

# Glyphosate

## Guideline

*The interim maximum acceptable concentration (IMAC) for glyphosate in drinking water is 0.28 mg/L (280 µg/L).*

## Identity, Use and Sources in the Environment

Glyphosate (C<sub>3</sub>H<sub>6</sub>NO<sub>5</sub>P), or N-phosphonomethyl glycine, is a systemic herbicide used in high volume (0.5–1 million kilograms in 1986 and over 2 million kilograms in 1990) for non-selective weed control on rights-of-way, in forestry plantations, in site preparation for plantings of many crops and as a foliage desiccant for selected crops (wheat, barley, legumes, mustard, flax and forage crops).<sup>1–3</sup>

Glyphosate is a weak organic acid. To increase its solubility, glyphosate is usually formulated as the isopropylamine salt (C<sub>6</sub>H<sub>17</sub>N<sub>2</sub>O<sub>5</sub>P, Roundup).<sup>3–5</sup> Surfactants (e.g., polyoxyethylene amine) and inerts are added to some formulations.<sup>6</sup>

Glyphosate is water soluble (12 g/L at 25°C),<sup>7</sup> and its vapour pressure is low (<1 × 10<sup>-5</sup> Pa at 25°C).<sup>6</sup> It is stable to hydrolysis in water but undergoes rapid microbial degradation in natural surface waters. Some photolysis can also occur.<sup>7</sup> Strong adsorption to particulate matter may be a factor in glyphosate's removal from water.<sup>8</sup> Glyphosate's half-life in surface waters after forestry spraying in Manitoba was less than 24 hours.<sup>9</sup>

In soils, glyphosate undergoes microbial degradation to the metabolite aminomethylphosphonic acid (AMPA), which is slowly degraded to carbon dioxide and simple inorganic compounds. Glyphosate is classed as moderately persistent in soil, with a half-life of 20–100 days, depending on soil conditions.<sup>10,11</sup> It is strongly adsorbed to soils,<sup>12</sup> especially soils with neutral or low pH or low phosphate levels<sup>10</sup> and in the presence of fulvic acid and the cations Fe<sup>2+</sup>, Fe<sup>3+</sup> and Al<sup>3+</sup>. Glyphosate would therefore not be expected to migrate to groundwater supplies after application. The metabolite AMPA acts in a similar manner. Glyphosate was rated as a non-leacher by Agriculture Canada, ranking 72nd of the 86 pesticides considered.<sup>13,14</sup>

## Exposure

Glyphosate and AMPA have not been detected in drinking water supplies. This may be because of the lack of monitoring studies and technical difficulties with available analytical methods.

Owing to their physicochemical properties, glyphosate and AMPA would be expected only in surface waters after direct application or after soil erosion due to precipitation, which could lead to contamination of downstream drinking water supplies. Experimental data indicate that glyphosate concentrations of 200–300 µg/L immediately after direct spraying in standing water drop to half this value in approximately three weeks.<sup>15</sup> Direct spraying of glyphosate on lakes and ponds at 1 kg/ha resulted in an initial concentration of 1100 µg/L, dropping to 149 µg/L at two days and 55 µg/L after five days.<sup>9</sup> In Quebec, the effect of glyphosate application for standard forestry practice (buffer zones of 30 m) was tested by monitoring eight streams and several ponds and drainage ditches.<sup>16</sup> None of the 60 samples at the eight streams contained detectable levels (detection limit 1.0 µg/L), although glyphosate was detected in two drainage ditch samples (maximum 16.9 µg/L). In the ponds, which were sprayed directly, the concentration was 2800 µg/L immediately post-spraying and fell to 288 µg/L after 24 hours.

Residues of glyphosate may occur in wheat and barley, products made from these grains (including beer), lentils, soybeans and peas; concentrations in many cases are below or near the detection limit (0.05 mg/kg). The metabolite AMPA was only occasionally detected, usually at less than 2% of the total glyphosate residue; it was concluded that AMPA could be omitted from residue considerations.<sup>4,17</sup> The theoretical maximum dietary intake of glyphosate was calculated to be about 2.7 µg/kg bw per day, based on 1986 data.<sup>18</sup>

## Analytical Methods and Treatment Technology

Glyphosate in water can be determined using direct aqueous injection high-pressure liquid chromatography (HPLC) with post-column derivatization. In this method, a small aliquot (200 µL) of filtered water is injected into a reverse-phase HPLC column. The post-column reactions involve oxidation of glyphosate to glycine, which then reacts with o-phthalaldehyde to form an isoindole that is measured fluorometrically. The detection limit for this method is 6 µg/L for tap-water and 9 µg/L for groundwater.<sup>19</sup>

Glyphosate can be removed from drinking water by conventional treatment. Bench-scale treatability studies<sup>20</sup> indicate that oxidation, using chlorination or ozonation, is an effective treatment technique for glyphosate.

## Health Effects

### Pharmacokinetics

Glyphosate is incompletely absorbed (15–40%) by the oral route.<sup>21</sup> AMPA is also incompletely absorbed, at 20%.<sup>22</sup> Dermal absorption of glyphosate formulation (Roundup) in monkeys was only 2% after seven days of topical application.<sup>23</sup>

After oral or intraperitoneal administration of both a single dose and 12 days of repeated doses, glyphosate was excreted almost entirely in urine, largely in unchanged form, although small amounts of the metabolite AMPA were also found. Biliary excretion and enterohepatic circulation occurred only to a minor extent.<sup>4,21</sup> Absorbed doses of AMPA were also excreted almost entirely via the urine, with less than 0.1% of the dose eliminated as labelled carbon dioxide.<sup>22</sup> Clearance of a single dose of glyphosate after 120 hours was 94% in males and females. With daily administration in the diet for 14 days, tissue levels reached maximum values by the sixth day of administration, with levels decreasing in the order kidneys (<1 ppm), spleen, fat, liver, ovaries, heart and muscle. Residues declined quickly once treatment ceased, with kidney levels dropping to 0.1 ppm at the end of a 10-day recovery period.<sup>21</sup>

Some concern has been expressed over the possibility that glyphosate could react with nitrite in the diet to form N-nitrosophosphonomethyl glycine (NPMG), a putative carcinogen.<sup>24</sup>

### Effects in Laboratory Animals and Humans

Glyphosate is acutely toxic to rats via the oral or dermal route at doses as low as 3800 mg/kg bw, with most values above 5000 mg/kg bw.<sup>21</sup> LD<sub>50</sub> values thus approach 1% of body weight.<sup>25</sup> There appear to be few toxic effects except body weight reduction and increased kidney weights at high doses. Glyphosate was only

slightly irritating to skin and eyes when tested on 346 human volunteers, and there was no evidence of photoirritation or allergic or photoallergic contact dermatitis.<sup>26</sup> In animal tests for skin and eye irritation, glyphosate was classed as slightly irritating and the formulated product Roundup as moderately irritating.<sup>25</sup> Roundup was also more toxic (17–32 times) to fish than the parent compound, probably because of the amine salt or its surfactants.<sup>25</sup>

In a subchronic study, glyphosate was administered by gelatin capsule to beagle dogs (six per group) at doses of 0, 20, 100 or 500 mg/kg bw per day for one year.<sup>27</sup> There were no clinical signs of toxicity, and no treatment-related changes in body or organ weights or in ophthalmological, haematological, clinical chemistry or urinary parameters were observed.<sup>27</sup> A slightly increased incidence of lymphoid nodules was observed in the epididymis at the highest dose level, and a conservative NOAEL was considered to be 100 mg/kg bw per day.<sup>28</sup>

In a chronic toxicity/carcinogenicity study carried out with CD-1 mice (50 per sex per group), glyphosate was administered in the diet at 0, 0.1, 0.5 or 3% (0, 1000, 5000 and 30 000 ppm) for 24 months.<sup>29</sup> In high-dose males, a slight increase in liver necrosis (hepatic hypertrophy and centrilobular necrosis), some interstitial kidney nephrosis and hyperplasia of the urinary bladder were observed. Slight decreases in body weight gain were noted in both males and females at the high dose. There were no other treatment-related changes in body or organ weights, food and water consumption or haematological parameters, and there were no clinical signs of toxicity at any dose levels. The NOAEL was considered to be 5000 ppm, equivalent to 814 mg/kg bw per day for males.<sup>29</sup> There were no significant increases in the frequency of neoplastic lesions, although three small renal tubule adenomas were observed in high-dose males; their incidence was below that in the historical controls. Glyphosate was not considered to be tumorigenic to mice in this study.<sup>21,30</sup>

In a two-year feeding/oncogenicity study, Sprague-Dawley rats (50 per sex per dose) were administered technical glyphosate at 0, 60, 200 and 600 ppm in the diet (equivalent to intakes of 0, 3.0, 10.3 or 31.4 mg/kg bw per day for males and 0, 3.4, 11.2 or 34 mg/kg bw per day for females).<sup>31</sup> There was a consistent tendency for reduced body weight gains in treated males during most of the growth period, but effects on body weight were not considered to be treatment-related.<sup>21</sup> No other adverse effects were observed on mortality, food and water intake, absolute or relative organ weights, haematology, clinical chemistry or urinalysis. The incidence of interstitial cell testicular tumours was slightly elevated in low- and high-dose groups; however, it was not dose-related, it was close to historical control values and it was deemed unlikely to be

treatment-related. The highest dose (31.4 or 34 mg/kg bw per day) was considered to be the no-observed-adverse-effect level (NOAEL for this study.<sup>21,31,32</sup> Equivocal evidence of a slightly increased incidence of thyroid C-cell carcinomas was noted in high-dose females by Health Canada toxicologists. Because of concern over this finding, the lowest dose of 3.0 mg/kg bw per day was suggested as the NOAEL, based on the trend to body weight gain reductions seen in males.<sup>18\*</sup>

In a repeat study, the same strain of rats was administered glyphosate in the diet at higher doses of 0, 2000, 8000 or 20 000 ppm for two years.<sup>33</sup> At the highest dose level (20 000 ppm, or approximately 1000 mg/kg bw per day), body weight and body weight gains were reduced in females, increased liver weights, cataractogenic effects (degenerative lens changes) and testicular effects (not further defined) were noted in males, and an increased incidence of stomach irritation was observed in both sexes (statistically significant in females). One evaluation<sup>28</sup> reported no indication of any tumorigenic activity at any dose; however, a second evaluation<sup>6</sup> stated that the incidence of adenomas of the pancreatic islet cells was increased in low- and high-dose males but was not dose-related, and the trend test was negative. No pancreatic carcinomas were observed. The NOAEL was considered to be 8000 ppm, equivalent to 362 mg/kg bw per day.<sup>28,33</sup>

Glyphosate was not mutagenic in a battery of *in vitro* and *in vivo* short-term tests, including the Ames test, with and without metabolic activation, on four strains of *Salmonella typhimurium*, a recombination assay with *Bacillus subtilis* H17(rec+) and M45(rec-), a reverse mutation test with *Escherichia coli* WP2her, a forward mutation assay with Chinese hamster ovary cells and an unscheduled DNA repair assay using rat hepatocytes. Negative *in vivo* tests included a mouse dominant lethal assay at oral doses of 200–1000 mg/kg bw and a host-mediated assay on rat bone marrow at intraperitoneal doses of 200–1000 mg/kg.<sup>21,34</sup>

No teratogenic effects were observed in rabbit and rat studies at doses as high as 350 and 3500 mg/kg bw per day, respectively. In the rat study (25 per group), gavage dose levels were 0, 300, 1000 and 3500 mg/kg bw. Severe maternal toxicity was observed at the high dose, with diarrhoea, red nasal discharge, reduced body weight gain and six deaths by day 17. Reproduction, including total implants, viable foetuses and resorptions, was adversely affected at this dose level, and foeto-toxicity was evident, with observations of unossified sternbrae and kidney anomalies (three pups).<sup>21,34</sup> In the rabbit study, groups of 16 females received 0, 75, 175 and 350 mg/kg bw per day by gavage on days 6–27 of

gestation. Maternal toxicity was apparent at both middle and high dose levels (diarrhoea, nasal discharge, transient body weight reduction and deaths in two and 10 females from the mid- and high-dose groups, respectively). Treatment-related effects on the number of viable foetuses and on early or late resorptions and an increased incidence of skeletal variation were noted in the high-dose group.<sup>21,34</sup> The NOAELs for maternal and foetal toxicity were 75 and 175 mg/kg bw per day, respectively.

No adverse reproductive effects were noted in a two-litter, three-generation rat study in which groups of 12 male and 24 female S-D rats were given glyphosate in the diet at dose levels of 0, 3, 10 or 30 mg/kg bw for 60 days, continued throughout mating, gestation and lactation, for three generations. The no-observed-effect-level (NOEL) was considered to be at or above the highest dose level of 30 mg/kg bw.<sup>21</sup>

## Rationale

Based on evaluations by the Food Directorate of Health Canada,<sup>18</sup> a negligible daily intake (NDI) for glyphosate was established as follows:

$$\text{NDI} = \frac{3.0 \text{ mg/kg bw per day}}{100} = 0.03 \text{ mg/kg bw per day}$$

where:

- 3.0 mg/kg bw per day was the NOAEL for reduced body weight gain in a two-year rat feeding/oncogenicity study<sup>31</sup>
- 100 is the uncertainty factor ( $\times 10$  for interspecies variation and  $\times 10$  for intraspecies variation in an adequate long-term study).

The interim maximum acceptable concentration (IMAC) for glyphosate in drinking water is derived from the NDI as follows:

$$\text{IMAC} = \frac{0.03 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.20}{1.5 \text{ L/d}} = 0.28 \text{ mg/L}$$

where:

- 0.03 mg/kg bw per day is the NDI established by the Food Directorate of Health Canada
- 70 kg is the average body weight of an adult
- 0.20 is the proportion of total daily intake of glyphosate allocated to water (theoretical maximum intake from food is 9% of the NDI)
- 1.5 L/d is the average daily consumption of drinking water for an adult.

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\* A later independent analysis by three pathologists discounted the relationship between treatment and the C-cell tumours.<sup>28</sup>

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