

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Glyphosate is a phosphonoglycine non-selective herbicide, first registered for use by the EPA in 1974. Glyphosate is typically manufactured for commercial use as a salt available in soluble liquid and granule formulations. Herbicide formulations employing glyphosate salts are commonly produced in combination with additives, inert ingredients, and surfactants. The salt derivatives enhance absorption of glyphosate from the surface of the plant or leaf structure, but are not the herbicidally active portion of the compound. Specific formulations vary in composition and are marketed under numerous trade names (NPIRS 2017; PAN 2009). Commercial products containing glyphosate may have concentrations ranging from 0.96 to 94 w/w%. For example, the common herbicide, Roundup®, has product formulations containing glyphosate in concentrations ranging from 0.96% to as much as 71% (w/w) (NPIRS 2017; PAN 2016b).

Glyphosate is the active ingredient in a variety of broad spectrum herbicidal products for residential, commercial, and agricultural purposes. Selected agricultural commodities such as roundup-ready corn and soybeans have been genetically modified to be resistant to damage when glyphosate is applied to control undesirable weeds. Glyphosate is produced commercially in the United States as a technical-grade substance (glyphosate technical) with a purity of $\geq 80\%$, though the purity is usually $>90\%$ (IPCS 1994, McBean 2011). In 2007, U.S. agricultural use of glyphosate was approximately 82,800 tons and non-agricultural use of glyphosate was approximately 9,300 tons (Battaglin et al. 2014). For the purposes of this Profile, the phrase “non-agricultural use” refers to the use of glyphosate outside of agriculture or farmland, such as to control weeds on a roadside, in a garden, or other use by homeowners.. In 2014, U.S. agricultural use of glyphosate was approximately 124,953 tons and non-agricultural use of glyphosate was approximately 13,260 tons (Benbrook 2016). The manufacture and use of glyphosate has led to its direct release into the environment (EPA 1993). Once glyphosate enters the environment, it has low potential for environmental bioavailability and is unlikely to bioaccumulate; the chemical is either degraded by microbial processes or inactivated by adsorption to soil (Shushkova et al. 2010; Smith and Oehme 1992). Glyphosate is expected to adsorb to soils under most environmental conditions; therefore, leaching into groundwater is minimal (Smith and Oehme 1992). Glyphosate may enter surface waters due to its use in some aquatic environments. Volatilization of glyphosate is not an important fate process based on its low vapor pressure and ionic nature (Smith and Oehme 1992). Transport in the air after spray applications is

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dependent on meteorological conditions; ground and aerial applications can result in spray drift, which may affect non-target plants (PAN 2009; Yates et al.1978).

The general population may be exposed to glyphosate by dermal contact with consumer products, crops, foliage, or soils containing residues of this chemical; ingestion of plants, crops, foods, or waters containing residues of this chemical; and inhalation of mist or spray during the use of products containing this chemical. As a result of its widespread usage, glyphosate is present at low levels in a wide range of foods (FAO and WHO 2016). The greatest potential for exposure can be expected for people who use glyphosate products at home and for populations residing near agricultural areas and crop farms, manufacturing and processing plants where glyphosate is produced or used, and hazardous waste disposal sites containing glyphosate.

Occupational exposure of glyphosate may occur via inhalation, dermal contact, and/or ocular contact during manufacture, transport, use, and disposal. Farmers and home gardeners using herbicides containing glyphosate may be exposed to glyphosate via inhalation, dermal contact, and/or ocular contact as well. People may be exposed to glyphosate upon entering areas where it has been recently applied. Dermal contact appears to be the major route of exposure to glyphosate for people involved in its application.

Children are expected to be exposed to glyphosate by the same routes as adults in the general population. Products containing glyphosate should be kept out of the reach of children. Due to increased hand-to-mouth activity and playing habits, children are more likely to come into contact with glyphosate residues that may be present in soil. Glyphosate is not likely to bioaccumulate in breast milk (Bus 2015) and was not detected in breast milk from lactating mothers with detectable glyphosate in their urine (McGuire et al. 2016). In one small study, neither glyphosate nor its major degradation product, aminomethylphosphonic acid (AMPA), were detected in the maternal or fetal cord serum of pregnant subjects (Aris and LeBlanc 2011).

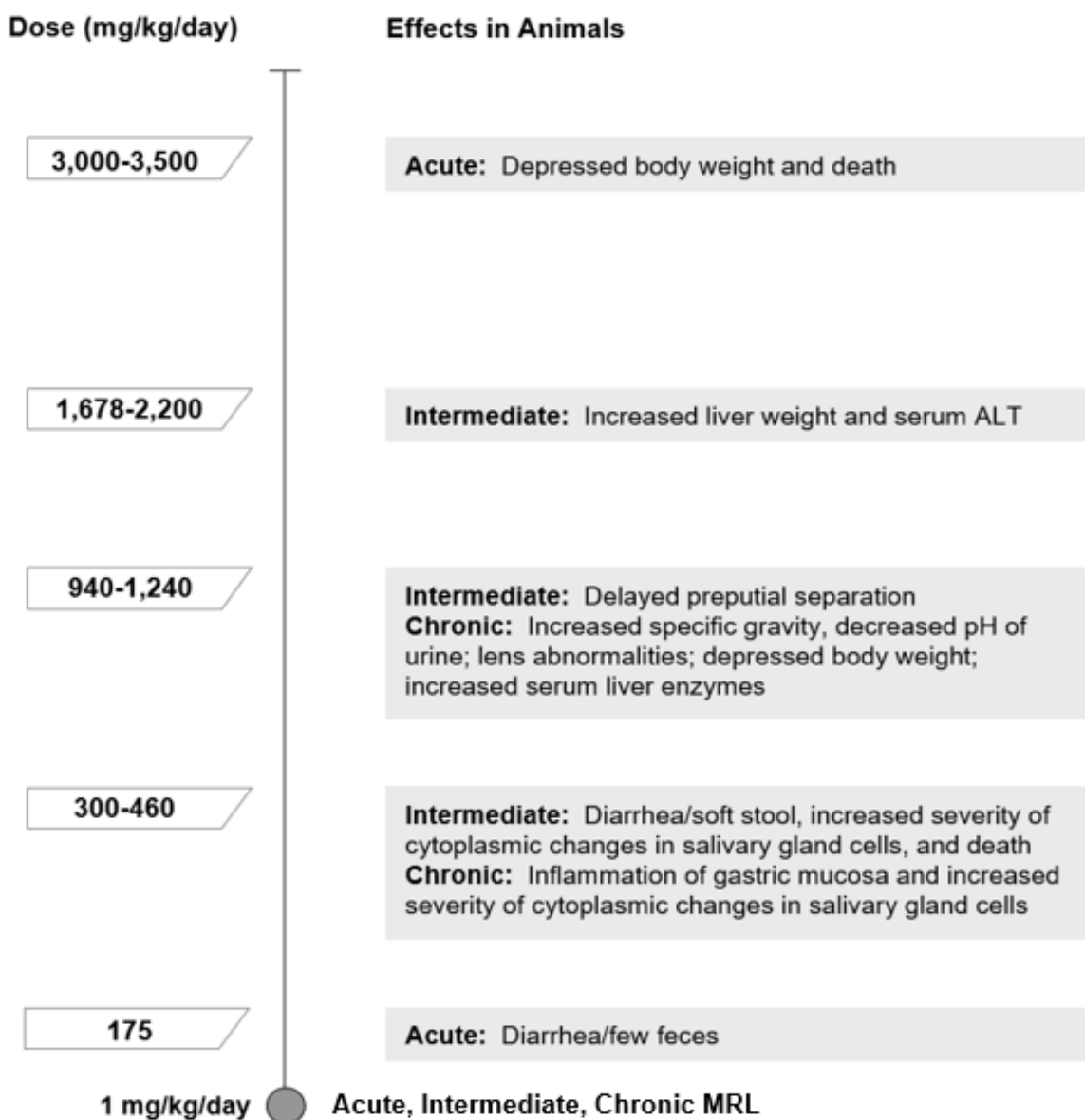
See Chapter 5 for more detailed information regarding concentrations of glyphosate in environmental media.

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1.2 SUMMARY OF HEALTH EFFECTS

Information regarding the toxicity of glyphosate comes primarily from oral studies in laboratory animals exposed to glyphosate technical. No information was located regarding health effects in humans exposed to glyphosate technical; human exposures are to herbicides that contain glyphosate and other ingredients or to glyphosate residues in selected food sources. Human studies have reported possible associations between glyphosate herbicide use and various health outcomes. A few animal studies evaluated the effects of inhalation or oral exposure to glyphosate formulations containing surfactant and additional unspecified substances. Reported effects may be due, at least in part, to the surfactant. Furthermore, glyphosate formulations vary in specific components and their relative proportions, thus precluding meaningful comparisons of toxic effect levels. Therefore, Figure 1-1 contains summary information related only to glyphosate technical.

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Figure 1-1. Noncancer Health Effects Found in Animals Following Oral Exposure to Glyphosate Technical

Exposure Durations: Acute (≤ 14 days); Intermediate (15-364 days); Chronic (≥ 365 days)

* Classification of glyphosate used in each study is based on author-report. Technical-grade glyphosate has a purity of $\geq 80\%$, though the purity is usually $>90\%$ (IPCS 1994, McBean 2011).

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As illustrated in Figure 1-1, gastrointestinal disturbance and effects on the salivary gland appear to be the most sensitive noncancer effects in animal studies that employed oral exposure to glyphosate technical. Ocular, hepatic, renal, and body weight effects have been reported as well. Developmental effects were observed at dose levels resulting in maternal toxicity. Effects observed in animals are considered relevant to human health in the absence of experimental data to indicate otherwise.

Gastrointestinal Effects. Gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain, sore throat, mucosal damage in mouth and esophagus) are commonly reported in patients ingesting glyphosate products (Chang et al. 1999; Lee et al. 2000, 2008; Moon and Chun 2010; Roberts et al. 2010; Sawada et al. 1988; Talbot et al. 1991; Tominack et al. 1991). Gastrointestinal effects have frequently been seen in animal studies. For example, soft stool/diarrhea were reported in pregnant rabbits gavaged with glyphosate technical during gestation (EPA 1992f, 2017b) and rats administered glyphosate technical in the diet for 2 generations (EPA 1992a). Inflammation of gastric mucosa was observed in female rats orally exposed to glyphosate technical for 2 years (EPA 1991a, 1991b). Cytoplasmic alterations were reported in salivary glands of glyphosate-treated rats and mice; the toxicological significance of these salivary gland changes is uncertain (NTP 1992).

Body Weight Effects. Depressed body weight was observed during intermediate- and chronic-duration oral exposure of laboratory animals to glyphosate technical at doses $\geq 1,183$ mg/kg/day (EPA 1985a, 1991a, 1991b, 1992a).

Hepatic Effects. Increased liver weight and increased serum markers of liver effects (alkaline phosphatase [AP], alanine aminotransferase [ALT], and/or bile acids) were observed in rats administered glyphosate technical for 13 weeks at $\geq 1,678$ mg/kg/day (NTP 1992). Centrilobular hepatocellular necrosis was observed in livers from male mice administered glyphosate technical for 2 years at an estimated dose of 4,945 mg/kg/day (EPA 1985a). Other studies found less conclusive signs of hepatic effects such as changes in thiobarbituric acid reactive substances (Almeida et al. 2017; Milic et al. 2018) and significantly increased ROS levels in the liver (Milic et al. 2018).

Renal Effects. Increased specific gravity of urine and decreased urinary pH were noted among male rats administered glyphosate technical for 2 years at 940 mg/kg/day (EPA 1991a, 1991b). Female mice administered glyphosate technical for 2 years at 6,069 mg/kg/day exhibited significantly increased incidence of renal proximal tubule epithelial basophilia and hypertrophy (EPA 2015a).

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Ocular Effects. In a report of human case series of 1,513 ocular exposures to glyphosate products, minor symptoms (primarily transient irritation) were observed in 70% of the cases; most (99%) complained of eye pain (Acquavella et al. 1999). Lens abnormalities were observed in male rats orally administered glyphosate technical for 2 years at 940 mg/kg/day (EPA 1991a, 1991b). According to EPA (1993), glyphosate is considered mildly irritating to the eye following ocular instillation.

Developmental Effects. Limited epidemiology studies provided suggestive evidence of associations between maternal preconception exposure to glyphosate and increased risk of spontaneous abortion (Arbuckle et al. 2001) and parent-reported attention deficit disorder/attention deficit hyperactivity disorder (Garry et al. 2002). Depressed weight and increased incidence of unossified sternebrae were observed in gestation day (GD) 20 fetuses from rat dams treated with glyphosate technical by gavage at 3,500 mg/kg/day during GDs 6–19 (EPA 1992e). In a study of rats exposed via the diet for 2 generations, up to 14–20% depressed pup body weight and/or body weight gain were noted at an estimated glyphosate technical dose of 3,134 mg/kg/day (EPA 1992a). In another 2-generation oral rat study, an estimated glyphosate technical dose of 1,234 mg/kg/day resulted in delayed preputial separation (EPA 2013a). A 3-generation study in Sprague-Dawley rats using only 25 mg/kg/day glyphosate technical found delays in puberty in F1 males and significant increases in organ system diseases in F2 and F3 rats of both sexes (Kubsad et al. 2019).

Cancer Effects. The carcinogenic potential of glyphosate has been evaluated in six meta-analyses (Chang and Delzell 2016; IARC 2017; Schinasi and Leon 2014; Leon et al. 2019; Pahwa et al. 2019; Zhang et al. 2019a) and a number of case-control and cohort epidemiology studies (see Section 2.19 for detailed information and specific citations). The meta-analyses reported positive associations between glyphosate use and selected lymphohematopoietic cancers. Most of the case-control and cohort studies used self-reported ever/never glyphosate use as the biomarker of exposure, and subjects were likely exposed to other pesticides as well. Numerous studies reported risk ratios greater than 1 for associations between glyphosate exposure and risk of non-Hodgkin's lymphoma or multiple myeloma; however, the reported associations were statistically significant only in a few studies.

Glyphosate-Containing Herbicide Formulations. Collectively, animal studies in which glyphosate-containing herbicide formulations were tested by the oral exposure route have identified the following targets of toxicity:

- Body weight effects (depressed body weight gain in mice),

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- Hematological effects (decreases in red blood cells, hematocrit, and hemoglobin, and increases in mean corpuscular volume and neutrophils in mice),
- Hepatic effects (increased serum liver enzyme activity and histopathologic liver lesions in male rats),
- Renal effects (histopathologic kidney lesions in male rats), and
- Reproductive effects (increased percentage of morphologically abnormal sperm in rats).

A summary figure of sensitive targets of glyphosate-containing herbicide formulations is not included in this toxicological profile for glyphosate because formulations were not equivalent across studies and other ingredients (in addition to glyphosate as active ingredient) may have influenced the observed effects.

1.3 MINIMAL RISK LEVELS (MRLs)

Animal studies submitted to EPA's Office of Pesticides Programs to fulfill requirements for the registration of a particular glyphosate formulation for use in the United States involve exposure to glyphosate technical (typically >90% purity). Some animal studies in the open literature used glyphosate formulations that typically included 1–41% glyphosate technical (or glyphosate salts) and up to 18% surfactant (along with other “inert” ingredients). Surfactants in glyphosate formulations may be at least partly responsible for the toxic effects from overexposure to glyphosate formulations (Adam et al. 1997; Sawada et al. 1988; Williams et al. 2000). Human exposure to glyphosate formulations via its use in weed control includes exposure to all substances in a particular glyphosate formulation. No MRLs were derived for glyphosate formulations due to the wide variation in glyphosate content and surfactants used in various glyphosate formulations and the fact that surfactants can contribute to the toxicity of glyphosate formulations. However, because exposures of the general population via food or water sources with measurable glyphosate residues most likely involve glyphosate and/or its breakdown products rather than the intact glyphosate-based formulation, health effects data associated with oral exposure to glyphosate technical are considered relevant to potential derivation of oral MRLs for glyphosate. Oral MRLs based on glyphosate technical would not be applicable to intentional or accidental ingestion of a glyphosate formulation.

Available data for inhalation exposure to glyphosate technical are limited to a summary from a single 4-week repeated-exposure rat study in which no effects were observed at the highest exposure level (EPA 1985c). The inhalation database was, therefore, not considered adequate for derivation of inhalation MRLs for glyphosate. As presented in Figure 1-1, available data have identified the gastrointestinal tract

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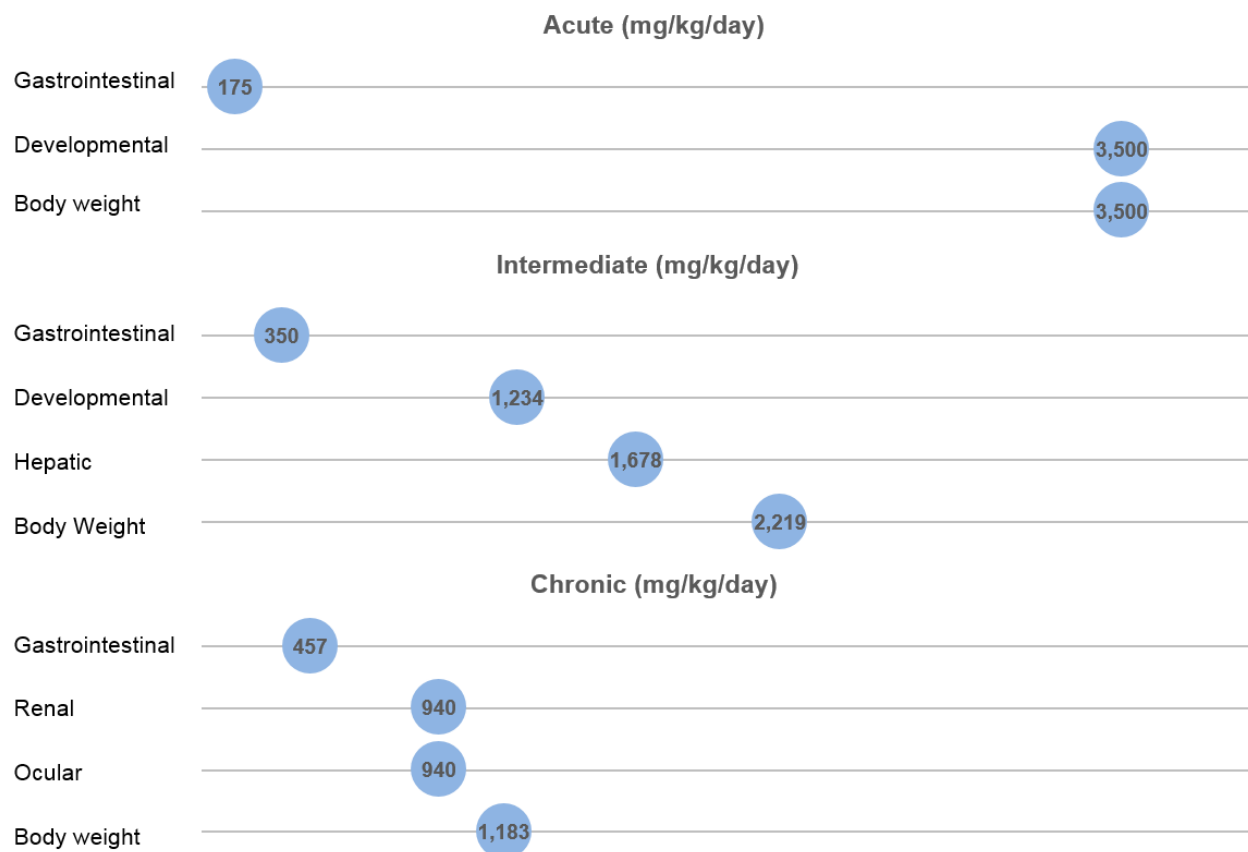
as the most sensitive target of glyphosate toxicity following oral exposure. The oral database was considered adequate for derivation of acute- and chronic-duration oral MRLs for glyphosate. These MRLs are summarized in Table 1-1 and discussed in detail in Appendix A. The chronic-duration MRL value is adopted as the intermediate-duration oral MRL for glyphosate (see Appendix A).

As illustrated in Figure 1-2, gastrointestinal disturbances (e.g., loose stools/diarrhea, decreased fecal production, inflammation of gastric mucosa, cytoplasmic alterations in salivary glands) appear to be the most sensitive effects of glyphosate technical toxicity in animals. The lowest-observed-adverse-effect levels (LOAELs) in Figure 1-2 reflect actual doses (levels of exposure) employed in animal studies.

Figure 1-2. Summary of Sensitive Targets of Glyphosate Technical – Oral

The gastrointestinal tract is the most sensitive target of ingested glyphosate technical.

Numbers in circles are the lowest LOAELs for all health effects in animals; no reliable dose-response data were available for humans.



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Table 1-1. Minimal Risk Levels (MRLs) for Technical Glyphosate^a

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	1	Gastrointestinal effects	100 (NOAEL)	100	EPA 2017b
Intermediate	The chronic-duration oral MRL of 1 mg/kg/day is adopted as the intermediate-duration oral MRL.				
Chronic	1	Gastrointestinal effects	113 (NOAEL)	100	EPA 1991a, 1991b

^aSee Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level