deposition in bones with unknown consequences for bone development. Consistent treatment-related increases in serum alkaline phosphatase (ALP) were reported in multiple rodent and dog studies, generally at doses more than 200 times higher than short-term, subchronic and chronic RfDs. Elevated ALP occurs when there is increased osteoblast activity in bones and can be related to either bone metabolic disease or liver injury. In the absence of liver injury, it is possible that ALP came from bones, but none of the studies characterized the source of ALP or sufficiently evaluated bone quality, strength or remodeling to be able to rule out possible adversity at high doses.

4 Glyphosate was not a reproductive toxicant in the majority of rodent multigenerational reproductive studies up to the highest doses tested with HED doses greater than 170 times higher than the short-term RfD and more than 800 times higher than the subchronic RfD. One multigenerational reproductive study reported decreased spermatid counts and delayed male puberty at an HED dose about 750 times higher than the subchronic RfD, but effects were not replicated in other studies. One study reported effects on reduced sperm and increased estrous cycle length at HED doses about 1,700 times higher than the subchronic RfD. However, another study found increased testes weights but no effects on sperm motility, sperm counts, or estrous cycles at comparable doses. Increased testes and ovary weights were reported in a chronic mouse study at HEDs over 6,000 times higher than the chronic RfD.

5 Glyphosate was not neurotoxic to rats in a 13-week neurotoxicity study at doses 900 times higher than the subchronic RfD. In an acute neurotoxicity study, no effects were reported in rats up to the highest HED dose tested which was 220 times higher than the short-term RfD. In a one-year rat study, landing foot splay was decreased in rats with no effects on motor activity at an HED dose over 3,000 times higher than the chronic RfD. Parasympathetic nervous system effects related to the ß-adrenergic system are believed to be responsible, in part, for the mechanism-of-action for salivary gland histopathology. The ß-adrenergic effects occurred at an HED dose 390 times higher than the short-term RfD in a 14-day study; however, only one dose group was tested.
Resources Consulted During Review:


