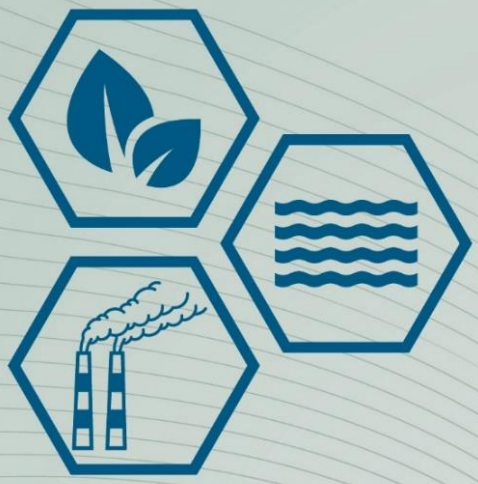

Toxicological Profile for Glyphosate

August 2020

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

Date	Description
August 2020	Final toxicological profile released
April 2019	Draft for public comment toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

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 ≥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

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.

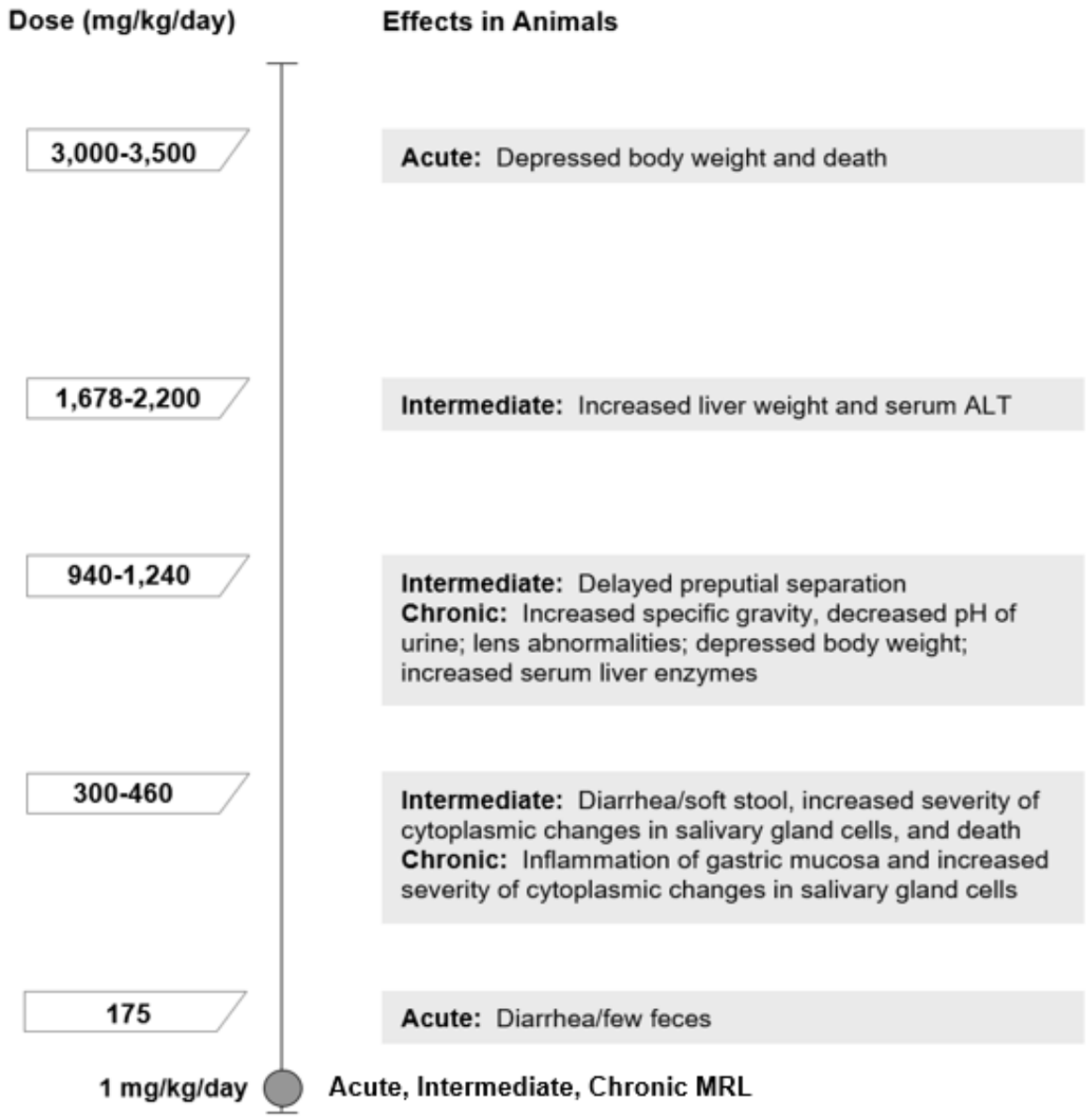
Children are expected to be exposed to glyphosate by the same routes as adults in the general population. Products containing glyphosate should be kept out of the reach of children. Due to increased hand-to-mouth activity and playing habits, children are more likely to come into contact with glyphosate 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.

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.

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



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

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 ≥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 ≥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).

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),

- 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

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.

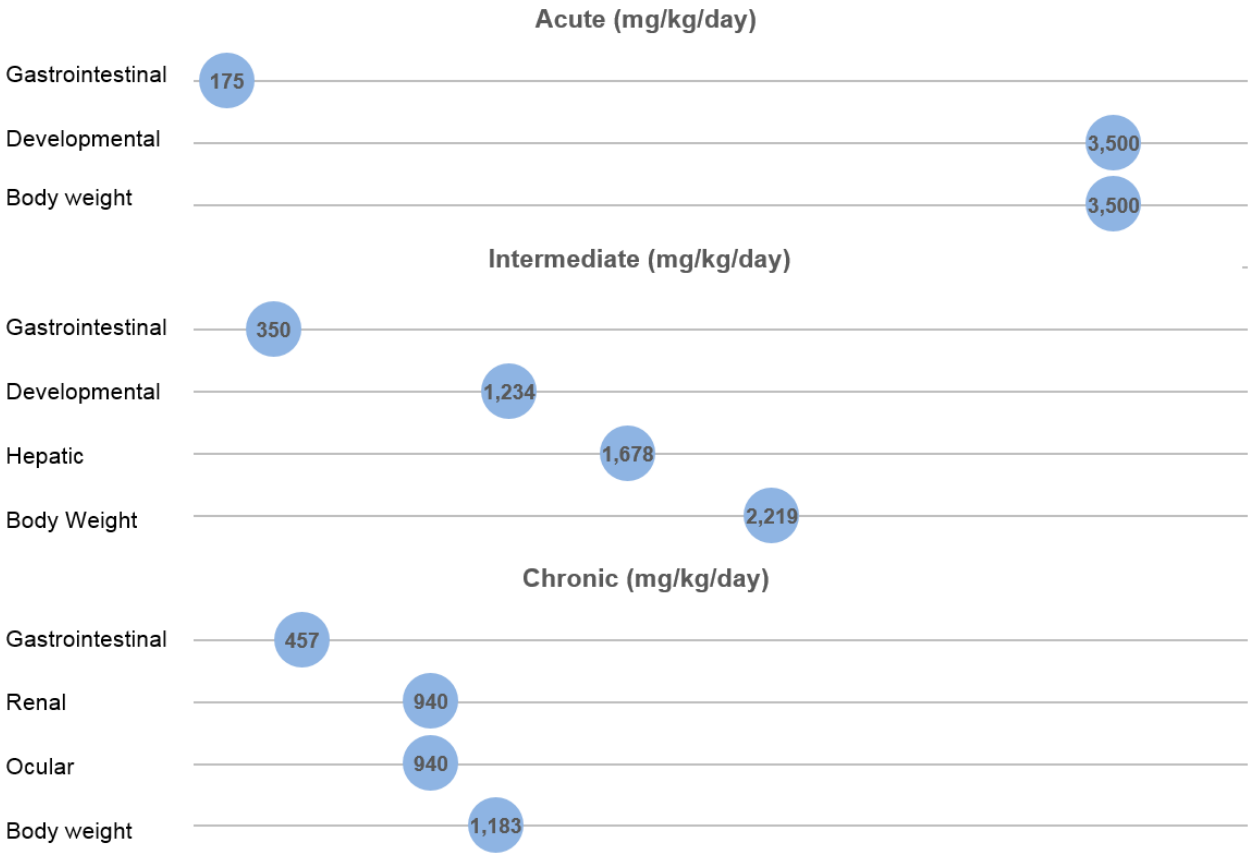


Table 1-1. Minimal Risk Levels (MRLs) for Technical Glyphosate[a]

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

[a]See Appendix A for additional information.

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

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of glyphosate. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, as well as people exposed during production and/or use of glyphosate-containing products, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 for glyphosate technical and Figure 2-2 for glyphosate formulations provide an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to glyphosate, but may not be inclusive of the entire body of literature.

This ATSDR Toxicological Profile for Glyphosate includes data for glyphosate technical (purity typically >90%) and glyphosate formulations (typically 1–41% v/v glyphosate technical or glyphosate salts and ≤18% polyoxyethyleneamine [POEA] surfactant). Surfactants in glyphosate formulations may be at least partly responsible for the toxic effects from exposure to glyphosate formulations (Adam et al. 1997; Sawada et al. 1988; Williams et al. 2000; Mesnage et al. 2013). As such, health effects observed in studies of animals exposed to relatively high levels of glyphosate technical may not accurately reflect health effects from human exposure to glyphosate formulations during application as an herbicide. However, because the general population may be exposed to glyphosate and/or its breakdown products (rather than to a particular glyphosate formulation) in selected food sources or contaminated drinking

water, health effects from animal studies in which glyphosate technical was used as a test substance are considered relevant to human health.

Product names and reported descriptions for glyphosate-containing products included in this toxicological profile are summarized in Table 2-1 by reference (alphabetical order). Hereafter, each glyphosate-containing formulation will generally be identified only by the reported product name.

Table 2-1. Description of Selected Glyphosate Formulations

Reference	Product name	Product description[a]
Adam et al. 1997	Roundup®	41% w/v glyphosate isopropylamine salt and 18% w/v POEA
Benedetti et al. 2004	Glyphosate-Biocarb®	360 g/L glyphosate and 18% w/v POEA
Bolognesi et al. 1997	Roundup®	30.4% glyphosate
Caglar and Kolankaya 2008	Roundup®	Monsanto of Brazil; 360 g/L glyphosate, 18% w/v POEA
Cassault-Meyer et al. 2014	Roundup® Grand Travaux Plus	607 g/L glyphosate isopropylamine salt and adjuvants such as POEA
Contardo-Jara et al. 2009	Roundup Ultra®	360 g/L glyphosate isopropylamine salt and surfactants of unspecified composition
Dallegrave et al. 2003, 2007	Roundup®	Monsanto of Brazil; 360 g/L glyphosate, 18% w/v POEA
Dimitrov et al. 2006	Roundup®	Ingredients and proportions not specified
EPA 1985c	Roundup®	33.3% use dilution (41.56% isopropylamine salt of glyphosate in concentrate)
Feng et al. 1990a	Roundup®	Unspecified proportion of glyphosate isopropylamine salt
Gasnier et al. 2009	Roundup Grands Travaux®	40% glyphosate
George et al. 2010	Roundup Original®	41% glyphosate and 15% POEA
Grisolia 2002	Roundup®	48% glyphosate isopropylammonium salt; 12% inerts, including POEA
Holečková 2006	Unspecified technical herbicide	62% w/w isopropylamine salt of glyphosate and 38% unspecified inerts
Jasper et al. 2012	Roundup Original®	41% glyphosate and 16% POEA
Kale et al. 1995	Roundup®	Glyphosate isopropylamine salt of unspecified concentration
Koller et al. 2012	Roundup Ultra Max®	450 g/L glyphosate acid
Maibach 1986	Roundup®	41% glyphosate as isopropylamine salt, water, surfactant
Mao et al. 2018	Roundup®	Composition not specified
Moriya et al. 1983	Roundup®	Composition not specified

Table 2-1. Description of Selected Glyphosate Formulations

Reference	Product name	Product description[a]
Panzacchi et al. 2018	Roundup Bioflow®	41.5% glyphosate isopropylamine salt, 42.5% water, and 15% proprietary surfactant
Paz-y-Miño et al. 2007	Roundup-Ultra®	Unspecified proportions of glyphosate, POEA, and the adjuvant Cosmoflux 411F
Peluso et al. 1998	Roundup®	30.4% glyphosate isopropylammonium salt
Piešová 2004, 2005	Unspecified product from Monsanto, Antwerp, Belgium	62% w/w isopropylamine salt of glyphosate and 38% unspecified inerts
Prasad et al. 2009	Roundup®	>41% glyphosate isopropylamine salt
Raipulis et al. 2009	Roundup BIO®	Ingredients not specified
Rank et al. 1993	Roundup®	480 g/L glyphosate isopropylamine salt
Romano et al. 2010	Roundup Transorb®	648 g/L isopropylamine salt of glyphosate and 594 g/L inerts
Šiviková and Dianovskỳ 2006	Unspecified product from Monsanto Europe S.A., Belgium	62% glyphosate; 38% unspecified inerts
Vigfusson and Vyse 1980	Roundup®	Ingredients not specified
Wester et al. 1991	Roundup®	Ingredients not specified
Wildeman and Nazar 1982	Unspecified commercial formulation	Glyphosate-containing product (no additional details on composition)
Wunnapuk et al. 2014	Concentrate Roundup® Weedkiller	Monsanto Australia, containing 360 g/L of glyphosate (only ingredient specified)

[a]Limited to the glyphosate-containing substance description in the corresponding study report.

POEA = polyoxyethyleneamine (surfactant)

Animal oral study information for glyphosate technical is presented in Table 2-2 and Figure 2-3. Animal oral study information for glyphosate formulations is presented in Table 2-3. Animal dermal study information for glyphosate technical is presented in Table 2-4.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. LSE tables and figures for animal inhalation studies of glyphosate technical and glyphosate formulations are precluded by lack of data. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear.

ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

Glyphosate-containing products are among the most widely-used herbicides in commercial, agricultural, and residential settings (NPIC 2015). Selected field crops have been genetically modified to resist damage from glyphosate; such crops can be sprayed with glyphosate formulations to control weed growth without harming the genetically-modified plants. Selected glyphosate-containing products are labeled for use as desiccants on some grain crops a few weeks prior to harvest.

Glyphosate technical (purity typically >90%) has been evaluated in numerous animal studies, most of which employed the oral exposure route and were submitted to EPA’s Office of Pesticide Programs through the pesticide registration program as directed by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Federal Food, Drug and Cosmetic Act (FFDCA), and Food Quality Protection Act (FQPA). The submitted studies are generally unpublished proprietary studies. EPA evaluated submitted study reports and produced summaries termed Data Evaluation Records or Data Evaluation Reports (DERs) that include study details and EPA’s own conclusions regarding study design, results, and conclusions of the study authors. Information from DERs received from EPA is summarized in this ATSDR Toxicological Profile for Glyphosate (note: selected DERs can be requested at: https://www.epa.gov/foia or viewed from a list of cleared reviews for glyphosate or glyphosate salts at https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/a.html). EPA evaluated and produced DERs for selected proprietary animal studies submitted by various chemical companies to agencies or organizations outside the United States for product registration purposes. Results from the DERs available to ATSDR were included in the Toxicological Profile for Glyphosate.

Epidemiological studies of glyphosate are predominantly case-control and cohort studies that examined possible associations between exposure to glyphosate (in glyphosate-containing herbicides) and selected health outcomes (noncancer and cancer endpoints), or case reports following accidental or intentional ingestion of glyphosate-containing products. These epidemiology studies are summarized in Table 2-5 (noncancer) and Table 2-7 (cancer). The majority of the studies used self-reported (or proxy reported) ever/never glyphosate use as the measure of exposure and some studies included a metric for frequency of exposure. There is no information regarding health effects in humans exposed to glyphosate technical.

Most reliable dose-response health effects data come from oral studies of animals administered glyphosate technical (seeFigure 2-1 for an overview of the number of animal studies examining potential endpoints of concern from oral exposure to glyphosate technical). No information was located regarding the effects of inhaled glyphosate technical. In a 4-week study that employed repeated inhalation exposure of rats to Roundup®, no adverse effects were observed at the highest exposure concentration tested (360 mg Roundup®/m^3) (EPA 1985c). Limited animal data for dermal exposure to glyphosate technical indicate that glyphosate is not a dermal irritant. Results from the oral animal studies identify the following targets of glyphosate toxicity, albeit at relatively high dose levels:

- **Gastrointestinal effects:** Clinical signs and/or pathological evidence of glyphosate-induced irritation were observed in several animal studies; the lowest dose level resulting in gastrointestinal effects was 175 mg/kg/day for diarrhea and few feces in pregnant rabbits administered glyphosate acid by gavage. Gastrointestinal disturbances are signs and/or symptoms following ingestion of large amounts of glyphosate-containing products.

- **Developmental effects:** Glyphosate treatment-related developmental effects were noted in a few studies at dose levels (≥1,234 mg/kg/day) resulting in maternal toxicity as well.

- **Body weight effects:** Depressed body weight and/or depressed body weight gain resulted from repeated dosing of glyphosate technical at dose levels ≥1,183 mg/kg/day.

- **Hepatic effects:** Increases in liver weight and serum ALT activity were observed in one repeated-dose study at a dose level of 1,678 mg/kg/day.

- **Ocular effects:** Lens abnormalities were observed in one repeated-dose study at a dose level of 940 mg/kg/day.

- **Renal effects:** Indicators of renal toxicity were noted in rats and mice administered glyphosate technical in the diet for 2 years at high doses (940 and 6,069 mg/kg/day, respectively).

- **Other effects:** Neurological, hematological, immunological, and reproductive endpoints have been evaluated, but do not appear to be particular targets of glyphosate toxicity.

- **Cancer:** Upon evaluation of available carcinogenicity studies in laboratory rodents, multiple agencies or organizations have concluded that glyphosate technical does not appear to be an animal carcinogen. In contrast, IARC considered the animal data to provide "*sufficient evidence*" of glyphosate carcinogenicity.

An overview of the number of human and animal studies examining potential endpoints of concern from exposure to glyphosate formulations is presented inFigure 2-2. Results from available animal studies identify the following targets of toxicity:

- **Developmental effects:** Histopathologic testicular lesions, decreased sperm production, and increased incidence of fetal skeletal malformations were reported in response to oral dosing of rat weanlings or pregnant rats with selected glyphosate formulations in the range of 5–500 mg/kg/day.

- **Endocrine effects:** Decreased serum testosterone was noted in male rat weanlings administered a glyphosate formulation orally at 5 mg/kg/day.

- **Body weight effects:** Seriously depressed body weight gain was observed in mice administered a glyphosate formulation orally at 50 mg/kg/day.

- **Renal effects:** Histopathologic kidney lesions were noted in male rats gavaged once with a glyphosate formulation at 250 mg/kg.

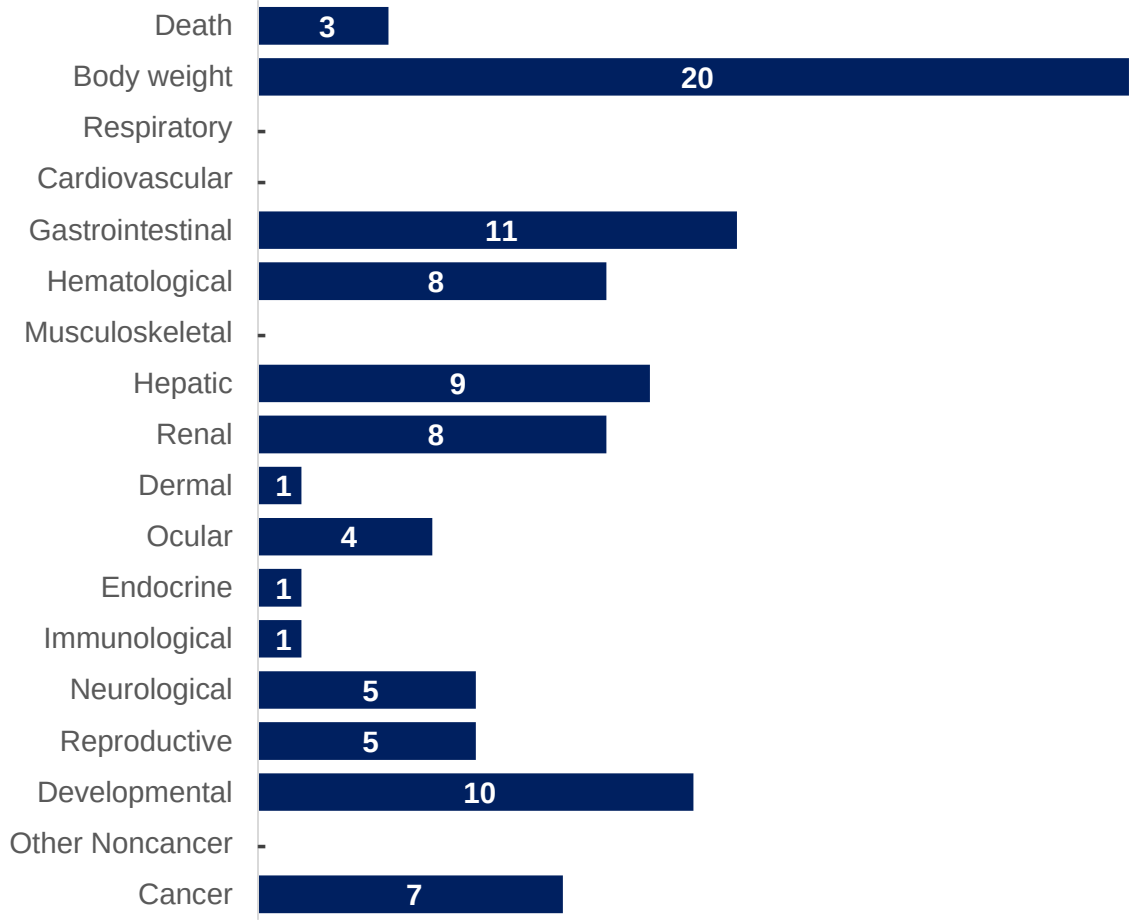
- **Hepatic effects:** Increased serum liver enzyme activity and histopathologic liver lesions were reported in male rats repeatedly gavaged with a glyphosate formulation at 487 mg/kg/day.

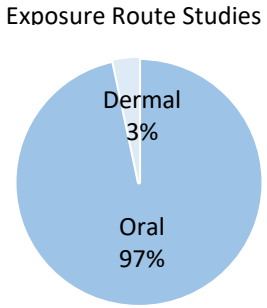
- **Hematological effects:** Decreases in red blood cells, hematocrit, and hemoglobin, and increases in mean corpuscular volume and neutrophils were reported in mice administered a glyphosate formulation orally at 500 mg/kg/day.

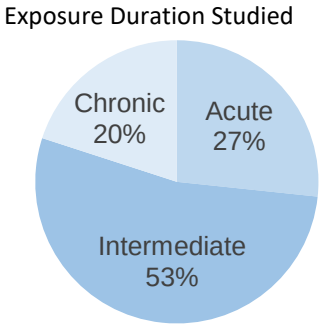
- **Reproductive effects:** Increased percentage of morphologically abnormal sperm was reported among rats receiving a glyphosate formulation from the drinking water for 8 days at 640 mg/kg/day.

Figure 2-1. Overview of the Number of Animal Studies Examining Glyphosate Technical Health Effects*

Most studies examined the potential body weight, gastrointestinal, hematological, hepatic, and developmental effects of glyphosate technical (counts represent studies examining endpoint)





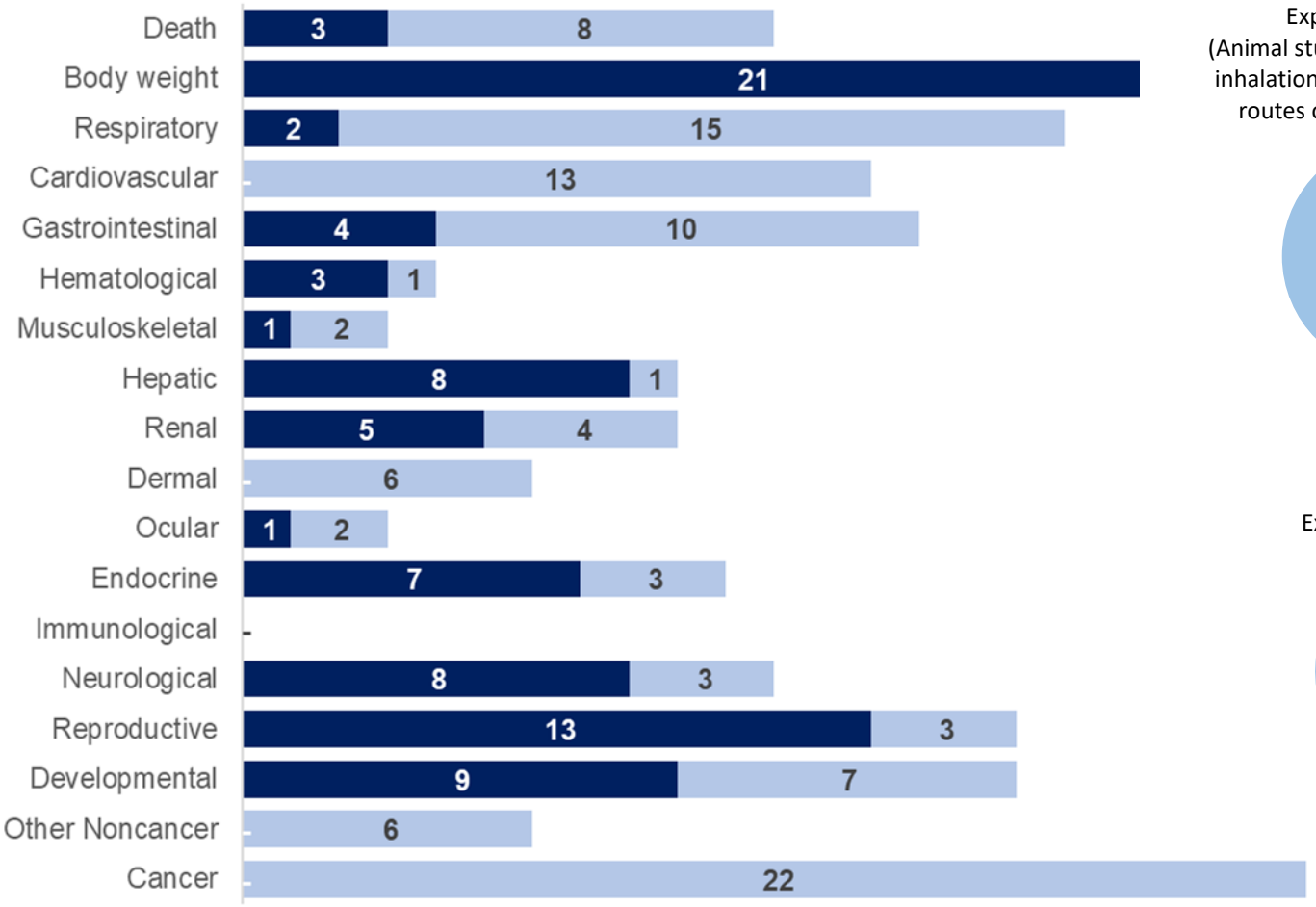


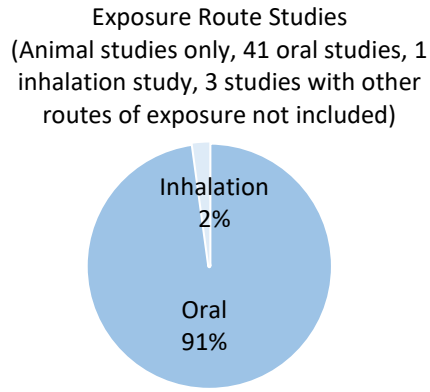
*Includes only animal studies that employed oral exposure to glyphosate technical as discussed in Chapter 2. A total of 30 studies include those finding no effect. Most studies examined multiple endpoints.

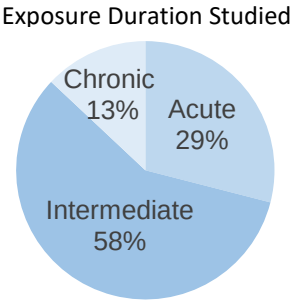
Figure 2-2. Overview of the Number of Studies Examining Glyphosate Formulations Health Effects*

Most epidemiological studies examined potential cancer, respiratory, and developmental effects associated with glyphosate-containing products; most animal studies examined potential body weight and developmental effects associated with glyphosate-containing products

More studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)







*A total of 85 studies, including those finding no effect. Many studies examined multiple endpoints. Reliable exposure route and duration information was not typically available for humans. Therefore, relative exposure route and duration proportions are plotted only for animal studies.

Table 2-2. Levels of Significant Exposure to Glyphosate Technical[a] – Oral

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	RAT (Wistar) 8M	Once (G)	0, 2,000 mg/kg	CS, GN, HP, LE, OW	Gastro		2000 M		Diarrhea in 2/8 rats for 6 hours postdosing, prior to sacrifice at 24 hours
Adam et al. 1997 – Glyphosate technical, purity not specified									
2	RAT (Sprague-Dawley) 5 mixed	Once (GW)	3,160, 3,980, 5,010, 6,310	CS, GN, LE	Death			4320	LD50
EPA 1992b – Glyphosate technical, purity not specified									
3	RAT (Sprague-Dawley) 25 F	GDs 6–19 1 time/day (GW)	0, 300, 1,000, 3,500	BW, CS, DX, FX, GN, LE, MX, TG	Death			3500 F	6/25 Dams died
					Bd wt	1000 F		3500 F	28.5% depressed mean maternal body weight gain
					Gastro	1000 F		3500 F	Diarrhea, soft stools
					Develop	1000 F	3500 F		9% depressed mean fetal body weight, increased incidence of unossified sternebrae at serious maternally-toxic dose level
EPA 1992e – Glyphosate technical, purity 98.7%									
4	RAT (Alpk: APfSD) 10 M, 10 F	Once (GW)	0, 500, 1,000, 2,000 mg/kg	BW, CS, FI, GN, HP, LE, OF, OW	Bd wt	2000			
					Gastro	1000	2000		Diarrhea

Table 2-2. Levels of Significant Exposure to Glyphosate Technical[a] – Oral

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro	1000	2000		Decreased activity, subdued behavior, hunched posture
					Other noncancer	1000	2000		Hypothermia
EPA 2013c – Glyphosate technical, purity 95.6%									
5	RAT (Alpk: APfSD) 24 F	GDs 7–16 1 time/day (GW)	0, 250, 500, 1,000	BW, CS, DX, FI, FX, GN, LE, MX, OW	Bd wt	1000 F			
					Develop	1000 F			
EPA 2017b – Glyphosate acid, purity 95.6%									
6	RAT Sprague-Dawley 10M	2 wk-once/d (W)	0, 2.5, 25	HP BI	Endocr	25 M			
					Repro	25 M			
Johansson et al. 2018 – glyphosate technical, purity 96%									
7	RABBIT (New Zealand white) 20 F	GDs 8-20 1 time/day (GW)	0, 100, 175, 300	BW, CS, DX, FI, FX, GN, LE, MX, OW	Bd wt	300 F			NOAEL for maternal body weight
					Gastro	100 F[c]	175 F		Diarrhea, few feces
					Develop	300 F			
EPA 2017b – glyphosate acid, purity 95.6%									
INTERMEDIATE EXPOSURE									
8	RAT (Sprague-Dawley) 30 M, 30 F	2 Generation, up to 19 weeks/generation (F)	F0 M: 0, 137, 754, 2,219 F0 F: 0, 160, 802, 3,134 F1 M: 0, 165, 818, 2,633 F1 F: 0, 194, 947, 3,035	NS	Bd wt	802 F	3134 F		Up to 18% depressed mean maternal body weight gain

Table 2-2. Levels of Significant Exposure to Glyphosate Technical[a] – Oral

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Bd wt	754 M	2219 M		Up to 12% depressed mean paternal body weight gain
					Gastro	802 F	3134 F		Soft stool
					Gastro	754 M	2219 M		Soft stool
					Repro	3134 F			
					Repro	2219 M			
					Develop	802		3134	Up to 14–20% depressed mean pup body weight or body weight gain during lactation at maternally-toxic dose level
EPA 1992a – Glyphosate technical, purity 97.67%									
9	RAT (Sprague-Dawley) 12 M, 12 F	3-Generation (F)	0, 3, 10, 30	BW, CS, DX, FI, FX, GN, HP, LE, MX, OW	Bd wt	30			
					Repro	30			
EPA 1992g – Glyphosate technical, purity 98.7%									
10	RAT (Sprague-Dawley) 28 M, 28 F	2 Generation, up to 19 weeks/generation (F)	M: 0, 121, 408, 1,234; F: 0, 126, 423, 1,273	BW, CS, DX, FI, FX, GN, HP, LE, MX, OF, OW, TG	Bd wt	1273 F			
					Bd wt	1234 M			
					Hepatic	1273 F			
					Hepatic	1234 M			
					Renal	1273 F			

Table 2-2. Levels of Significant Exposure to Glyphosate Technical[a] – Oral

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal	1234 M			
					Repro	1273 F			
					Repro	1234 M			
					Develop	408 M	1234 M		Delayed preputial separation
EPA 2013a – Glyphosate technical, purity 95.7%									
11	RAT (Alpk: APfSD) 12 M, 12 F	13 weeks (F)	M: 0, 155.5, 617.1, 1,546.5 F: 0, 166.3, 672.1, 1,630.6	BW, CS, FI, GN, HP, LE, OF, OW	Neuro	1630.6 F			
					Neuro	1546.5 M			
EPA 2013c – Glyphosate technical, purity 95.6%									
12	RAT (F344/N) 10 M, 10 F	13 weeks (F)	M: 0, 205, 410, 811, 1,678, 3,393 F: 0, 213, 421, 844, 1,690, 3,393	BC, BW, CS, EA, FI, GN, HE, HP, LE, OF, OW	Bd wt	3393 F			
					Bd wt	1678 M	3393 M		18% lower mean body weight and body weight gain
					Gastro	213 F	421 F		Increased severity of basophilia and hypertrophy of acinar cells in parotid and submandibular salivary glands

Table 2-2. Levels of Significant Exposure to Glyphosate Technical[a] – Oral

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Gastro	205 M	410 M		Increased severity of basophilia and hypertrophy of acinar cells in parotid and submandibular salivary glands
					Hemato	3393			
					Hepatic	1690 F	3393 F		Increases in liver weight and serum AP, ALT, and bile acids
					Hepatic	811 M	1678 M		Increases in liver weight and serum ALT
NTP 1992 – Glyphosate technical, purity 99%									
13	RAT Sprague-Dawley F0 8F	GD 6 to PND 120-once/d (W)	0, 1.75	RX GN BC HP BI BW	Bd wt	1.75 F			
					Repro	1.75 F			
Manservisi et al. 2019 – glyphosate technical, 99.5%									
14	RAT Sprague-Dawley F1 8	GD 6 to PND 120-once/d, 6 wk-once/d (W)	0, 1.75	RX GN BC HP BI FI WI BW	Bd wt	1.75			
					Endocr	1.75			
					Repro	1.75 M			
					Develop		1.75 M		increased anogenital distance at PND 4
Manservisi et al. 2019 – glyphosate technical, 99.5%									

Table 2-2. Levels of Significant Exposure to Glyphosate Technical[a] – Oral

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
15	RAT Sprague-Dawley F1 10	GD 6 to PND 120-once/d, 13 wk-once/d (W)	0, 1.75	RX GN BC HP BI FI WI BW	Bd wt	1.75			
					Endocr	1.75			
					Repro	1.75 M			
					Develop		1.75 M		increased anogenital distance at PND 4
Manservisi et al. 2019 – glyphosate technical, 99.5%									
16	MOUSE (B6C3F1/Crl) 10 F	28 Days (F)	0, 150.1, 449.1, 1,447.5	BW, CS, FI, GN, OF, OW, WI	Bd wt	1447.5 F			
					Immuno	1447.5 F			
EPA 2013b – Glyphosate technical, purity 85.2%									
17	MOUSE (B6C3F1) 10 M, 10 F	13 weeks (F)	M: 0, 507, 1,065, 2,273, 4,776, 10,780 F: 0, 753, 1,411, 2,707, 5,846, 11,977	BW, CS, FI, GN, HP, LE, OF, OW	Bd wt	5846 F	11977 F		10% lower mean final body weight
					Bd wt	2273 M	4776 M		11% lower mean final body weight
					Gastro	1411 F	2707 F		
					Gastro	1065 M	2273 M		Increased severity of basophilia of acinar cells in parotid salivary gland
					Hepatic	11977 F			
					Hepatic	10780 M			
NTP 1992 – Glyphosate technical, purity 99%									

Table 2-2. Levels of Significant Exposure to Glyphosate Technical[a] – Oral

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
18	RABBIT (Dutch belted) 16 F	GDs 6-27 1 time/day (GW)	0, 75, 175, 350	BW, CS, DX, FX, GN, LE, MX, TG	Death			350 F	10/16 maternal rabbits died
					Bd wt	350 F			
					Gastro	175 F	350 F		
					Develop	350 F			Increased incidence of soft stool and/or diarrhea
EPA 1992f – Glyphosate technical, purity 98.7%									
CHRONIC EXPOSURE									
19	RAT (Sprague-Dawley) 60 M, 60 F	Up to 24 months (F)	M: 0, 89, 362, 940 F: 0, 113, 457, 1,183	BC, BW, CS, Fl, GN, HE, HP, LE, OW	Bd wt	457 F	1183 F		13% lower mean body weight at treatment week 81
					Bd wt	940 M			
					Gastro	113 F[d]	457 F		Inflammation of gastric squamous mucosa
					Gastro	940 M			
					Hemato	1183 F			
					Hemato	940 M			
					Hepatic	1183 F			
					Hepatic	940 M			
					Renal	1183 F			
					Renal	362 M	940 M		Increased specific gravity and decreased pH of urine
					Ocular	1183 F			
					Ocular	362 M	940 M		Increased incidence of lens abnormalities

Table 2-2. Levels of Significant Exposure to Glyphosate Technical[a] – Oral

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
EPA 1991a, 1991b – Glyphosate technical, purity 96.5%									
20	RAT (Sprague-Dawley) 50 M, 50 F	26 months (F)	M: 0, 3.05, 10.30, 31.45 F: 0, 3.37, 11.22, 34.02	BC, BW, CS, Fl, GN, HE, HP, LE, OF, OW, UR	Bd wt	34.02 F			
					Bd wt	31.45 M			
					Gastro	34.02 F			
					Gastro	31.45 M			
					Hemato	34.02 F			
					Hemato	31.45 M			
					Hepatic	34.02 F			
					Hepatic	31.45 M			
					Renal	34.02 F			
					Renal	31.45 M			
EPA 1992d – Glyphosate technical, purity 98.7%									
21	RAT Alpk: APfSD Wistar) 64 M, 64 F	Up to 2 years (F)	M: 0, 121, 361, 1,214 F: 0, 145, 437, 1,498	BC, BH, BW, CS, EA, Fl, GN, HE, HP, LE, OF, OP, OW, UR	Bd wt	1498 F			
					Bd wt	1214 M			
					Gastro	1498 F			
					Gastro	361 M	1214 M		Exocrine hyperplasia in pancreas in males
					Hemato	1498 F			
					Hemato	1214 M			
					Hepatic	437 F	1498 F		Increased serum AP and ALT
					Hepatic	361 M	1214 M		Increased serum AP, ALT, bilirubin

Table 2-2. Levels of Significant Exposure to Glyphosate Technical[a] – Oral

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal	437 F	1498 F		Papillary necrosis in kidney
					Renal	361 M	1214 M		Papillary necrosis in kidney; decreased pH of urine
					Ocular	1498 F			
					Ocular	1214 M			
					Neuro	1498 F			
					Neuro	1214 M			
EPA 2015c – Glyphosate technical, purity 97.6%									
22	RAT (Sprague-Dawley) 85 M, 85 F	Up to 2 years (F)	0, 10, 100, 300, 1,000	BC, BW, CS, EA, Fl, GN, HE, HP, LE, OF, OP, OW, UR	Bd wt	300	1000		11–14% lower mean body weight and body weight gain
					Gastro	100	300		Increased severity of basophilia and hypertrophy of acinar cells in parotid and mandibular salivary glands
					Hemato	1000			
					Hepatic	1000			
					Renal	1000 F			
					Renal	300 M	1000 M		Decreased pH of urine
					Ocular	1000			
EPA 2015c – Glyphosate technical, purity 98.7 and 98.9%									

Table 2-2. Levels of Significant Exposure to Glyphosate Technical[a] – Oral

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
23	MOUSE (CD-1) 50 M, 50 F	24 months (F)	M: 0, 161, 835, 4,945 F: 0, 195, 968, 6,069	BW, CS, Fl, GN, HE, HP, LE	Bd wt	6069 F			
					Bd wt	4945 M			
					Gastro	6069 F			
					Gastro	4945 M			
					Hemato	6069 F			
					Hemato	4945 M			
					Hepatic	6069 F			
					Hepatic	835 M		4945 M	Centrilobular hepatocellular necrosis
					Renal	968 F	6069 F		Renal tubular epithelial basophilia
					Renal	4945 M			
EPA 2015a – Glyphosate technical, purity 99.7%									
24	MOUSE (CD-1) 50 M, 50 F	104 weeks (F)	0, 100, 300, 1,000	BW, CS, Fl, GN, HE, HP, LE, WI	Bd wt	1000			
					Hepatic	1000			
					Renal	1000			
EPA 2015c – Glyphosate technical, purity ≥97.5%									
25	DOG (Beagle) 6 M, 6 F	1 year (C)	0, 20, 100, 500	BC, BW, CS, Fl, GN, HE, HP, LE, OP, OW, UR, WI	Bd wt	500			
					Hemato	500			
					Ocular	500			
EPA 1986a, 1987 – Glyphosate technical, purity 96.13%									

[a] Purities reported in this table are the information provided by the study authors in the study methodologies regarding the chemical used in the experiments.
[b]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[c]Used to derive an acute-duration oral MRL for glyphosate; NOAEL divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[d]Used to derive a chronic-duration oral MRL for glyphosate; NOAEL divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

ALT = alanine aminotransferase; AP = alkaline phosphatase; BC = biochemistry; BW or Bd Wt = body weight; C = capsule; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EA = enzyme activity; (F) = exposure in feed; F = female(s); FI = food intake; FX = fetal toxicity; G = gavage, neat; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; GW = gavage in water vehicle; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; MX = maternal toxicity; NOAEL = no observed-adverse-effect level; NS = not specified; OF = organ function; OP = ophthalmology; OW = organ weight; Repro = reproductive; TG = teratogenicity; UR = urinalysis; WI = water intake

Figure 2-3. Levels of Significant Exposure to Glyphosate Technical – Oral
Acute (≤14 days)

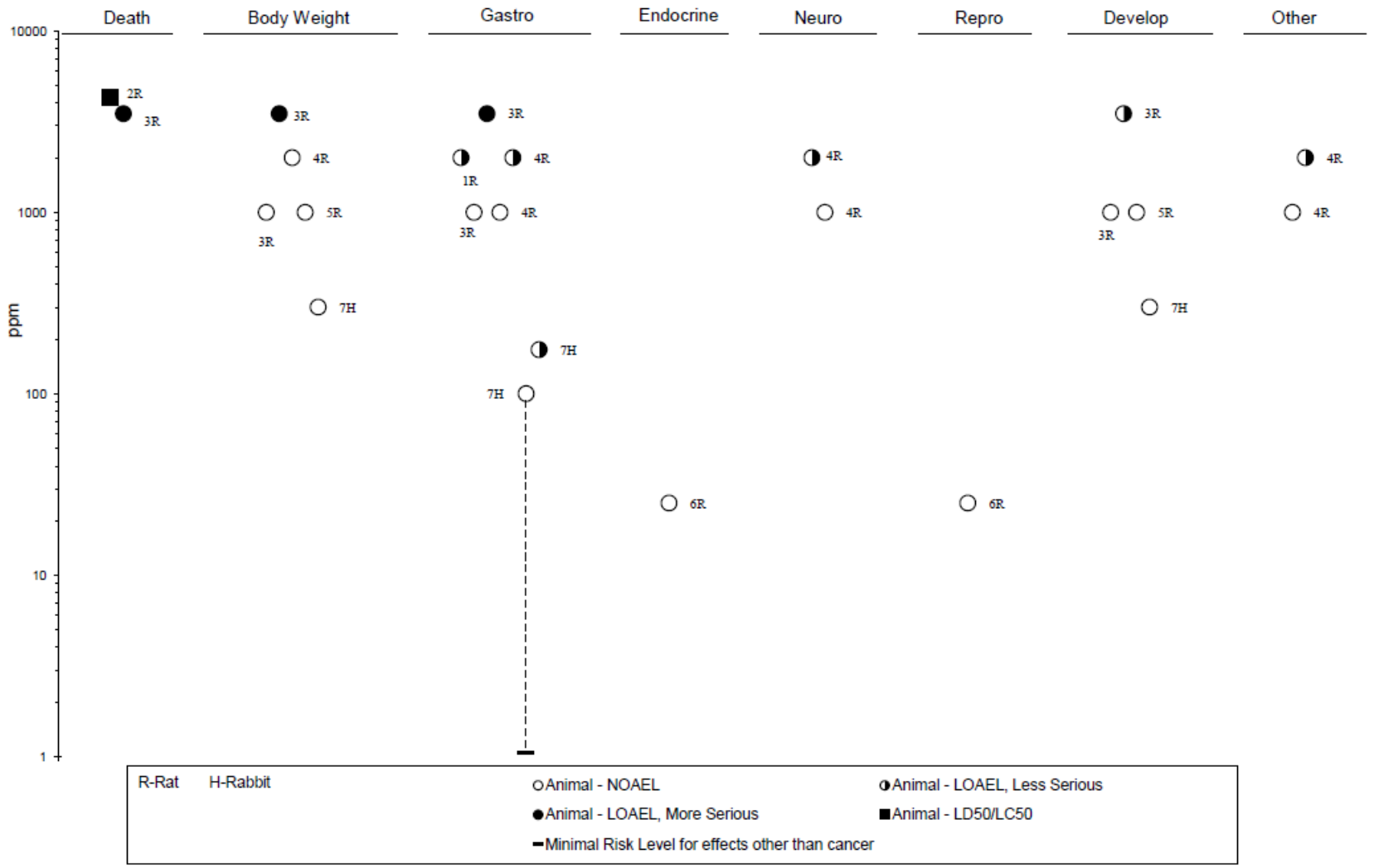


Figure 2-3. Levels of Significant Exposure to Glyphosate Technical – Oral
Intermediate (15-364 days)

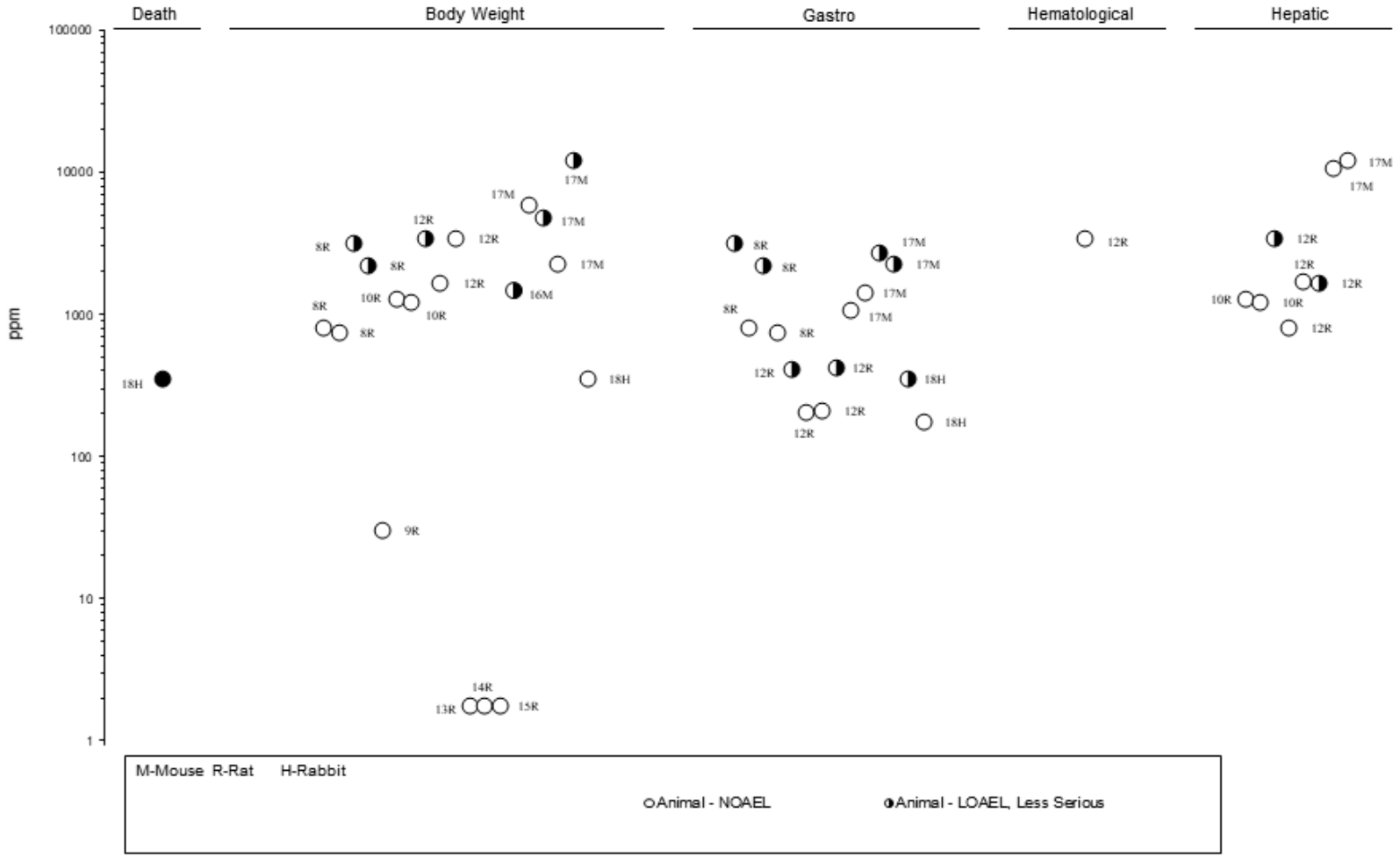


Figure 2-3. Levels of Significant Exposure to Glyphosate Technical – Oral
Intermediate (15-364 days)

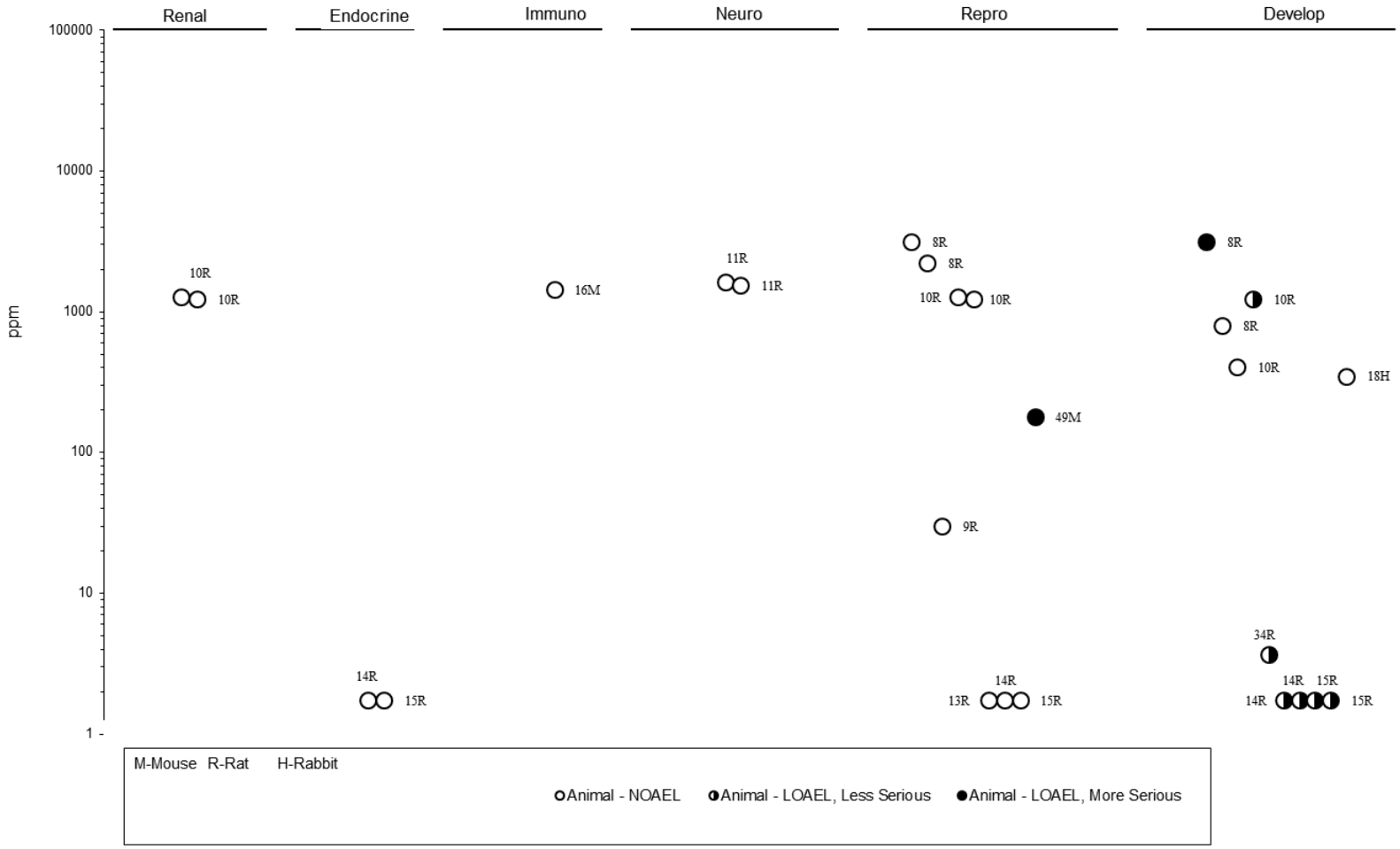


Figure 2-3. Levels of Significant Exposure to Glyphosate Technical – Oral
Chronic (≥365 days)

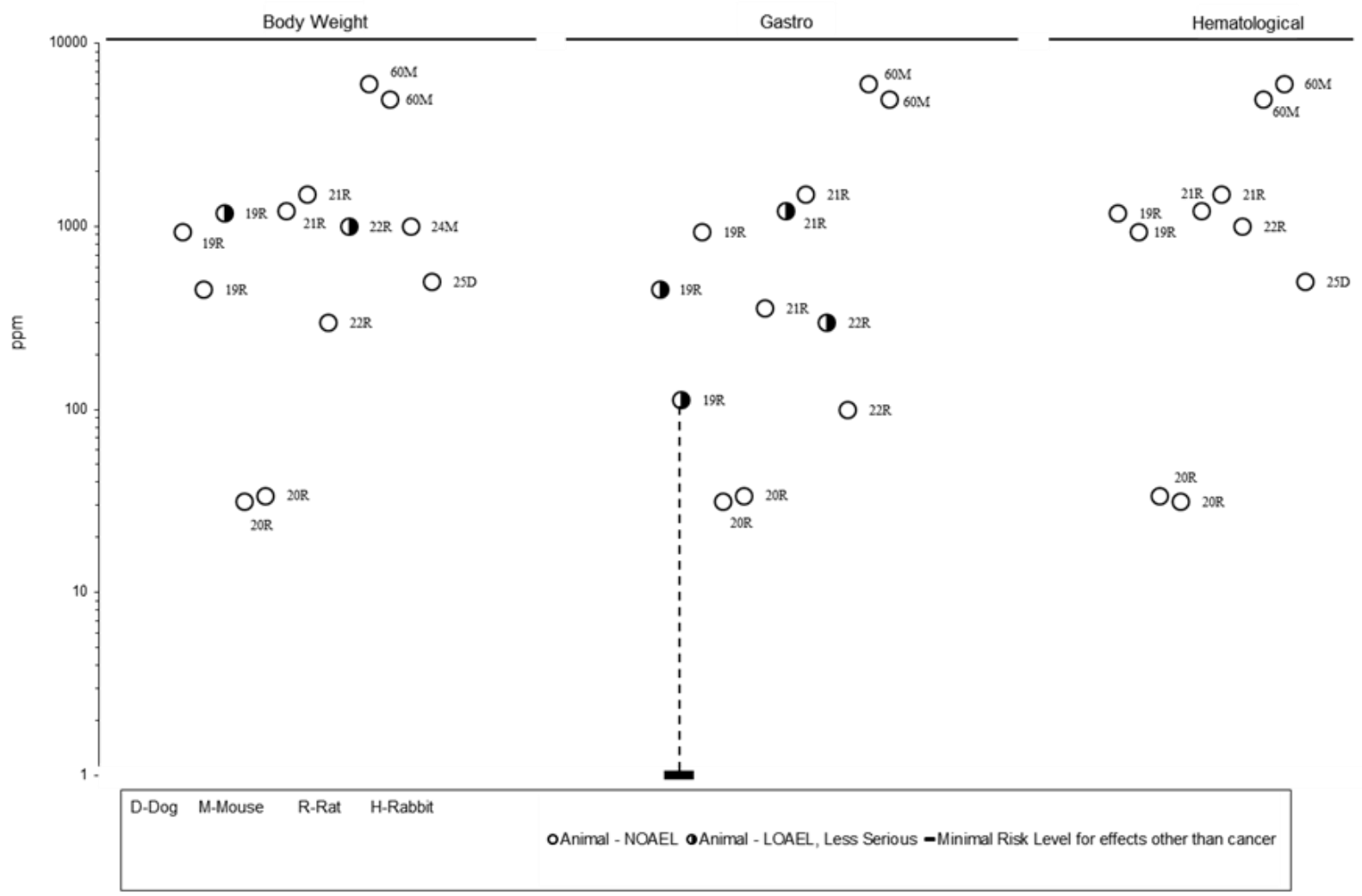


Figure 2-3. Levels of Significant Exposure to Glyphosate Technical – Oral
Chronic (≥365 days)

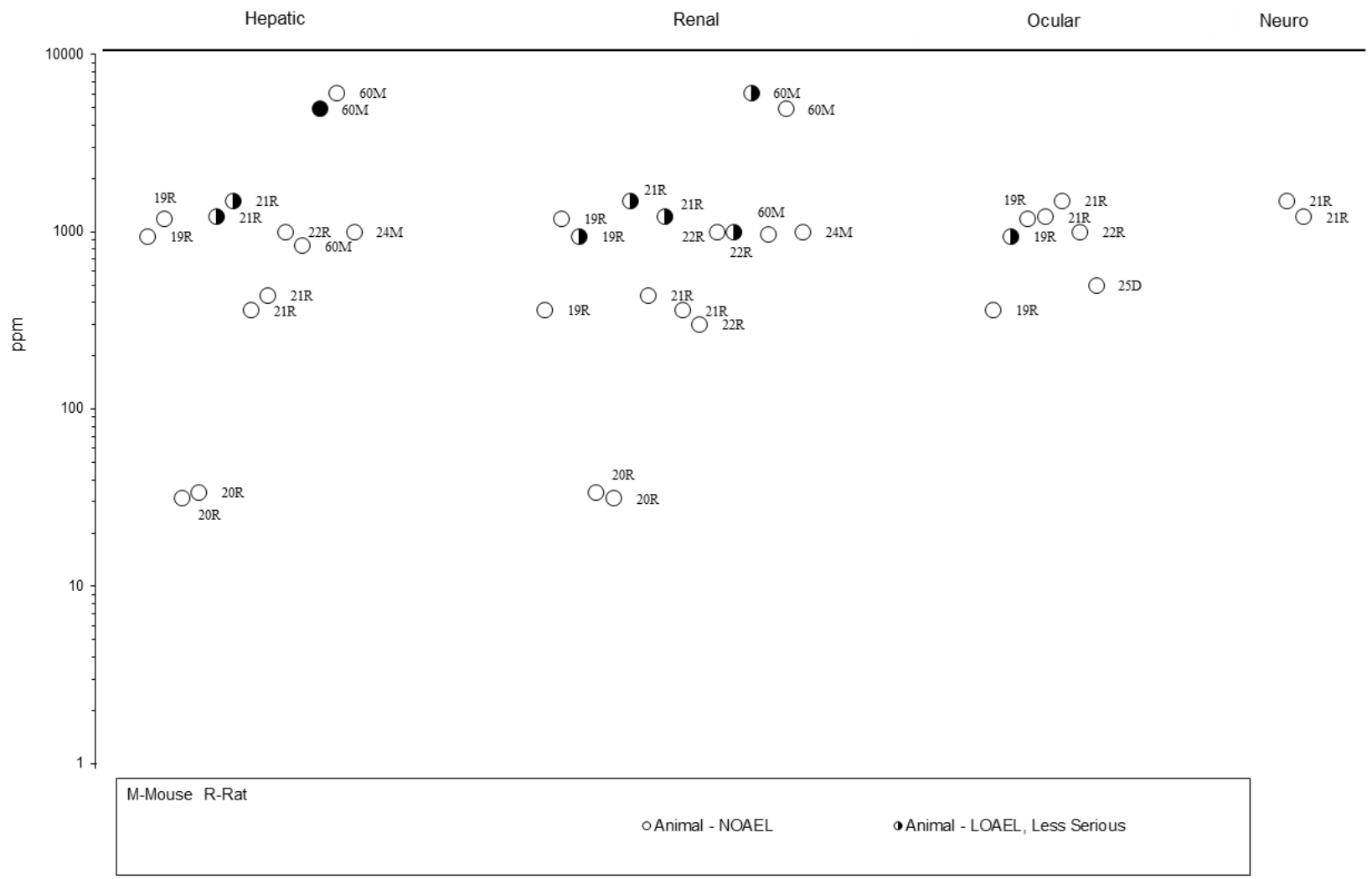


Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE								
RAT (Wistar) 15 F	GDs 6–15, 1 time/day (GW)	0, 500, 750, 1,000	BW, DX, FI, FX, GN, HP, LE, MX, OW, TG, WI	Death			1000 F	8/15 died
				Bd wt	1000 F			
				Develop		500		Increased incidence of fetal skeletal malformations
Dallegrave et al. 2003 – Glyphosate Formulation – Roundup® (Monsanto of Brazil; 360 g/L glyphosate, 18% w/v POEA)								
RAT (Wistar) 4 M	Once (GW)	0, 250, 500, 1,200, 2,500 mg/kg	HP, OF	Renal	48.7 M	487 M		Histopathologic kidney lesions.
Wunnapuk et al. 2014 – Glyphosate Formulation – Concentrate Roundup® Weedkiller (Monsanto Australia, containing 360 g/L of glyphosate)								
RAT (Wistar) 8M	Once (G)	0, 2,000 mg/kg	CS, GN, HP, LE, OW	Gastro			2000 M	Diarrhea in rats administered Roundup® (41% w/v glyphosate isopropylamine salt and 18% w/v polyoxyethyleneamine [POEA]) or glyphosate isopropylamine salt + POEA at the same concentrations as contained in the Roundup® formulation
Adam et al. 1997 – Glyphosate Formulation – Roundup® (41% w/v glyphosate isopropylamine salt and 18% POEA)								
RAT (Sprague-Dawley) 15 M	8 days (W)	0, 640	BW, OF, OW, WI	Repro		640 M		Up to 18% increased percent abnormal sperm morphology
Cassault-Meyer et al. 2014 – Glyphosate formulation – Roundup® Grand Travaux Plus (607 g/L glyphosate isopropylamine salt and adjuvants such as POEA)								

Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
RAT (Wistar) 5F	Day 1 to 7 of pregnancy (G)	0, 500	BI BW HP RX	Hepatic		500 F		significantly higher (19-23%) thiobarbituric acid reactive substances (TBARS) levels in liver tissue compared to control
				Neuro		500 F		16-26% decrease of glutathione
				Repro			500 F	lighter ovaries, decreased number of implanted sites (42% less than controls), reduced total number of corpus luteum (seen after Roundup exposure alone and co-exposures to multiple pesticides), increased percentage of pre-implantation loss
Almeida et al. 2017 – Glyphosate formulation – Roundup® (360 g/L of glyphosate (N-phosphonomethyl glycine))								
RAT Sprague-Dawley 10M	2 wk-once/d (W)	0, 25	HP BI	Endocr	25 M			
				Repro	25 M			
Johansson et al. 2018 – Glyphosate formulation – Glyfonova 450 Plus® (FMC Corporation, 450 g/L glyphosate acid equivalent)								
RAT 5M	14 d-once/d (NS)	0, 5, 10, 25, 50, 100, 250	HP BI BW	Bd wt			100 M	estimated decrease of 37%
				Hepatic		100 M		increased liver index and liver weight (approximately 17%), increased cytokine expression
Pandey et al. 2019 – Glyphosate formulation – Roundup® (Monsanto India, 41% w/w glyphosate)								
MOUSE (Swiss) 6M	Once (G)	0, 250, 500	BW NX	Bd wt	500 M			
				Neuro	500 M			
Ait Bali et al. 2017 – Glyphosate formulation – Roundup® (glyphosate concentration 360 g/L in the form of glyphosate isopropylamine salt 486 g/L)								

Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
MOUSE (Swiss) 6M	Once (G)	0, 250, 500	GN NX	Gastro	500 M			
				Neuro	500 M			
Aitbali et al. 2018 – Glyphosate formulation – Roundup® (glyphosate concentration 360 g/L in the form of glyphosate isopropylamine salt 486 g/L)								
MOUSE (Swiss) 6M	Once (G)	0, 250, 500	NX	Neuro			250 M	decrease in aversive memory performance
Ait Bali et al. 2019 – Glyphosate formulation – Roundup® (glyphosate concentration 360 g/L in the form of glyphosate isopropylamine salt 486 g/L)								
INTERMEDIATE EXPOSURE								
RAT (Wistar) 14 or 16 M	75 days, 1 time/2 days (GW)	0, 4.87, 48.7, 487	EA, OF	Hepatic	48.7 M	487 M		Increased serum liver enzyme activity, histopathologic liver lesions
Benedetti et al. 2004 – Glyphosate Formulation – Glyphosate-Biocarb® (360 g/L glyphosate and 18% w/v POEA)								
RAT (Wistar) NS	5 weeks, 1 time/day (GW)	0, 56, 560	BW, EA, FI, HE, HP, OF, OW, WI	Bd wt	560			
				Hepatic	560			
Caglar and Kolankaya 2008 – Glyphosate formulation – Roundup® (Monsanto of Brazil; 360 g/L glyphosate and 18% w/v POEA)								
RAT (Wistar) NS	13 weeks, 1 time/day (GW)	0, 56, 560	BW, EA, FI, HE, HP, OF, OW, WI	Bd wt	560			
				Hepatic	560			
Caglar and Kolankaya 2008 – Glyphosate Formulation – Roundup® (Monsanto of Brazil; 360 g/L glyphosate and 18% w/v POEA)								
RAT (Wistar) 15 F	42–44 days (gestation, lactation) (GW)	0, 50, 150, 450	BW, CS, DX, FX, HP, LE, MX, OW, TG	Bd wt	450 F			

Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
				Develop			50 M	Decreased sperm production, histopathologic testicular lesions
Dallegrave et al. 2007 – Glyphosate Formulation – Roundup® (Monsanto of Brazil; 360 g/L glyphosate and 18% w/v POEA)								
RAT (Wistar) 16-18 M	30 days, (PPDs 23–53) (GW)	0, 5, 50, 250	BW, DX, HP, OF, OW	Bd wt	250 M			
				Endocr		5 M		Decreased serum testosterone
				Develop		5 M		Decreased epithelial thickness and increased luminal diameter in seminiferous tubules
Romano et al. 2010 – Glyphosate Formulation – Roundup Transorb® (648 g/L isopropylamine salt of glyphosate and 594 g/L inerts)								
RAT (Wistar) 7M	daily 8 weeks (F)	0, 375	HP RX	Repro			375 M	significant decrease in abnormal sperm rate in both GLF exposed groups; increased testes MDA levels, decreased GSH levels; DNA damage in sperm cells; decreased sperm concentration and degeneration of Sertoli cells in testes
Avdatek et al. 2018 – Glyphosate formulation – Knockdown 48 SL (Hektaş company; glyphosate formulation not otherwise described)								
RAT (Wistar) 6 M,F	Continuously 120 days (NS)	0, 500	BC BI BW HP	Resp	500			
				Hepatic		500		increase in mean liver MDA levels, decrease SOD concentration, decrease CAT activity, and decreased enzymatic activity of GSH-Px compared to control; moderate hepatocytic degeneration and necrosis; increase in ALT, AST, and LDH in all exposed groups compared to control

Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Dar et al. 2019 – Glyphosate formulation – Roundup® (glyphosate 41% EC, not otherwise described)								
RAT (Wistar) 4F (F0), 16M (F1)	maternal exposure GD 5 to PND 21 then offspring exposed from PND 21 to 60 (W)	0, 70	BI BW CS GN HP NX	Neuro		70 M		23% inhibition of hippocampus cholinesterase after post-natal day 60; glutamate excitotoxicity, misregulation of cholinergic transmission, oxidative damage and astrocyte dysfunction in offspring hippocampus
				Develop		70 M		14% decreased body weight gain in offspring at day 60 compared to controls
Cattani et al. 2017 – Glyphosate formulation – Roundup Original® (360 g/L glyphosate, not otherwise described)								
RAT (Wistar) 6-12F	Daily 60 days (GW)	0, 126, 315	BI HP LX RX OW	Death			126 F	6/12 rats died
				Bd wt	315 F			
				Repro		126 F	315 F	38% decrease in relative ovary weight compared to control (58% decrease in the high-dose group); 109% increase in percent atretic follicles; 14% increased MDA levels in ovary homogenates; decreased enzymatic antioxidant activity in ovaries; necrosis, vacuolization of follicles and oocytes in ovaries
Hamdaoui et al. 2018 – Glyphosate formulation – Kalach 360 SL (KL) commercial formulation (Monsanto Europe, 360 g/L glyphosate, 41.5% isopropylamine salt of n-phosphonomethylglycine, 15.5% surfactant and 43% water)								

Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
RAT (Wistar) 5-10M, 5-10F	GD 0 to weaning on PND 21 (maternal exposure) (W)	0, 100, 200	BI HP NX	Develop			100 F	impaired recognition memory, oxidative stress in whole brain, decrease in lipid peroxidation and enzyme activity alterations in female F1 offspring
				Develop		100 M	200 M	SLOAEL: impaired recognition memory LOAEL: 23% inhibition of striatum acetylcholinesterase activity; oxidative stress in whole brain; enzyme activity alterations
Gallegos et al. 2018 – Glyphosate formulation – Glifloglex® (480 g/L glyphosate isopropylamine salt equivalent to 35.6% w/v of Gly acid with unspecified mix of inerts and adjuvants)								
RAT Wistar 10M	36 wk-once/d (GW)	0, 14.4, 375, 750	HP BC	Endocr		14.4 M		degeneration of pancreatic acinar cells and islets of Langerhans
Tizhe et al. 2018 – Glyphosate formulation – Bushfire® (360 g glyphosate/L)								
RAT Wistar F0 7F	GD 9 to LD 21-once/d (F)	0, 3.69, 352.20	RX DX BW	Bd wt	352.2 F			
				Repro	352.2 F			
Milesi et al. 2018 – Glyphosate formulation – MAGNUM SUPER II (Grupo Agros S.R.L., Argentina, 66.2% glyphosate potassium salt)								
RAT Wistar F1 20-25F	GD 9 to LD 21-once/d (F)	0, 3.69, 352.20	RX DX BW	Bd wt	352.2 F			
				Repro			3.69 F	increased rate of preimplantation loss (estimated 71% increase), fewer implantation sites in the uterus (not otherwise described)

Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
				Develop		3.69 F	352.2 F	LOAEL: 2% decrease in fetal length, 6% decrease in body weight, and an increased relative risk of small for gestational age F2 fetuses SLOAEL: increased fetal anomalies (conjoined fetuses and abnormal limbs)
Milesi et al. 2018 – Glyphosate formulation – MAGNUM SUPER II (Grupo Agros S.R.L., Argentina, 66.2% glyphosate potassium salt, equivalent to 54% w/v of glyphosate acid)								
RAT Albino 8M	12 wk-once/d (G)	0, 3.6, 50.4, 248.4	BC HP RX	Endocr		3.6 M		decrease in testosterone (about 13%), FSH (about 17%), and LH (about 14%), increase in prolactin (about 31%)
				Repro			3.6 M	testicular degeneration and increased sperm abnormalities
Owagboriaye et al. 2017 – Glyphosate formulation – Roundup® (Monsanto, Belgium, 360 g/L glyphosate)								
RAT Sprague-Dawley F0 8F	GD 6 to PND 120-once/d (W)	0, 1.75	RX GN BC HP BI BW	Bd wt	1.75 F			
				Repro	1.75 F			
Manservisi et al. 2019 – Glyphosate formulation – Roundup® Bioflow (360 g/L of glyphosate acid, 42.5% water, 16% surfactant)								
RAT Sprague-Dawley F1 8	GD 6 to PND 120-once/d, 6 wk-once/d (W)	0, 1.75	RX GN BC HP BI FI WI BW	Bd wt	1.75			
				Endocr	1.75			
				Repro	1.75 M			

Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
				Develop		1.75		increased anogenital distance at PND 4 in males; delayed first estrous in females
Manservisi et al. 2019 – Glyphosate formulation – Roundup® Bioflow (360 g/L of glyphosate acid, 42.5% water, 16% surfactant)								
RAT Sprague-Dawley F1 10	GD 6 to PND 120-once/d, 13 wk-once/d (W)	0, 1.75	RX GN BC HP BI FI WI	Bd wt	1.75			
				Endocr		1.75 F		increased serum TT hormone, decreased DHT/TT ratio, increased E2/TT ratio
				Endocr		1.75 M		decreased serum DHT hormones, increased plasma TSH hormones, decreased DHT/TT and fT/TT ratios
				Repro	1.75 F			
				Repro	1.75 M			
				Develop		1.75 M		increased anogenital distance at PND 4
Manservisi et al. 2019 – Glyphosate formulation – Roundup® Bioflow (360 g/L of glyphosate acid, 42.5% water, 16% surfactant)								
MOUSE (albino Swiss) 10 M, 10 F	15 days 1 time/day (GW)	0, 50, 500	BW, EA, HE, HP, OF	Bd wt			50	60–66% depressed mean body weight gain
				Hemato	50		500	Decreased red blood cells, hematocrit, hemoglobin; increased mean corpuscular volume, neutrophils
				Hepatic	500			
Jasper et al. 2012 – Glyphosate Formulation – Roundup® Original (41% glyphosate and 16% POEA								

Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
MOUSE (Swiss) 6M	Daily 6 weeks (G)	0, 250, 500	BW BC NX OW	Bd wt			250 M	significant reduced body weight gain (46%) after 40 days
				Resp	500 M			
				Hepatic			500 M	43% decrease in relative liver weight
				Renal	500 M			
				Neuro			250 M	decreased locomotor activity, increased anxiety-like behavior and anxiety index ($p<0.001$) compared to control, decreased grooming time
Ait Bali et al. 2017 – Glyphosate formulation – Roundup® (glyphosate concentration 360 g/L in the form of glyphosate isopropylamine salt 486 g/L)								
MOUSE (Swiss) 6M	Daily 6 weeks (G)	0, 250, 500	GN NX	Gastro		250 M		decrease in total bacterial count in gut ($p<0.001$) compared to control
				Neuro			250 M	increase in anxiety index ($p<0.001$)
Aitbali et al. 2018 – Glyphosate formulation – Roundup® (glyphosate concentration 360 g/L in the form of glyphosate isopropylamine salt 486 g/L)								
MOUSE (Swiss) 6M	Daily 6 weeks (G)	0, 250, 500	NX	Neuro			250 M	decreased recognition and aversive memory performance
Ait Bali et al. 2019 – Glyphosate formulation – Roundup® (glyphosate concentration 360 g/L in the form of glyphosate isopropylamine salt 486 g/L)								
MOUSE Kumming 8M	35 d-once/d (W)	0, 60, 180, 540	BW OW RX	Bd wt	540 M			

Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
				Repro	60 M		180 M	decreased sperm motility (estimated 10% decrease in rapid progressive sperm, estimated 13% increase in immotile sperm), increased sperm abnormality (estimated 8% increase in total sperm abnormality)
Jiang et al. 2018 – Glyphosate formulation – Roundup® (360 g/L glyphosate, 18% w/v POEA)								
MOUSE F0 C57B1/6 9-11F	GD 4 to PND 30-once/d (W)	0, 420	BW OW RX	Bd wt			420 F	17% decreased body weight and approximately 25% decreased body weight gain
				Renal	420 F			
				Endocr	420 F			
				Repro	420 F			
Teleken et al. 2019 – Glyphosate formulation – Roundup® Original (Monsanto, Brazil, not otherwise described)								
MOUSE F1 8-12M	GD 4 to PND 30-once/d (W)	0, 420	RX HP BI BW	Bd wt	420 M			
				Endocr		420 M		intratesticular testosterone content 195% higher than control mice, approximately 60% increase in plasma LH concentration, 111% increase in β-LH pituitary protein content

Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
				Repro		420 M		70% reduction of sperm in cauda epididymis, estimated 5% decreased epithelial height delayed testes descent
				Develop		420 M		
Teleken et al. 2019 – Glyphosate formulation – Roundup® Original (Monsanto, Brazil, not otherwise described)								
MOUSE (Swiss) 6M	Daily 12 weeks (G)	0, 250, 500	BW IX NX OW	Bd wt			250 M	significant reduced body weight gain (33%) after 90 days, decreased grooming time
				Resp			250 M	50% decrease in relative lung weight
				Hepatic			250 M	44% decrease in relative liver weight
				Renal			250 M	50% decrease in relative kidney weight
				Neuro			250 M	decreased locomotor activity, increased anxiety-like behavior and anxiety index ($p<0.001$) compared to control
Ait Bali et al. 2017 – Glyphosate formulation – Roundup® (glyphosate concentration 360 g/L in the form of glyphosate isopropylamine salt 486 g/L)								
MOUSE (Swiss) 6M	Daily 12 weeks (G)	0, 250, 500	GN NX	Gastro		250 M		decrease in total bacterial count in gut ($p<0.001$) compared to control
				Neuro			250 M	increase in anxiety index ($p<0.01$) and decreased grooming time ($p<0.001$) compared to controls
Aitbali et al. 2018 – Glyphosate formulation – Roundup® (glyphosate concentration 360 g/L in the form of glyphosate isopropylamine salt 486 g/L)								

Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
MOUSE (Swiss) 6M	Daily 12 weeks (G)	0, 250, 500	NX	Neuro			250 M	decreased recognition, working, and aversive memory performance; >60% decrease of whole brain acetylcholinesterase activity after 12 weeks

Ait Bali et al. 2019 – Glyphosate formulation – Roundup® (glyphosate concentration 360 g/L in the form of glyphosate isopropylamine salt 486 g/L)

[a] Purities reported in this table are the information provided by the study authors in the study methodologies regarding the chemical used in the experiments.

Bd Wt or BW = body weight; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EA = enzyme activity; Endocr = endocrine; F = female(s); FI = food intake; FX = fetal toxicity; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; GW = gavage in water vehicle; HE = hematology; Hemato = hematological; HP = histopathology; IT = intratracheal; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MX = maternal toxicity; NOAEL = no observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; POEA = polyoxyethyleneamine; PPD = post-parturition day; Repro = reproductive; TG = teratogenicity; W = water vehicle; WI = water intake

Table 2-4. Levels of Significant Exposure to Glyphosate Technical[a] – Dermal

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
INTERMEDIATE EXPOSURE								
Rabbit (New Zealand) 10 M, 10 F	21 days, 5 days/week, 6 hours/day	0, 100, 1,000, 5,000	BC, BW, CS, EA, FI, GN, HE, HP, LE, OW	Bd Wt	5,000			
				Hemato	5,000			
				Hepatic	5,000			
				Dermal	1,000	5,000		Very slight erythema and edema at application site

EPA 1992c – glyphosate technical, purity not specified

[a] Purities reported in this table are the information provided by the study authors in the study methodologies regarding the chemical used in the experiments.

BC = biochemistry; BW or Bd wt = body weight; CS = clinical signs; EA = enzyme activity; F = female(s); FI = food intake; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no observed-adverse-effect level; OW = organ weight

2.2 DEATH

Several case report series have reported deaths in individuals intentionally ingesting glyphosate products (Chen et al. 2009; Kim et al. 2014; Moon et al. 2018; Roberts et al. 2010; Sawada et al. 1988; Talbot et al. 1991; Tominack et al. 1991). The predominant cause of death was often shock (hypovolemic or cardiogenic), hypotension, and respiratory failure, often due to aspiration (Chen et al. 2009; Kim et al. 2014; Moon et al. 2018; Talbot et al. 1991). Among 107 patients who ingested glyphosate isopropylamine salt, eleven fatalities were reported (10.3% rate) while none were observed in the glyphosate ammonium salt group, for which there were 40 patients (Moon et al. 2018). A retrospective cohort study reported that 14 of 150 patients with glyphosate surfactant herbicide poisoning died and that nonsurviving patients were statistically older compared to surviving patients (Cho et al. 2019).

An acute oral LD_{50} value of 4,320 mg/kg/day was reported following single oral dosing of rats with glyphosate technical (EPA 1992b). In a developmental toxicity study, 6/25 pregnant rats died during oral dosing of glyphosate technical at 3,500 mg/kg/day; there were no deaths during treatment at 1,000 mg/kg/day (EPA 1992e). No adequate sources were located regarding death in laboratory animals exposed to glyphosate technical by inhalation or dermal routes.

In a study of female Wistar rats exposed to 126 or 315 mg/kg/day of a glyphosate formulation for 60 days, 6/12 rats died (Hamdaoui et al. 2018). In a study that employed oral dosing of pregnant rats with Roundup®, 8/15 dams died during the first 8 days of treatment at 1,000 mg/kg/day glyphosate (Dallegrave et al. 2003). No deaths occurred in a 4-week study of rats intermittently exposed to Roundup® at exposure levels as high as 360 mg/m^3 (approximately 36 mg Roundup®/m^3) (EPA 1985c). No adequate sources were located regarding death in laboratory animals exposed to glyphosate formulations by the dermal route.

2.3 BODY WEIGHT

Oral exposure of rats to glyphosate technical at relatively high doses resulted in significant effects on body weight and/or body weight gain. Pregnant rats gavaged at 3,500 mg/kg/day during GDs 6–19 exhibited as much as 28.5% lower mean body weight gain than controls (EPA 1992e). Body weight gain was 12–18% less than that of controls in two generations of parental male and female rats exposed via the diet for 14–19 weeks at 2,219 or 3,134 mg/kg/day, respectively (EPA 1992a). No treatment-related effects on body weight were seen among young female mice treated for 28 days at estimated doses up to 1,447.5 mg/kg/day (EPA 2013b). In 13-week oral studies, body weight and/or body weight gain among

rats and mice at oral doses in the range of 2,273–11,977 mg/kg/day were 10–18% less than controls (NTP 1992). In a 2-year study, female rats dosed at 1,183 mg/kg/day exhibited 13% lower mean body weight than controls at treatment week 81 (EPA 1991a).

Evidence of treatment-related effects on body weight among laboratory animals receiving lower oral doses of glyphosate or glyphosate-based herbicides varied by study. Studies using doses of glyphosate technical at ≤1,000 mg/kg/day during acute-, intermediate-, or chronic-duration exposure found no effects on body weight (Baier et al. 2017; El-Shenawy 2009; EPA 1986a, 1987, 1991a, 1991b, 1992a, 1992d, 1992e, 1992f, 1992g, 2013a, 2013b, 2017b; Manservisi et al. 2019). In contrast, body weight changes were sometimes observed in lower dose oral studies using glyphosate formulations (Ait Bali et al. 2017; Almeida et al. 2017; Cattani et al. 2017; Hamdaoui 2018; Pandey et al. 2019; Teleken et al. 2019).

Several studies evaluated effects of oral exposure to glyphosate formulations on body weight. Limited results indicate that mice may be more sensitive than rats to body weight effects from repeated oral exposure to glyphosate formulations. In intermediate studies on male mice, significantly reduced body weight gain (>70%) occurred at 250 mg/kg/day after 6-12 week exposure (Ait Bali et al. 2017), and in offspring exposed in utero, during lactation and then orally from post-natal day 21 to 60 (14% less than controls) (Cattani et al. 2017). However, in another intermediate oral study, pregnant C57B1/6 mice showed a 17% decrease in body weight and an approximate 25% decrease in body weight gain, while their male offspring exposed in utero and during lactation did not have significantly different body weight or body weight gain when compared with controls (Teleken et al. 2019). Seriously-depressed mean body weight gain (60–66% less than controls) was reported for albino Swiss mice gavaged with Roundup Original® at 50 mg/kg/day for 15 days and approximately 10% body weight loss for mice dosed at 500 mg/kg/day (Jasper et al. 2012). When compared to controls, male rats orally exposed to a range of concentrations of Roundup® for two weeks showed an estimated 37% decrease in body weight when exposed to 100 mg/kg/day and an estimated 33% decrease in body weight when exposed to 250 mg/kg/day. Pregnant rats fed 500 mg/kg/day Roundup® via gavage for 7 days had 10% less body weight gain compared to controls, when exposed simultaneously with paraquat (Almeida et al. 2017). In rats, 8-10% less body weight gain was seen after exposure to 126 mg/kg/day in feed for 60 days (Hamdaoui 2018).

However, other studies found no effects of oral glyphosate exposure on body weight. No significant effects on body weight were observed among Wistar rats gavaged with Roundup® at 56 or 560 mg/kg/day for up to 13 weeks (Caglar and Kolankaya 2008), male mice orally exposed to Roundup® for

35 days (Jiang et al. 2018). pregnant Wistar rats gavaged with Roundup® at 1,000 mg/kg/day during GDs 6–15 (Dallegrave et al. 2003), or maternal Wistar rats gavaged with Roundup® at 50–450 mg/kg/day during gestation and lactation (Dallegrave et al. 2007). No effects on body weight were observed among male Wistar rats gavaged with Roundup Transorb® at 250 mg/kg/day during postnatal days (PNDs) 23–53 (Romano et al. 2010). After exposure to 1.75 mg/kg/day of glyphosate technical or Roundup® Bioflow during pregnancy and lactation, no weight changes were observed in Sprague-Dawley F0 females or their male offspring (Manservisi et al. 2019). At higher exposure levels to glyphosate formulations (3.69 mg/kg/d and 352.2 mg/kg/d) during pregnancy, F0 and F1 female Wistar rats showed no signs of glyphosate-associated weight changes (Milesi et al. 2018).

Non-oral exposure to glyphosate and glyphosate formulations was not associated with changes in body weight. No significant body weight effects occurred in a 4-week inhalation study of rats intermittently exposed to Roundup® at exposure levels as high as 360 mg/m^3 (approximately 36 mg Roundup®/m^3) (EPA 1985c). A study on male albino rats intraperitoneally exposed to 269.9 mg/kg/day of Roundup® for up to two weeks (El-Shenawy 2009) also found no changes in body weight, No significant treatment-related effects on body weight were observed among rabbits administered repeated dermal applications of glyphosate technical at doses in the range of 100–5,000 mg/kg/application for 21 days (EPA 1992c). When mice were acutely exposed subcutaneously to 2 mg/kg/bw, no effects on body weight were seen (Altamirano et al. 2018; Guerrero Schimpf et al. 2017; Guerrero Schimpf et al. 2018). No effects on body weight were seen in male mice after intranasal exposure to 50 mg/kg/day for 3 times a week for 4 weeks (Baier et al. 2017).

2.4 RESPIRATORY

As summarized in Table 2-5, several investigations of the Agricultural Health Study participants have examined the possible associations between use of glyphosate-containing products and increased risk of rhinitis, wheezing, atopic asthma, allergic asthma, or chronic bronchitis (Hoppin et al. 2002, 2006a, 2006b, 2007, 2008, 2009; Slager et al. 2009, 2010). No associations were found for diagnosed chronic bronchitis (Hoppin et al. 2007) or for wheezing after adjusting for confounding exposure to other pesticides (Hoppin et al. 2002, 2006a, 2006b). Current rhinitis was associated with glyphosate use among commercial applicators (Slager et al. 2009) and farmers (Slager et al. 2010), but no relationship between risk and the number of days of use per year was found among the commercial applicators (Slager et al. 2009). The relationship seen in commercial applicators was limited to applicators that also reported using 2,4-D. Applicators using 2,4-D or glyphosate alone did not show an increased risk of rhinitis (Slager et al.

2009). An association between glyphosate use and the risk of atopic asthma was found among farm women, but there was no association with nonatopic asthma (Hoppin et al. 2008). No associations were found between glyphosate use by male farmers and risk of allergic or nonallergic asthma (Hoppin et al. 2009). An association between glyphosate use and the risk of both allergic and nonallergic wheeze was found among male farmers, with an increase in risk for allergic wheeze with increasing days of use per year (Hoppin et al. 2017). It is noted that many of these studies did not account for use of other pesticides.

A study by Camacho and Mejia (2017) investigated the association between aerial applications of glyphosate in Colombia and health effects of individuals living in the sprayed areas. The association was assessed using individual medical record data and information about Colombia's aerial spraying program. Several health outcomes including respiratory illnesses was examined and a positive association was observed. For each additional square kilometer increase in area sprayed with glyphosate there was an increase in the proportion of respiratory diagnoses 7 to 15 days following exposure.

Respiratory failure or distress was reported in about 10–25% of the cases of intentional ingestion of glyphosate products (Lee et al. 2000; Moon and Chun 2010; Picetti et al. 2018; Tominack et al. 1991). Cho et al. (2019) found that the most common complication occurring in patients who had ingested glyphosate surfactant herbicide was acute respiratory distress syndrome.

Table 2-5. Noncancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study population	Exposure	Outcomes
Death		
Cho et al. 2019 Retrospective cohort study of 150 adults who presented with glyphosate poisoning at a Korean hospital between January 2006 and April 2017.	**Exposure:** ingestion of glyphosate-based herbicides **Multivariate logistic regression:** age, amount of glyphosate-based herbicide ingested, elapsed time since ingestion, qSOFA score	14/150 patients died (9.3% mortality), and age was determined to be a statistically significant factor (p<0.001). Higher qSOFA scores were associated with greater odds of death (OR:2.73, 95% CI: 1.41–5.76) and life-threatening complications (OR: 17.19, 95% CI: 6.25–72.65).
Respiratory		
Camacho and Mejia 2017 Cross-sectional study examining individual health records from the general public over a five-year period (2003 to 2007) merged with data of aerial spraying events. The study examined the data under several specifications: • Complete sample set: 39,766,259 observations • Municipalities with positive aerial spraying: 7,264,691 observations • Municipalities with non-immigrant population: 37,736,485 observations • High and low income municipalities: 20,131,375and 19,634,884 observations, respectively	**Exposure:** aerial spraying of glyphosate on coca crops and the general population living in the spray areas within study period 2003 to 2007 **Regression Adjustments:** age, age square, health regime, municipal tax income, population, area in square km, rurality index, average monthly rainfall, municipal spending on education and health, subsidized regime coverage, year and month dummy	Increased number of respiratory illnesses consistent across all specifications analyzed (only statistically significant p values were presented).
Hoppin et al. 2002 Cohort study of 20,468 participants in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** glyphosate ever use and application frequency categories **Logistic regression adjustments:** age, state, smoking history, asthma-atopy status	Wheeze, self-reported OR 1.05 (0.95–1.17), p=0.04 for trend of increasing exposure days
Hoppin et al. 2006a	**Exposure:** glyphosate ever use in the year prior to enrollment	Wheeze, self-reported OR 1.05 (0.94–1.17), farmers

Table 2-5. Noncancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study population	Exposure	Outcomes
Prospective cohort study of 20,175 participants in the Agricultural Health Study in Iowa and North Carolina (17,920 farmers and 2,255 commercial pesticide applicators)	**Logistic regression adjustments:** age, state, smoking history, BMI	OR 1.14 (0.83–1.57), applicators
Hoppin et al. 2006b Cohort study of 2,255 commercial pesticide applicators participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** glyphosate ever use in the year prior to enrollment **Logistic regression adjustments:** age, smoking status, asthma and atopy history, BMI	Wheeze, self-reported OR 1.38 (1.03–1.86) OR 1.14 (0.83–1.57), with adjustment for use of chlorimuron-ethyl pesticide
Hoppin et al. 2007 Prospective cohort study of 20,908 participants in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** glyphosate ever use **Logistic regression adjustments:** age, state, sex, smoking (pack-years)	Chronic bronchitis OR 0.99 (0.82–1.19)
Hoppin et al. 2008 Prospective cohort study of 25,814 farm women participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** glyphosate ever use **Logistic regression adjustments:** age, state, smoking status, “grew up on farm”	Atopic asthma OR 1.31 (1.02–1.67) Nonatopic asthma OR 1.13 (0.92–1.39)
Hoppin et al. 2009 Prospective cohort study of 19,704 male farmers participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** glyphosate ever use **Logistic regression adjustments:** age, state, smoking status, BMI	Allergic asthma OR 1.37 (0.86–2.17) Nonallergic asthma OR 1.15 (0.87–1.51)
Hoppin et al. 2017 Prospective cohort study of 22,134 male farmers participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** glyphosate ever use **Logistic regression adjustments:** age, BMI, state, smoking status, current	Allergic wheeze OR 1.56 (1.19–2.03), higher prevalence with increasing use days per year Nonallergic wheeze OR 1.24 (1.07–1.44)

Table 2-5. Noncancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study population	Exposure	Outcomes
	asthma, days applying pesticides, days driving diesel tractors	
Slager et al. 2009 Prospective cohort study of 2,245 commercial applicators participating in the Agricultural Health Study in Iowa	**Exposure:** any glyphosate use and application frequency categories during the past year **Logistic regression adjustments:** age, education, "growing up on farm"	Current rhinitis OR 1.32 (1.08–1.61), p=0.735 for trend for increasing use days per year
Slager et al. 2010 Prospective cohort study of 19,565 farmers participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any glyphosate use and application frequency categories during the past year **Logistic regression adjustments:** age; race; education; state; BMI; currently working on farm; years mixing pesticides, repairing engines or pesticide equipment, welding, painting, handling stored grain or hay, working in swine areas, working with hogs or other farm animals, butchering animals, and growing cabbage, Christmas trees, field corn, sweet corn, and hay	Current rhinitis OR 1.09 (1.05–1.13)
Cardiovascular Effects		
Dayton et al. 2010 Case control study of 168 cases of nonfatal myocardial infarction and 22,257 controls in women in Iowa and North Carolina participating in the Agricultural Health Study	**Exposure:** glyphosate ever use **Logistic regression adjustments:** age, BMI, smoking, state	Nonfatal myocardial infarction OR 0.8 (0.6–1.2)
Mills et al. 2009 Prospective study of male participants in the Agricultural Health Study in Iowa and North Carolina (n=54,069 for fatal myocardial infarction and 32,024 for nonfatal incidence)	**Exposure:** glyphosate ever use **Cox proportional regression adjustments:** age, state, smoking, BMI (nonfatal analysis only)	Fatal myocardial infarction HR 0.99 (0.80–1.23) Nonfatal myocardial infarction HR 1.10 (0.93–1.31)

Table 2-5. Noncancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study population	Exposure	Outcomes
Musculoskeletal Effects		
De Roos et al. 2005b Nested case control study of 135 cases of physician-confirmed rheumatoid arthritis and 675 controls participating in the Agricultural Health Study in Iowa and North Carolina (female participants only)	**Exposure:** glyphosate ever use **Logistic regression adjustments:** birth date, state	Rheumatoid arthritis OR 1.2 (0.8–1.8)
Parks et al. 2016 Nested case-control study of cases of physician-confirmed rheumatoid arthritis or self-reported use of disease modifying antirheumatic drugs and noncases participating in the Agricultural Health Study in Iowa and North Carolina (female spouses of licensed pesticide applicators only); enrolled between 1993 and 1997 and followed through 2010	**Exposure:** glyphosate ever use **Logistic regression adjustments:** age, state, pack-years smoking	Rheumatoid arthritis OR 1.2 (0.95–1.6); based on 100 prevalent cases OR 1.4 (1.0–2.0); based on 54 incident cases
Hepatic Effects		
Mills et al. 2019 Case-control study of 97 participants, 63 with nonalcoholic steatohepatitis (NASH) and 34 without NASH	**Exposure:** glyphosate and glyphosate residue measured from fasting urine; glyphosate residue (calculated) which estimates dietary intake and exposure to residues **Multivariable linear adjustments:** age, sex, body mass index	Glyphosate residue significantly higher in patients with NASH compared with patents without NASH (p=0.008) Significant dose-dependent increase of glyphosate exposure with increase in fibrosis stage when comparing patients without advanced fibrosis to those with Stage 2,3 or 4 fibrosis (glyphosate: 0.230 mg/L, SD: 0.19 vs. 0.351 mg/L, SD: 0.45; glyphosate residue: 0.525 mg/L, SD 0.38 vs. 0.938 mg/L, SD: 0.372,p <0.001). NASH cases confirmed through liver biopsy.
Dermal Effects		

Table 2-5. Noncancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study population	Exposure	Outcomes
Camacho and Mejia 2017 Cross-sectional study examining individual health records from the general public over a five-year period (2003 to 2007) merged with data of aerial spraying events. The study examined the data under several specifications: • Complete sample set: 39,766,259 observations • Municipalities with positive aerial spraying: 7,264,691 observations • Municipalities with non-immigrant population: 37,736,485 observations • High and low income municipalities: 20,131,275 and 19,634,884 observations, respectively	**Exposure:** aerial spraying of glyphosate on coca crops and the general population living in the spray areas within study period 2003 to 2007 **Regression Adjustments:** age, age square, health regime, municipal tax income, population, area in square km, rurality index, average monthly rainfall, municipal spending on education and health, subsidized regime coverage, year and month dummy	Increased number of dermatological illnesses consistent across all specifications analyzed (only statistically significant p values were presented).
Maibach 1986 Experimental study of 24 males and females	**Exposure:** 0.1 mL applied to intact and Draize-type abraded skin; patch removed after 24 hours	No skin irritation 24 or 48 hours after application to intact skin Irritancy scores 24 hours after application to abraded skin were negative in 10 subjects, equivocal in 4 subjects and erythema was noted in 10 subjects; at 48 hours, the scores were negative in 10 subjects, equivocal in 6 subjects, and erythema was noted in 8 subjects
Maibach 1986 Experimental study of 23 males and females	**Exposure:** 0.1 mL applied 5 days/week for 21 days	The average score was 1.4 where a score of 1 indicates erythema and 2 indicates erythema and induration; none of the subjects reported burning, stinging, or itching from the test compound
Maibach 1986 Experimental study of 204 males and females	**Exposure:** 0.2 mL applied 3 days/week for 3 weeks with patches remaining in	No skin irritation was observed

Table 2-5. Noncancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study population	Exposure	Outcomes
	place for 48–72 hours; a challenge patch was applied after a 2-week rest period	
Maibach 1986 Experimental study of 15 males and females	**Exposure:** Full-strength glyphosate was applied to skin stripped of the stratum corneum; the test site received irradiation with ultraviolet A and ultraviolet B light	No positive results for photoirritation or photosensitization were found
Ocular Effects		
Kirrane et al. 2005 Prospective study of 31,173 female spouses of commercial pesticide applicators participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** glyphosate ever use **Hierarchical regression adjustments:** age, state	Retinal degeneration OR 1.1 (0.8–1.5)
Endocrine Effects		
Goldner et al. 2010 Prospective study of 16,529 participants (female spouses only) in the Agricultural Health Study in Iowa and North Carolina Thyroid disease was self-reported as clinically diagnosed	**Exposure:** glyphosate ever use **Polytomous logistic regression adjustments:** age, education, smoking status, hormone replacement therapy, BMI	Hyperthyroid disease OR 0.98 (0.78–1.2) Hypothyroid disease OR 1.0 (0.91–1.2) Other thyroid disease OR 0.97 (0.81–1.2)
Kongtip et al. 2019 Cross sectional study of 195 conventional farmers and 222 organic farmers in Thailand. Sera were collected and analyzed for the following thyroid levels: TSH, T3, T4, FT3 and FT4	**Exposure:** glyphosate use, amount recorded in a diary **Generalized linear regression adjustments:** sex, current smoking, current alcohol use, insecticide use at home in the past year, triglyceride levels, and any stress symptoms in the past 2–4 weeks	Log(e) estimates of thyroid hormone levels predicted by models of glyphosate sprayed in past year Exp^{β} (95%CI): TSH: 0.992 (0.957–1.027) FT3: 1.002 (0.998–1.007) FT4: 0.999 (0.993–1.005) T3: 1.006 (0.999–1.012) T4: 1.007 (1.001–1.014)

Table 2-5. Noncancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study population	Exposure	Outcomes
		Increased use of glyphosate sprayed (measured in moles) was found to increase T4 levels.
Shrestha et al. 2018 Prospective study of 35,150 male and female pesticide applicators in the Agricultural Health Study in Iowa and North Carolina followed over 20 years Thyroid disease was self-reported as clinically diagnosed	**Exposure:** glyphosate ever use **Logistic regression adjustments:** sex, education, state of residence, smoking	Hypothyroid disease HR 1.28 (1.07–1.52), ever use HR 1.27 (1.03–1.56), >0–≤686 intensity-weighted days HR 1.38 (1.12–1.69), >686–≤2,604 intensity-weighted days HR 1.17 (0.94≤1.45), >2,604 intensity-weighted days
Neurological Effects		
Kamel et al. 2007 Case control study of cases of self-reported Parkinson's disease (n=83 prevalent cases and 78 incident cases) and controls (n=79,557 prevalent controls and 55,931 incident controls) participating in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** glyphosate ever use **Logistic regression adjustments:** age, state, type of participant	Parkinson's disease OR 1.0 (0.6–1.7), prevalent disease OR 1.1 (0.6–2.0), incident disease Prevalent disease defined as reporting Parkinson's disease at enrollment and incident disease defined as Parkinson's disease reported at the study follow-up
Zhang et al. 2018 A cross-sectional study of 218 farmers in China. Abnormalities of peripheral nerve conduction including nerve conduction velocity, distal motor latency, and amplitude were measured with a conventional nerve conduction assessment.	**Exposure:** glyphosate agriculture use **Logistic regression adjustments:** age, gender, smoking habit, alcohol consumption, whether adopting personal protective equipment, and whether suffering from diabetes mellitus	Abnormalities in nerve conduction velocity OR 0.70 (0.38-1.30), overall OR 1.34 (0.30-6.03), motor OR 0.64 (0.35-1.18), sensory Abnormalities in nerve conduction distal motor latency OR 1.05 (0.81-1.37) Abnormalities in nerve conduction amplitude OR 1.21 (0.75-1.97)
Reproductive Effects		
Camacho and Mejia 2017	**Exposure:** aerial spraying of glyphosate on coca crops and the general population	Increased number of miscarriages consistent across all specifications analyzed (only

Table 2-5. Noncancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study population	Exposure	Outcomes
Cross-sectional study examining individual health records from the general public over a five-year period (2003 to 2007) merged with data of aerial spraying events. The study examined the data under several specifications: • Complete sample set: 39,766,259 observations • Municipalities with positive aerial spraying: 7,264,691 observations • Municipalities with non-immigrant population: 37,736,485 observations • High- and low-income municipalities: 20,131,275 and 19,634,884 observations, respectively	living in the spray areas within study period 2003 to 2007 **Regression Adjustments:** age, age square, health regime, municipal tax income, population, area in square km, rurality index, average monthly rainfall, municipal spending on education and health, subsidized regime coverage, year and month dummy	statistically significant p values were presented).
Curtis et al. 1999 Retrospective cohort study of 2,012 planned pregnancies among participants in the Canadian Ontario Farm Family Health Study	**Exposure:** glyphosate use on the farm **Cox proportional hazard adjustments:** age when beginning to try to conceive, recent oral contraceptive use, men's and women's smoking, and use of other pesticides	Fecundability CFR 0.61 (0.30–1.26), pesticide use on the farm and women reported pesticide activities CFR 1.30 (1.07–1.56), pesticide use on the farm, but no pesticide activities reported by women
Developmental Effects		
Arbuckle et al. 2001 Retrospective cohort study of 2,110 female participants in the Canadian Ontario Farm Family Health Study	**Exposure:** glyphosate use during gestation **Logistic regression adjustments:** none	Spontaneous abortion, preconception exposure OR 1.4 (1.0–2.1), all gestational ages OR 1.1 (0.7–1.9), <12 weeks gestation OR 1.7 (1.0–2.9), >12 weeks gestation Spontaneous abortion, postconception exposure OR 1.1 (0.7–1.7), all gestational ages OR 0.8 (0.4–1.6), <12 weeks gestation OR 1.4 (0.8–2.5), >12 weeks gestation
Garcia et al. 1998	**Exposure:** paternal glyphosate use	Congenital malformations

Table 2-5. Noncancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study population	Exposure	Outcomes
Case control study of 261 cases of congenital malformations and 261 matched controls in Spain	**Conditional logistic regression adjustments:** paternal age and paternal job and maternal history of spontaneous abortion, twins, drug consumption, heavy smoking, education, occupation	OR 0.94 (0.37–2.34) for the acute risk period (during 3 months preceding conception or during the first trimester of pregnancy or both for the father and during 1 month preceding conception or during the first trimester of pregnancy or both for the mother)
Garry et al. 2002 Cross sectional study of 695 families and 1,532 children in Minnesota	**Exposure:** glyphosate ever use **Regression adjustments:** maternal age, smoking status, alcohol use, season of conception	ADD/ADHD, parent reported OR 3.6 (1.35–9.65)
Parvez et al. 2018 Birth-cohort study of 71 women with singleton pregnancies in Central Indiana	**Exposure:** maternal glyphosate levels in urine specimens **Nonparametric Spearman correlation adjustments:** maternal age, pre-pregnancy BMI, tobacco use, alcohol use, trimester of pregnancy	Shortened gestational length (r = -0.30, *p* = 0.01) Reduced birth weight (r = -0.14, *p* = 0.27) Head circumference (r = -0.06, *p* = 0.64)
Rull et al. 2006 Case control study of 731 cases of neural tube defects and 940 controls in California	**Exposure:** maternal residential proximity to glyphosate application (within 1,000 m) **Logistic regression adjustments:** maternal ethnicity, education, periconceptional smoking, vitamin use	Neural tube defects OR 1.5 (1.0–2.4) OR 1.5 (0.8–2.9) with adjustment for other pesticide exposure

Table 2-5. Noncancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study population	Exposure	Outcomes
Sathyanarayana et al. 2010 Prospective study of 2,246 women whose most recent singleton birth occurred within 5 years of enrollment in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** maternal glyphosate ever use (n=700) **Linear regression adjustments:** maternal BMI and height, parity, preterm status, state, maternal smoking during pregnancy	Multiple regression estimates of change in birth weight (g) in relation to maternal self-reported glyphosate use (coefficient = 4 g; 95% CI -40 to +48 g) indicate no significant association between birth weight and maternal use of glyphosate
Savitz et al. 1997 Retrospective cohort study of 1,898 couples participating in the Canadian Ontario Farm Family Health Study	**Exposure:** any paternal glyphosate use from 3 months prior to conception through the month of conception **Logistic regression adjustments:** maternal age, parity, maternal and paternal education, income, maternal and paternal off farm job, maternal smoking and alcohol use during pregnancy, conception to interview interval	Miscarriage OR 1.5 (0.8–2.7) Preterm delivery OR 2.4 (0.8–7.9) Small for gestational age OR 0.8 (0.2–2.3)
Other Noncancer Effects		
Montgomery et al. 2008 Prospective study of 33,457 participants (white males only) in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** glyphosate ever use **Logistic regression adjustments:** age, state, BMI	Diabetes incidence OR 0.85 (0.74–0.98)
Saldana et al. 2007 Prospective study of 11,273 participants in the Agricultural Health Study in Iowa and North Carolina	**Exposure:** any agricultural glyphosate exposure during the first trimester **Logistic regression adjustments:** BMI at enrollment, mother's age at pregnancy, parity, race, state, commonly used pesticides by women	Gestational diabetes mellitus OR 0.7 (0.2–1.75)

ADD/ADHD = attention deficit disorder/attention deficit hyperactivity disorder; BMI = body mass index; CFR = conditional fecundability ratio; CI = confidence interval; HR = hazard ratio; OR = odds ratio

Available data regarding respiratory effects in laboratory animals exposed to glyphosate are limited. In mice, a 50% decrease in relative lung weight was observed following exposure to 250 mg/kg/day for 12 weeks (Ait Bali et al. 2017). No other observations were made in the lungs. Kumar et al. (2014) reported an inflammatory respiratory response (evidenced by increased eosinophil and neutrophil counts, mast cell degranulation, and production of IL-33, TSLP, IL-13, and IL-5) in anesthetized mice exposed intranasally to glyphosate. Adam et al. (1997) designed a study to evaluate the effects of glyphosate technical (200 mg/kg), glyphosate + POEA (200 and 100 mg/kg, respectively), POEA alone (100 mg/kg), and Roundup® in rats evaluated for 24 hours following intratracheal instillation (Adam et al. 1997). Control rats received normal saline. Obvious clinical signs of adverse pulmonary effects and mortalities occurred in each group except the saline controls. The study authors stated that the pulmonary effects were more severe and lasted longer in rats treated with POEA alone or in combination with glyphosate compared to responses in glyphosate only-treated rats. These results suggest POEA was more acutely toxic than glyphosate to the lungs. No respiratory effects occurred in a 120-day study where rats were exposed to 250 mg/kg/day (Dar et al. 2019). No respiratory effects occurred in a 4-week study of rats intermittently exposed to Roundup® at exposure levels as high as 360 mg/m^3 (approximately 36 mg Roundup®/m^3) (EPA 1985c).

2.5 CARDIOVASCULAR

Two studies of Agricultural Health Study participants did not find associations between the use of glyphosate-containing products and the risk of myocardial infarctions (Dayton et al. 2010; Mills et al. 2009); see Table 2-5 for details. An association was found between using a glyphosate-based herbicide and vasculitic neuropathy in a 70 year old man who sprayed approximately 2,000 mL of the herbicide for several hours without using protective gear 4 months before presenting with symptoms (Kawagashira et al. 2017). In case series reports, abnormal electrocardiogram (EKG) readings have been found in patients ingesting large doses of glyphosate-containing products (Kim et al. 2014; Lee et al. 2000, 2008; Moon and Chun 2010; Moon et al. 2018; Talbot et al. 1991). The most commonly reported alterations included prolonged QTc interval and sinus tachycardia. In the most severe poisoning cases, hypotension and shock have been reported (Picetti et al. 2018; Roberts et al. 2010; Sawada et al. 1988; Tominack et al. 1991). Additionally, adverse cardiovascular events (myocardial injury, shock, ventricular dysrhythmia, or cardiac arrest) have been reported among patients who ingested glyphosate (Moon et al. 2018).

No data were available regarding evaluation of cardiovascular endpoints in laboratory animals exposed to glyphosate technical or glyphosate formulations by any exposure route.

2.6 GASTROINTESTINAL

Gastrointestinal symptoms are commonly reported in case series reports of patients who ingested glyphosate products. In numerous reports, over 40% of the patients reported nausea/vomiting (Eriguchi et al. 2019; Lee et al. 2000, 2008; Luo et al. 2019; Picetti et al. 2018; Roberts et al. 2010; Sawada et al. 1988; Tominack et al. 1991). Other effects reported included abdominal pain (Lee et al. 2000, 2008; Moon and Chun 2010; Roberts et al. 2010; Sawada et al. 1988; Talbot et al. 1991), sore throat (Lee et al. 2000; Tominack et al. 1991), poor appetite (Luo et al. 2019), and damage to mucosal tissue in the mouth and esophagus (Chang et al. 1999; Picetti et al. 2018; Sawada et al. 1988; Talbot et al. 1991; Tominack et al. 1991). One case study reported gastric ulcer and a large pyloric antrum ulcer (Luo et al. 2019). In a woman who accidentally ingested glyphosate-surfactant herbicide, a CT scan showed aspiration pneumonitis and ileus of the intestine (Ozaki et al. 2017).

Several studies evaluated effects of glyphosate technical oral exposure in laboratory animals. The most common effect was clinical signs of gastrointestinal disturbances. Such clinical signs are commonly observed in studies of laboratory animals receiving bolus gavage doses of test substances, in which cases the clinical signs may be at least partially the result of the method of gavage dosing. Diarrhea was observed among rats gavaged once with glyphosate technical at 2,000 mg/kg (EPA 2013c). Gastrointestinal disturbances (e.g., soft stool, diarrhea, few feces) were reported among pregnant rats gavaged at 3,500 mg/kg/day during GDs 6–19 (EPA 1992e) and pregnant rabbits gavaged at 350 mg/kg/day during GDs 6–27 (EPA 1992f) or 175 mg/kg/day during GDs 8–20 (EPA 2017b). A slight increase in observations of soft stool and/or diarrhea was noted in the rabbits dosed at 175 mg/kg/day during GDs 6–27 as well (EPA 1992f). Soft stools were observed in rats exposed via the diet for 2 generations at concentrations resulting in estimated doses in the range of 2,219–2,633 and 3,035–3,134 mg/kg/day for parental males and females, respectively (EPA 1992a). Mao et al. (2018) reported that glyphosate added to the drinking water of rat dams from GD 6 through lactation and to F1 offspring up to PND 125 at a concentration resulting in a daily dose of 1.75 mg/kg/day (the U.S. acceptable daily intake [ADI]) resulted in modifications to the gut microbiota in early development, particularly among prepubertal rats.

In a 2-year study of rats exposed via the diet (EPA 1991a, 1991b), inflammation of gastric squamous mucosa was observed in females at an estimated dose level of 457 mg/kg/day; there were no signs of gastrointestinal effects in males at estimated doses as high as 940 mg/kg/day. In another chronic-duration oral rat study (EPA 1992d), there were no signs of treatment-related gastrointestinal effects at the highest

estimated dose level (31.45–34.02 mg/kg/day). No clinical signs or histopathological evidence of treatment-related gastrointestinal effects were seen among male or female mice exposed via the diet for 24 months at estimated doses as high as 4,945 and 6,069 mg/kg/day, respectively (EPA 1985a, 2015a). Increased incidence of exocrine hyperplasia in the pancreas was reported for male rats receiving glyphosate technical from the diet for up to 2 years at an estimated dose of 1,214 mg/kg/day (EPA 2015c). Increased severity of cytoplasmic changes in salivary gland cells (basophilia and hypertrophy of acinar cells in parotid and submandibular salivary glands) was reported for male and female rats receiving glyphosate from the diet for 13 weeks at 410 and 421 mg/kg/day, respectively (NTP 1992) and other rats similarly treated at 300 mg/kg/day for up to 2 years (EPA 2015c). Similar effects on salivary glands were observed in male and female mice treated for 13 weeks at much higher doses (1,065 and 2,707 mg/kg/day, respectively; not observed at 507 and 753 mg/kg/day, respectively) (NTP 1992). Although salivary gland cytoplasmic changes were noted in rats at doses <300 mg/kg/day as well, the changes were reported to be only of minimal or mild severity; therefore, they are not considered adverse effects. The toxicological significance of the glyphosate treatment-related effects on salivary glands is uncertain.

Limited information was located regarding gastrointestinal effects in laboratory animals following oral exposure to glyphosate formulations. Rats exposed daily for 6-12 weeks to 250 mg/kg/day exhibited a decreased in total bacterial count in the gut (Aitbali et al. 2018). Lozano et al. (2018) reported significant differences in microbiome genomic diversity, characterized by an increase in the *Bacteroidetes* family S24-7 and a decrease in *Lactobacillaceae*, between treated female rats exposed to 5,000 ppm of Roundup for 673 days when compared to control males, control females, and treated males. The study found that Roundup had a direct selective bactericidal action on isolated gastrointestinal strains. In a study designed to evaluate the effects of glyphosate technical (2,000 mg/kg), rats were administered glyphosate + POEA (2,000 and 1,000 mg/kg, respectively), POEA alone (1,000 mg/kg), or Roundup® by gavage, followed by 24 hours of posttreatment observation (Adam et al. 1997). Control rats received normal saline. Two rats in the POEA-only treatment group died. Diarrhea was noted in all groups except the control group. The study authors stated that the groups given POEA or mixtures that included POEA experienced more rapid and severe diarrhea than those given glyphosate alone. These results suggest that POEA was more acutely toxic than glyphosate to the gastrointestinal system. Mao et al. (2018) reported that Roundup® added to the drinking water of rat dams from GD 6 through lactation and to F1 offspring up to PND 125 at a concentration designed to deliver a daily dose of 1.75 mg glyphosate/kg/day (the U.S. glyphosate ADI) resulted in modifications to the gut microbiota in early development, particularly among prepubertal rats.

2.7 HEMATOLOGICAL

After the accidental ingestion of 100 mL of glyphosate-surfactant herbicide a woman exhibited hypoxemia, hyperkalemia, hypotension, and hemoconcentration (Ozaki et al. 2017). Results from available animal studies do not implicate the hematological system as a sensitive target of glyphosate toxicity. There were no apparent treatment-related hematological effects in chronic-duration oral studies of rats, mice, or dogs administered glyphosate technical at oral doses as high as 940–1,183 mg/kg/day for rats (EPA 1991a, 1991b, 1992d), 4,945–6,069 mg/kg/day for mice (EPA 2015a), and 500 mg/kg/day for dogs (EPA 1986a, 1987). Rabbits administered repeated dermal applications of glyphosate technical at doses in the range of 100–5,000 mg/kg/application for 21 days exhibited no evidence of treatment-related hematological effects (EPA 1992c). Small changes in hematological parameters were seen in both male and female rats following dietary exposure to glyphosate technical in the 13-week NTP (1992) study. These were considered to be unremarkable and most likely due to mild dehydration.

Available information regarding hematological effects related to glyphosate formulations is limited. No hematological effects occurred in a 4-week study of rats intermittently exposed to Roundup® at exposure levels as high as 360 mg/m^3 (approximately 36 mg Roundup®/m^3) (EPA 1985c). Decreases in red blood cell count, hematocrit, and hemoglobin, and increases in corpuscular volume and neutrophil count were reported in mice gavaged with Monsanto Roundup® Original for 15 days at 500 mg/kg/day (Jasper et al. 2012).

2.8 MUSCULOSKELETAL

De Roos et al. (2005b) did not find an association between glyphosate use and the risk of rheumatoid arthritis among participants of the Agricultural Health Study. In a subsequent study of female spouses of licensed pesticide applicators, Parks et al. (2016) reported a weakly positive association between spousal use of glyphosate and risk of rheumatoid arthritis (based on incident cases). See Table 2-5 for additional study details.

No data were available regarding evaluation of musculoskeletal endpoints in laboratory animals exposed to glyphosate technical or glyphosate formulations by any exposure route.

2.9 HEPATIC

Human studies evaluating the relationship between glyphosate and hepatic endpoints is limited. One retrospective cohort study reported acute liver failure as a complication associated with organ injury (Cho et al. 2019). In a case-control study evaluating the association between glyphosate and patients with nonalcoholic steatohepatitis (NASH), Mills et al. (2019) reported significantly higher levels of glyphosate residue in NASH patients compared to non-NASH ($p=0.008$) patients. Furthermore, a dose-dependent increase of glyphosate exposure was observed with advanced stages of fibrosis (stage 2, 3 or 4). No other information was located regarding hepatic effects in humans exposed to glyphosate-containing products.

The potential for glyphosate technical to cause liver toxicity was evaluated in studies of rats and mice. In a 7-day study of pregnant rats, the liver had a 19-23% increase in thiobarbituric acid reactive substances (TBARS) levels in liver tissue compared to controls, following exposure to 500 mg/kg/day by oral gavage (Almeida et al. 2017). In rats orally administered glyphosate for 28-days up to 10 mg/kg bw/day, no treatment related findings were reported after gross necropsy. Further, no significant differences in liver weights were reported between glyphosate treated groups and the control (Milic et al. 2018). However, ROS levels in the liver were significantly increased at 10 mg/kg bw/day, while TBARS concentrations decreased at 0.5, 1.75 and 10 mg/kg bw/day compared to controls. GHS levels in liver decreased by 22.7% and 27% at 1.75 and 10 mg/kg bw/day concentrations, respectively (Milic et al. 2018). Similarly, GHS peroxidase (GSH-Px) activity in the liver was noticeably higher among rats exposed to 0.5, 1.75 and 10 mg/kg bw/day glyphosate compared to controls. Elevated levels of GSH-Px is reflective of glyphosate inducing the antioxidant defense system in the liver (Milic et al. 2018).

In a 13-week rat dietary study of glyphosate technical, increases in liver weight and serum ALT were observed in males at 1,678 mg/kg/day; increased liver weight and increased serum AP, ALT, and bile acids were noted in females at 3,393 mg/kg/day. There were no indications of treatment-related liver effects among male and female rats treated via the diet for 2 generations at estimated doses as high as 1,234–1,273 mg/kg/day (EPA 2013a) or other rats treated for 2 years to doses as high as 940–1,183 mg/kg/day (EPA 1991a, 1991b). Male mice exposed via the diet for 13 weeks at doses ≥2,273 mg/kg/day exhibited increased mean relative liver weight (4–9% greater than controls) in the absence of histopathologic liver lesions; there were no effects on liver weight in similarly-treated female mice at doses up to and including 11,977 mg/kg/day (NTP 1992). Male mice exposed via the diet for 2 years at an estimated dose of 4,945 mg/kg/day exhibited increased incidence of histopathologic central lobular hepatocyte necrosis; there was no evidence of treatment-related liver effects in similarly-treated female mice at an estimated dose of 6,069 mg/kg/day (EPA 2015a).

Following oral exposure to glyphosate (1.0 g/L in drinking water) for 72 weeks, wild type and multiple myeloma model mice (Vk*MYC strain) showed hepatic fibrosis and hematological abnormalities including decreases in hemoglobin levels (i.e. anemia); lower levels of platelet counts and hematocrit were observed in model multiple myeloma mice (Wang et al. 2019). This study was part of a larger effort to understand the effect of glyphosate on multiple myeloma development, which is discussed in Section 2.19.

Available information regarding hepatic endpoints in animals exposed to glyphosate formulations is limited. No hepatic effects occurred in a 4-week study of rats intermittently exposed to Roundup® at exposure levels as high as 360 mg/m^3 (approximately 36 mg Roundup®/m^3) (EPA 1985c). Increased serum ALT and aspartate aminotransferase (AST) activity and histopathologic liver lesions (increased Kupffer cells in hepatic sinusoids and deposition of reticulin fibers) were seen in male rats treated with Glyphosate-Biocarb® by gavage for 75 days (one dose every 2 days) at 487 mg/kg/dosing (Benedetti et al. 2004). In an acute oral exposure study, a significant increase in liver index, liver weight, and cytokine expression (IL-1β and TNF-α) was observed in male rats exposed to 100 or 250 mg/kg/day Roundup®. Lower doses of Roundup®, including exposure to 25 or 50 mg/kg/day, resulted in increased liver weight, higher numbers of liver macrophages, and changes in glycogen storage. However, these results were less consistent and did not adhere to a dose-response relationship (Pandey et al. 2019). Following a 120-day exposure to 500 mg/kg/day Roundup®, rats exhibited increased mean liver malondialdehyde levels, decreased superoxide dismutase concentration, catalase activity, increased alanine aminotransferase, aspartate amino transferase, lactate dehydrogenase and enzymatic activity of GSH-Px, moderate hepatocytic degeneration and necrosis (Dar et al. 2019). Following 6-12 weeks of daily exposure to ≥250 mg/kg/day of Roundup ®, mice showed a 44% decrease in relative liver weight, no other liver observations were made (Ait Bali et al. 2017).

Rabbits administered repeated dermal applications of glyphosate technical at doses in the range of 100–5,000 mg/kg/application for 21 days exhibited no evidence of treatment-related hepatic effects (EPA 1992c). However, male albino rats intraperitoneally exposed to 134.95 mg/kg/day glyphosate technical for up to two weeks showed significantly increased serum AST, ALT, and ALP, decreased serum GSH, increased hepatic nitric oxide, and increased hepatic lipid peroxidation, which the author attributed to impairment of liver enzymes and hepatic metabolism (El-Shenawy 2009).

Two-week intraperitoneal exposure of albino rats to 269.9 mg/kg/day Roundup® demonstrated the same liver effects as intraperitoneal exposure to 134.95 mg/kg/day glyphosate technical, including increased

serum AST, ALT, and ALP, decreased serum GSH, increased hepatic nitric oxide, and increased hepatic lipid peroxidation. Most of these observed effects were similar in both Roundup®-exposed and glyphosate-exposed rats. However, compared to controls, rats exposed to glyphosate technical showed a larger increase in hepatic nitric oxide than rats exposed to Roundup® (72% increase and 21% increase respectively). Conversely, the increase in hepatic lipid peroxidation compared to controls was much more pronounced in Roundup ®-exposed rats than in glyphosate-exposed rats (630% increase and 432% increase respectively) (El-Shenawy 2009).

In vivo metabolome and proteome profiling of liver obtained from rats chronically exposed to long-term exposure at low levels of Roundup® (4 ng/kg bw/day) for two years indicate effects to the liver including metabolite alterations associated with non-alcoholic fatty liver disease and steatohepatosis (Mesnage et al. 2017). Metabolome profiling, or the analysis of metabolites characterizing the range of chemical processes, analogous to chemical fingerprinting, revealed a lipotoxic condition, oxidative stress, and markers of hepatotoxicity in the liver (Mesnage et al. 2017). Results from the proteome analysis, which characterizes the expression of protein products and their interaction, reported rats exposed to Roundup ® had alterations reflective of peroxisomal proliferation, steatosis, and necrosis (Mesnage et al. 2017).

2.10 RENAL

Available human data regarding the possible association between exposure to glyphosate and risk of renal effects is limited to a few case-control studies, two case reports and one retrospective cohort study. One case-control study of patients with chronic kidney disease found an increased risk of chronic kidney disease among glyphosate applicators (Jayasumana et al. 2015). However, uncertainty regarding an association between exposure to glyphosate-containing products and risk of chronic kidney disease includes the finding that the applicators were also exposed to high levels of calcium, magnesium, barium, strontium, iron, titanium, and vanadium by drinking water from abandoned wells. In the case of a 55 year old man who ingested 200 mL of a glyphosate formulation, acute renal failure occurred (Picetti et al. 2018). Acute kidney injury and metabolic acidosis occurred in a woman who accidentally ingested glyphosate-surfactant herbicide (Ozaki et al. 2017). Acute kidney injury associated with glyphosate-based herbicide ingestion was also reported in a retrospective cohort study as a complication associated with organ injury (Cho et al. 2019).

Several studies evaluated possible renal toxicity in laboratory animals treated with glyphosate technical. In a 2-generation reproductive toxicity study (EPA 2013a), slightly increased absolute and relative kidney weights (7–11% greater than controls) were reported among F0 parental female rats dosed at

1,273 mg/kg/day; there was no evidence of histopathologic kidney lesions. Therefore, the slightly increased kidney weight was not considered to represent an adverse effect. During 2 years of dietary treatment of rats, urinalysis revealed increased specific gravity of urine and decreased urinary pH among males treated at an estimated dose of 940 mg/kg/day (NOAEL=362 mg/kg/day); there were no signs of treatment-related renal effects in urinalysis results from females treated at an estimated dose as high as 1,183 mg/kg/day (EPA 1991a, 1991b). Papillary necrosis (males and females) and decreased pH of urine (males only) were observed in a study of rats administered glyphosate in the diet for up to 2 years at estimated doses of 1,214 mg/kg/day (males) and 1,498 mg/kg/day (females); respective NOAELs were 361 and 437 mg/kg/day (EPA 2015c). Another 2-year rat study reported decreased pH of urine among males treated at 1,000 mg/kg/day (NOAEL=300 mg/kg/day); no renal effects were observed in females at doses as high as 1,000 mg/kg/day (EPA 2015c). Female mice treated for 2 years at an estimated dose of 6,069 mg/kg/day exhibited significantly increased incidence of renal proximal tubule epithelial basophilia and hypertrophy (NOAEL=968 mg/kg/day); there was no evidence of renal effects in similarly-treated male mice at doses as high as 4,945 mg/kg/day (EPA 2015a).

Shorter-term studies on rodents exposed to glyphosate technical found signs of potential renal damage. Myeloma model mice orally exposed to glyphosate (1.0 g/L in drinking water) for 72 weeks showed renal damage, including tubular obstruction by casts (Wang et al. 2019). This study was part of a larger effort to understand the effect of glyphosate on myeloma development, which is discussed in Section 2.19. In a two-week study albino rats exposed intraperitoneally to 134.95 mg/kg/day glyphosate showed serum changes indicative of potential kidney effects. Compared to control rats, glyphosate-exposed rats had 33.8% decreased serum creatinine, 110% increased serum urea, and 146% increased uric acid. Similar results were seen in the male rats exposed to 269.9 mg/kg/day Roundup® (El-Shenawy 2009).

Information regarding renal effects in animals exposed to glyphosate formulations is limited. A multigenerational study on reproductive effects measured F0 dam kidney weight and found no difference between controls and dams exposed to 420 mg/kg/day of Roundup® (Teleken et al. 2019). In mice, decreased relative kidney weight (50% less than controls) was reported after daily exposure to ≥250 mg/kg/day for 12 weeks (Ait Bali et al. 2017). No other kidney observations were made. No renal effects occurred in a 4-week study of rats intermittently exposed to Roundup® at exposure levels as high as 360 mg/m^3 (approximately 36 mg Roundup®/m^3) (EPA 1985c). Histopathologic kidney lesions (necrotic and apoptotic cells, localized primarily in tubular epithelium of the proximal straight tubule and thick ascending limb of the loop of Henle) were reported in male rats gavaged once with Concentrate

Roundup® Weedkiller at dose levels ranging from 250 to 2,500 mg/kg (Wunnapuk et al. 2014). There is some uncertainty regarding the role of glyphosate in the reported effects.

2.11 DERMAL

One woman developed skin lesions after accidental dermal exposure to glyphosate in an herbicide and was diagnosed with toxic hand dermatitis (Elsner et al. 2018). After treatment did not fully resolve the lesions, she was diagnosed with koebnerization of psoriasis caused by acute irritant contact dermatitis.

In another study, Camacho and Mejia (2017) evaluated the association between aerial applications of glyphosate in Colombia and health effects of individuals living in the sprayed areas. The association was assessed using individual medical record data and information about Colombia's aerial spraying program. Several health outcomes including dermatological effects. Their results observed that for each additional square kilometer increase in area sprayed with glyphosate there was an increase in the proportion of dermatological diagnoses 7 to 15 days following exposure.

One study evaluated the potential dermal toxicity of glyphosate in humans. In an experimental study (see Table 2-5), a single application of Roundup® to intact skin for 24 hours did not result in irritation (Maibach 1986). When applied to abraded skin, erythema was noted in 42% of the subjects after 24 hours. Mild skin irritation was observed in a repeated exposure test study (Maibach 1986). No skin irritation was observed in a Draize skin sensitization test or in a photosensitivity/photoirritation test (Maibach 1986).

Available information regarding dermal effects in animals is limited. Minor dermal irritation was reported in response to dermally-applied glyphosate technical. At the application site, very slight erythema and edema were observed in rabbits during 21 days of repeated dermal application of glyphosate technical at 5,000 mg/kg/application; no dermal effects were seen at doses ≤1,000 mg/kg/application (EPA 1992c). According to EPA (1993), glyphosate is considered a slight dermal irritant following acute dermal application.

2.12 OCULAR

In a study of wives of commercial pesticide applicators, no association was found between glyphosate use among the wives and retinal degeneration (Kirrane et al. 2005); see Table 2-5 for details. In a case series report of 1,513 ocular exposures to glyphosate, minor symptoms (primarily transient irritation) were

observed in 70% of the cases; most (99%) complained of eye pain (Acquavella et al. 1999). Moderate effects, such as persistent irritation or low-grade corneal burns or abrasions, were observed in about 2% of the cases. Among the cases with moderate effects, 93% reported eye pain, 20% reported lacrimation, and 27% reported blurred vision.

Two chronic-duration oral studies included ophthalmoscopic examinations of laboratory animals exposed to glyphosate technical. EPA (1991a, 1991b) reported significantly increased incidence of lens abnormalities in male rats treated via the diet for 2 years at an estimated dose of 940 mg/kg/day; there were no indications of a treatment-related ocular effect in female rats at the highest estimated dose level (1,183 mg/kg/day). No signs of treatment-related ocular effects were seen among dogs treated via capsule for 1 year at estimated doses as high as 500 mg/kg/day (EPA 1986a).

According to EPA (1993), glyphosate is considered mildly irritating to the eye following ocular instillation. According to FAO and WHO (2016), glyphosate was moderate to severely irritating to the rabbit eye. EFSA (2015) stated that glyphosate acid was a severe ocular irritant, but that salts of glyphosate do not require classification as ocular irritants. There were no signs of exposure-related effects in ophthalmologic examinations of rats intermittently exposed to Roundup® for 4 weeks at exposure levels as high as 360 mg/m^3 (approximately 36 mg Roundup®/m^3) (EPA 1985c).

2.13 ENDOCRINE

Available human information regarding possible associations between exposure to glyphosate or glyphosate-containing products and risk of endocrinological effects is limited to three studies with conflicting results. Goldner et al. (2010) reported no associations between any glyphosate exposure and the risks of thyroid diseases. Shrestha et al. (2018) found a significant association between ever-use of glyphosate and hypothyroidism (HR 1.28; 95CI 1.07–1.52). Kongtip et al. (2019) reported a positive association between increasing use of glyphosate and increased T4 thyroid hormone levels (1.007; 95%CI 1.001–1.014). These studies are summarized in Table 2-5.

In a weight-of-evidence approach to evaluate the potential for glyphosate to affect the endocrine system, EPA (2015b) subjected glyphosate to the Endocrine Disruptor Screening Program Tier 1 (a battery of *in vitro* assays designed assist in evaluation of the potential for a substance to interact with estrogen, androgen, or thyroid signaling pathways). EPA evaluated results from the battery of *in vitro* assays and relevant laboratory mammalian and wildlife studies. Using this approach, EPA determined that there is

no convincing evidence of potential interaction between glyphosate and estrogen, androgen, or thyroid pathways in mammals or wildlife. Included in the evaluation of the estrogen pathway were estrogen receptor (ER) binding assays, an ER transactivation assay, aromatase and steroidogenesis assays, a fish short-term reproduction assay, and mammalian and wildlife studies that assessed female reproductive parameters. Included in the evaluation of the androgen pathway were androgen receptor (AR) binding and steroidogenesis assays, a fish short-term reproduction assay, Hershberger and male pubertal assays, an AR transactivation assay, and mammalian and wildlife studies that assessed male reproductive parameters. Included in the evaluation of the thyroid pathway were male and female pubertal assays, an amphibian metamorphosis assay, and mammalian and wildlife studies that assessed thyroid parameters Refer to EPA (2015b) for study summaries and EPA (2015d) for DERs from most studies that contributed to EPA's conclusions regarding the potential for glyphosate to affect the endocrine system.

Limited information was located regarding the potential for glyphosate formulations to affect the endocrine system. While one study reported degeneration of pancreatic acinar cells and islets of Langerhans after male Wistar rats were exposed to 14.4, 375, or 750 mg/kg/day of the herbicide Bushfire via drinking water (Tizhe et al. 2018), most of the observed endocrine effects in glyphosate formulation animal studies involved changes in hormone levels. Romano et al. (2010) reported dose-related 30–50% decreased serum testosterone in young male rats gavaged with Roundup Transorb® at 5–250 mg/kg/day during postpartum days 23–53. Romano et al. (2012) implicated disruption of gonadotropin expression as a mechanism of action for glyphosate-induced effects on male rat sexual development. Pregnant C57B1/6 mice exposed to 420 mg/kg/day Roundup® in their drinking water showed no difference in pancreas weight compared to controls, but their male F1 offspring had 195% higher intratesticular testosterone, an estimated 60% increase in plasma LH, and a 11% increase in β-LH pituitary protein compared with male F1 controls (Teleken et al. 2019).

A multi-generational study of F0 Sprague-Dawley rats exposed to either 1.75 mg/kg/day glyphosate technical or Roundup Bioflow® found no evidence of endocrine organ lesions in F1 offspring for either exposure. However, exposure to Roundup Bioflow® was associated with changes in hormone ratios in F1 offspring when compared to controls. Specifically, after 13 weeks of exposure to Roundup Bioflow® in addition to exposure during gestation and lactation, female F1 rats had increased serum total testosterone (TT), decreased 5α-dihydrotestosterone (DHT)/TT ratios, and increased 17β-estradiol (E2)/TT ratios, while male F1 rats had decreased serum DHT and increased plasma thyroid stimulating hormone (TSH) (Manservisi et al. 2019). A 12-week study on male albino rats orally exposed to Roundup® also found changes in hormone levels (13% decrease in testosterone, 17% decrease in follicle stimulating hormone,

approximately 14% decrease in luteinizing hormone, and approximately 31% increase in prolactin) at doses as low as 3.6 mg/kg/day (Owagboriaye et al. 2017).

However, in an exposure study that exposed male Sprague-Dawley rats to either glyphosate technical (2.5 mg/kg/day or 25 mg/kg/day) or the glyphosate formulation Glyfonova (25 mg/kg/day) via their drinking water, no changes in intratesticular testosterone levels were observed. While the rats exposed to Glyfonova showed a statistically significant upregulation in P450 encoding genes in the testes, the authors concluded this was not indicative of endocrine effects (Johansson et al. 2018). Nevertheless, other studies reported changes in gene and protein expression attributed to glyphosate formulation exposures (Romano et al. 2012; Teleken et al. 2019; Varayoud et al. 2017).

2.14 IMMUNOLOGICAL

Studies examining possible associations between glyphosate exposure and asthma risk or rheumatoid arthritis risk are discussed in Sections 2.4 and 2.8, respectively.

Limited information is available regarding immunological effects. There was no evidence of treatment-related effects on spleen or thymus of mice administered glyphosate technical in the diet for 28 days at estimated doses as high as 1,447.5 mg/kg/day and no evidence of treatment-related effects on splenic anti-sheep red blood cell (SRBC) anti-body forming cell (AFC) responses to SRBC (EPA 2013b). EPA (1992d) reported significantly increased incidences of lymphocytic hyperplasia in the thymus from female rats administered glyphosate technical in the diet for up to 26 months at doses of 3.37, 11.22, and 34.02 mg/kg/day (13/32, 18/37, and 17/34, respectively, versus 5/25 controls). However, EPA (1992d) did not consider the lesion to be compound-related because the lesion occurs spontaneously in older rats and is quite variable in the thymus, there was no apparent effect on lymphocytes in the spleen (a much less variable indicator for lymphocytic hyperplasia), and the severity of the lesion was similar among controls and glyphosate-treated groups. Kumar et al. (2014) reported an inflammatory respiratory response (evidenced by increased eosinophil and neutrophil counts, mast cell degranulation, and production of interleukin-33, thymic stromal lymphopoietin, interleukin-13, and interleukin-5) in anesthetized mice exposed intranasally to glyphosate.

2.15 NEUROLOGICAL

Available information regarding possible associations between exposure to glyphosate-containing products and risk of neurological effects in humans is limited. One case-control study did not find an

association between glyphosate exposure and Parkinson's disease (see Table 2-5 for details) (Kamel et al. 2007). In a cross-sectional study conducted on farmers in China, Zhang et al. (2018) reported glyphosate use was not associated with increased odds or incidence rates of abnormalities of peripheral nerve conduction.

One case study found that a man who ingested 200 ml of glyphosate developed Parkinson's symptoms 4 years after exposure (Eriguchi et al. 2019). A spatial analysis of exposure to pesticides in Washington State found an association between glyphosate exposure and increased odds of premature mortality attributable to Parkinson's disease (OR = 1.33; 95% CI = 1.06-1.67) (Caballero et al. 2018).

Several animal studies in rats and mice have evaluated the neurological effects of glyphosate. Mice exposed once to 250 mg/kg/day RoundUp® via gavage showed a decrease in aversive memory performance (Ait Bali et al. 2019). However, no neurological effects were seen in mice given ≤500 mg/kg/day once by oral gavage (Ait Bali et al. 2017; Aitbali et al. 2018). At 6-12 weeks of daily exposure, mice showed behavioral changes in locomotor activity, increase of anxiety and depression-like behavior levels, decreased memory performance and decreased grooming time with 250 mg/kg/day RoundUp® exposure (Ait Bali et al. 2017; Ait Bali et al. 2019; Aitbali et al. 2018). The observed neurobehavioral changes were attributed to neurodevelopmental impairment as evidenced by a reduction in serotonin (5-HT) immunoreactivity following 6 or 12 weeks of oral exposure to 250 or 500 mg/kg/day RoundUp® and a reduction in tyrosine hydroxylase (TH) immunoreactivity following 12 weeks of exposure to 250 or 500 mg/kg/day RoundUp® (Ait Bali et al. 2017).

Ait Bali et al. (2019), measured acetylcholinesterase activity in rat whole brain, prefrontal cortex and hippocampus, which was inhibited at ≥250 mg/kg/day by >25%, >35%, >25%, respectively. Inhibition in all measured parts was dose-dependent (Ait Bali et al. 2019). In pregnant rats, glutathione was decreased by 16-26% following exposure to 500 mg/kg/day RoundUp® on days 1 to 7 of pregnancy (Almeida et al. 2017). In male offspring exposed in utero, during lactation then from post-natal day 21 to 60 to 70 mg/kg/day RoundUp®, there was a 23% inhibition of hippocampus cholinesterase after post-natal day 60 (Cattani et al. 2017). Oxidative damage, astrocyte dysfunction, glutamate excitotoxicity, and misregulation of cholinergic transmission were also seen (Cattani et al. 2017).

In rats treated via the diet for 13 weeks at doses as high as 1,547–1,631 mg/kg/day and in rats administered glyphosate technical once by gavage at up to 2,000 mg/kg, there was no evidence of treatment-related neurotoxicity seen by functional observational battery, motor activity testing, and gross

and histopathologic examination of brain and peripheral nervous tissue (EPA 2013c). However, clinical signs included decreased activity, subdued behavior, and hunched posture.

Glyphosate technical was observed to affect monoaminergic neurotransmitters in the central nervous system. In rats administered glyphosate orally up to 800 mg/kg bw/day for 6 days, serotonin neurotransmitter levels were significantly decreased in a dose dependent manner at 75, 150 and 800 mg/kg bw in various regions of the brain including the striatum, hippocampus, prefrontal cortex, hypothalamus and midbrain region (Martinez et al. 2018). Similarly, dopamine and norepinephrine levels were reported to decrease with increasing concentrations of glyphosate starting at 75 mg/kg bw/day. Turnover rates of the neurotransmitters were measured, and their metabolites were altered; there was a significant increase in turnover between serotonin and dopamine, and a decrease in turnover with norepinephrine (Martinez et al. 2018).

Rats orally exposed to 5 mg/kg/day of glyphosate or glyphosate-based formulation perinatally from day 9 gestation to day 22 post-natal were found to have increased expression of synaptophysin a marker of synaptic terminals in the hippocampus of both groups (Dechartres et al. 2017). Maternal behavior was also observed; at day 1 post-natal, dams were observed to spend less time licking and grooming offspring whereas between day 2 and 6 post-natal, more time was spent with offspring.

In vitro studies have also examined glyphosate and glyphosate-based herbicides for neurotoxicity. Glyphosate and an herbicide containing glyphosate isopropylamine as its active ingredient were tested *in vitro* at concentrations of 0.005% to 0.0005%. Although no effect was observed for pure glyphosate, glyphosate-based herbicides were reported to interfere with myelination and also as a demyelinating agent in a dose-dependent manner (Szepanowski et al. 2018). However, after testing for demyelination using glyphosate and isopropylamine additively (rather than as formulated), the authors note that this effect may be due to undisclosed additives. Neither glyphosate (pure) nor glyphosate-based herbicide were found to impair neurite development (Szepanowski et al. 2018).

2.16 REPRODUCTIVE

No association between glyphosate use and fecundability was found among women living at farms in which pesticides were used and were involved in pesticide activities (Curtis et al. 1999). This study also reported an association with improved fecundability when the women were not involved in pesticide activities; see Table 2-5 for additional information. Sanin et al. (2009) examined the fertility of women

living in regions of Columbia with varying agricultural usage of glyphosate. Although time to pregnancy varied widely by region, no significant associations were found with level of glyphosate usage.

In another study, Camacho and Mejia (2017) evaluated the association between aerial applications of glyphosate in Colombia and miscarriages by women living in the sprayed areas. Their results observed a positive association. For each additional square kilometer increase in area sprayed with glyphosate there was an increase in the number of miscarriage diagnoses. However, the authors note the way miscarriage was defined in the study may overestimate the number of actual miscarriages. In the study, miscarriage was defined when a mother was observed to have attended a prenatal care visit, but a corresponding birth registry was not located after 10 months.

Rodent studies frequently reported reproductive effects in males. Increased incidence of prostatitis was reported among male rats receiving glyphosate technical from the diet for up to 2 years at estimated doses of ≥361 or 1,214 mg/kg/day (EPA 2015c). In male rats exposed to 375 mg/kg/day of glyphosate for 8 weeks, a significant decrease in abnormal sperm rate, increased testes malondialdehyde levels, decreased glutathione levels, DNA damage in sperm cells, decreased sperm concentration, and degeneration of Sertoli cells in testes were observed (Avdatek et al. 2018). Cassault-Meyer et al. (2014) reported increased abnormal sperm morphology in rats receiving Roundup® Grand Travaux Plus from the drinking water for 8 days at 640 mg/kg/day (the only dose level tested). Male F1 offspring of C57B1/6 mice exposed to 420 mg/kg/day Roundup® *in utero* through the end of lactation showed an estimated 5% decrease in epithelial height and a 70% reduction of sperm in the cauda epididymis (Teleken et al. 2019). Male Kumming mice exposed to 60, 180, or 540 mg/kg/day Roundup® showed no reproductive effects at the lowest dose, but had significantly decreased sperm motility and increased sperm abnormality at the higher two doses (Jiang et al. 2018). Two low dose studies using glyphosate and glyphosate-based herbicides with exposures ranging from 1.75 mg/kg/day to 25 mg/kg/day showed no effects on sperm parameters or evidence of lesions or degeneration (Johansson et al. 2018; Manservisi et al. 2019). However, male albino rats orally exposed to Roundup® for 12 weeks showed testicular degeneration and increased sperm abnormalities in doses as low as 3.6 mg/kg/day (Owagboriaye et al. 2017).

While most studies on male rodents showed reproductive effects, reproductive effects in female rodents exposed to glyphosate or glyphosate formations were not observed consistently. In female rats exposed to 126 mg/kg/day of a glyphosate-based herbicide for 60 days, relative ovary weight decreased by 38% compared to controls (Hamdaoui 2018). Additionally, there was a 109% increase in atretic follicles, 14% increase in malondialdehyde levels in ovary homogenates, decreased enzymatic antioxidant activity in

ovaries, necrosis, and vacuolization of follicles and oocytes in ovaries (Hamdaoui 2018). In pregnant rats acutely exposed, ovaries were lighter, implanted sites decreased by 42%, total number of corpus luteum were reduced, and pre-implantation loss increased following exposure to 500 mg/kg/day (Almeida et al. 2017). However, no reproductive effects were reported in pregnant female C57B1/6 mice orally exposed to 420 mg/kg/day (Teleken et al. 2019) or in female Wistar rats subcutaneously exposed to 0.5, 5, or 50 mg/kg/day of a glyphosate formulation (Varayoud et al. 2016).

In multi-generational studies on female rodents, reproductive effects varied by generation. While F0 female Wistar rats exposed to 1.75 mg/kg/day of Roundup® showed no signs of reproductive effects (no changes in gestational length, litter size, sex ratio, or mean live birth index), their female F1 offspring who were exposed postnatally for an additional 6 to 13 weeks had a significantly delayed first estrous (Manservisi et al. 2019). Similarly, F0 Wistar rats exposed via feed to 3.69 or 352.52 mg/kg/day of the glyphosate-based herbicide MAGNUM SUPER II did not show changes in litter size or length of gestation at either dose, but their female F1 offspring had an increased rate of preimplantation loss and fewer implantation sites at both doses of exposure (Milesi et al. 2018). There was no evidence of treatment-related reproductive effects among parental male or female rats administered glyphosate technical in the diet for 2 generations at estimated doses as high as 1,234–3,134 mg/kg/day (EPA 1992a, 2013a). See Section 2.17 for information regarding treatment-related effects on the reproductive system of male rats exposed to glyphosate formulations during *in utero* and/or postnatal development.

Anifandis et al. (2017) investigated the effects of direct exposure of human sperm samples to 1 mg/L Roundup® (corresponding to 0.36 mg/L of glyphosate) on mitochondrial integrity and motility. Results found that the percentage of sperm motility in Roundup-treated samples upon one hour of incubation was significantly lower than in controls; after three hours of incubation, the percentage of sperm motility in Roundup-treated samples was also significantly lower than in controls. Mitochondrial incorporation of CMX dye was reduced in sperm samples exposed to Roundup at the first hour of incubation, indicating mitochondrial dysfunction. Anifandis et al. (2018) also found that human sperm motility decreased more significantly in samples exposed to 0.36 mg/L of glyphosate than in control samples at the first hour of incubation. This study also found that sperm DNA fragmentation of glyphosate-treated samples was not significantly different than sperm DNA fragmentation in controls.

Zhang et al. 2019b evaluated *in vitro* the effect of glyphosate on the maturation of oocytes. Mouse oocytes were exposed up to 500 µM glyphosate for either 2 or 14 hours. Glyphosate was reported to reduce the rates of germinal vesicle breakdown (GVBD) and first polar body extrusion (PBE), which are

key events in oocyte maturation. Glyphosate was also observed to increase ROS levels, damage DNA, induce abnormal spindle morphology, and impair mitochondrial aggregation. Consequently, findings suggest glyphosate disrupts the development and maturation of oocytes by generating oxidative stress and inducing early apoptosis (Zhang et al. 2019b).

Vanlaeys et al. (2018) investigated the effects of various concentrations of glyphosate and glyphosate-based herbicide formulations on the immature mouse Sertoli cell line (TM4). During the first 24 hours of treatment, glyphosate at concentrations ranging from 10 ppm to an agricultural dilution 1000 times greater did not impact cell viability, while glyphosate-based formulations resulted in dose-dependent cell death. Glyphosate–based formulations also inhibited glutathione-S-transferase activity, but glyphosate alone did not. Additionally, glyphosate-based formulations induced accumulation of intracellular lipids. Both glyphosate and glyphosate-based formulations resulted in mitochondrial dysfunction signified by reduced Succinate dehydrogenase activity. The authors concluded that herbicide-induced mitochondrial function alterations are formulation-dependent. The study also assessed TM4 cell viability after acute or 24-hour exposure to Glyphogan formulants or Glyphogan, and results indicate that this mixture of compounds leads to rapid induction of cell mortality. Glyphogan formulants at sub-agricultural doses were able to rapidly penetrate and accumulate in cells.

2.17 DEVELOPMENTAL

Several epidemiology studies have examined possible associations between glyphosate use and developmental toxicity; these studies are summarized in Table 2-5. Given that only one study examined each endpoint and the lack of quantification of glyphosate exposure across studies, these results were not considered sufficient for drawing conclusions on the risk of developmental toxicity associated with glyphosate exposure in humans. Arbuckle et al. (2001) reported a positive association between maternal preconception exposure to glyphosate and increased risk of spontaneous abortion (miscarriage). Garry et al. (2002) reported a positive association between phosphonamino- herbicides (glyphosate, Roundup®) exposure and parent-reported attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD). No associations were found between paternal exposure and risk of miscarriages (Savitz et al. 1997), preterm delivery (Savitz et al. 1997), small for gestational age risk (Savitz et al. 1997), or congenital malformations (Garcia et al. 1998). Similarly, no associations were found between maternal glyphosate exposure and birth weight (Sathyanarayana et al. 2010; Parvez et al. 2018), neural tube defects (Rull et al. 2006), or head circumference (Parvez et al. 2018).

Developmental endpoints were evaluated in animals orally exposed to glyphosate technical. Depressed weight and increased incidence of unossified sternebrae were observed in fetuses from rat dams treated by gavage at 3,500 mg/kg/day during GDs 6–19 (EPA 1992e). This dose level resulted in maternal toxicity, thus the developmental effects noted may be secondary to the maternal effects. Increased incidence of kidney tubular dilation was reported for F3b male weanlings in a 3-generation study of glyphosate technical (98.7% purity) administered to male and female Sprague-Dawley rats in the diet at an estimated dose level of 30 mg/kg/day; the reported NOAEL was 10 mg/kg/day (EPA 1992g). However, there were no signs of treatment-related effects on kidneys of rat offspring in two subsequent 2-generation rat studies at dose levels up to 1,234 mg/kg/day (EPA 2013a) or 3,134 mg/kg/day (EPA 1992a). Therefore, the finding of increased incidence of kidney tubular dilation in the 3-generation rat study (EPA 1992g) was considered a spurious result rather than a glyphosate-induced adverse developmental effect. In one 2-generation oral rat study, exposure via the diet at an estimated dose level of 1,234 mg/kg/day resulted in delayed preputial separation in male pups (EPA 2013a). In the other 2-generation study, the highest dose level (3,134 mg/kg/day) resulted in up to 14–20% depressed pup body weight and/or body weight gain during the lactation period (EPA 1992a), though the authors state it is unclear if this effect is compound related or due to the ingestion of the treated diet. There were no apparent treatment-related developmental effects in a study of rabbits treated by gavage at up to 350 mg/kg/day glyphosate technical during GDs 6–27 (EPA 1992f). No developmental effects were seen in rat pups exposed to 2 mg/kg/day every 48 hours on post-natal day 1 to 7 (Guerrero Schimpf et al. 2017). Depressed mean fetal weight (8% less than controls) was noted in a study of pregnant rabbits administered glyphosate acid at 300 mg/kg/day during GDs 8–20 (EPA 2017b). However, on a per litter basis, there was no statistically significant difference between controls and glyphosate-treated groups. Therefore, the 300 mg/kg/day dose level is considered a NOAEL for fetal body weight. In a 3-generation study, female Sprague-Dawley rats were acutely exposed to 25 mg/kg/day of glyphosate technical during GDs 8-14 (Kubsad et al. 2019). Offspring in the F1 generation showed delays in puberty in males and decreases in weaning weights of both sexes. More serious effects were observed in the F2 and/or F3 generations: significant increases in testis disease, prostate disease, kidney disease, ovary disease, obesity, tumors and parturition abnormalities. Almost a third of F2 generation females (7/20) died during late gestation or experienced litter mortality, whereas neither of these abnormalities were observed in the 16 controls.

Pham et al. (2019) administered glyphosate or Roundup® 3 Plus at doses of 0.5, 5 or 50 mg/kg/day to pregnant rats from embryonic day 10.5 to 20 days postpartum. Male offspring were assessed for reproductive effects after sacrifice at 5 days, 20 days, 35 days, or 8 months old. Significant decreases in sperm counts were observed in males prenatally exposed to both formulations of glyphosate: 0.5

mg/kg/day of Roundup® and 5 mg/kg/day of glyphosate were associated with 89% and 84% reductions, respectively. Exposure to glyphosate technical was associated with decreased serum testosterone and altered testes morphology in rats sacrificed at 20 days old. Testosterone was also reduced in 8-month old rats exposed to Roundup®.

Developmental endpoints were evaluated in three open-literature studies that employed oral exposure to glyphosate formulations. The specific role of glyphosate in the reported results is uncertain. Dallegrave et al. (2003) observed an increased incidence of skeletal malformations in fetuses from rat dams gavaged with Roundup® at 500 mg/kg/day during GDs 6–15. Dallegrave et al. (2007) reported decreased sperm production and histopathologic testicular lesions in offspring of rat dams gavaged with Roundup® at 50 mg/kg/day during gestation and lactation. Romano et al. (2010) reported decreased epithelial thickness and increased luminal diameter in seminiferous tubules of male rat pups treated with Roundup Transorb® by gavage at 5 mg/kg/day on postpartum days 23–53 and delayed preputial separation at a dose level of 50 mg/kg/day. An additional study on C57B1/6 mice also documented developmental effects on the reproductive system when male F1 offspring exposed to 420 mg/kg/day Roundup® in utero through the end of lactation showed increased age at testes descent (Teleken et al. 2019).

Multi-generational rat studies using intermediate oral exposure to glyphosate-based herbicides found developmental effects of varying severity. When pregnant F0 Sprague-Dawley dams were exposed to 1.75 mg/kg/day Roundup® Bioflow in their drinking water from gestation day 6 to postnatal day 120, male and female offspring showed increased anogenital distance at postnatal day 4. Increased anogenital distance was also observed in offspring of F0 dams exposed to glyphosate technical, but, unlike Roundup® Bioflow exposure, glyphosate exposure was only associated with this effect in male offspring (Manservisi et al. 2019). When pregnant F0 Wistar dams fed paste with 3.69 or 352.2 mg/kg/day of the glyphosate-based herbicide MAGNUM SUPER II from gestation day 9 to lactation day 21, developmental effects were observed in F2 offspring. F1 females from the lower exposure group gave birth to offspring with a 2% decrease in fetal length, 6% decrease in body weight, and an increased risk of being small for gestational age (RR= 2.43, 91% CI: 1.66, 3.55) compared to controls. F1 females from the higher exposure group gave birth to offspring that showed increased fetal anomalies (conjoined fetuses and abnormal limbs) compared to controls, as well as the fetal growth effects found in the lower exposure group (Milesi et al. 2018).

In a study on rats exposed from gestation day 0 to post-natal day 21, exposure to a glyphosate formulation was associated with impaired neurological development. Impaired recognition memory, whole brain oxidative stress, decreased lipid peroxidation, and enzyme activity alterations were seen in female

offspring rats exposed to 100 mg/kg/day Glifloglex® (Gallegos et al. 2018). In male offspring, impaired memory was only seen at higher doses of 200 mg/kg/day. At 100 mg/kg/day, striatum acetylcholinesterase activity was inhibited by 23%, in addition to other effects seen in females at the same dose (Gallegos et al. 2018).

Chronic glyphosate exposure to pregnant mice at 0.5% glyphosate solution altered several biochemical indices related to liver status and metabolism in the offspring. Serum triglyceride levels increased in gestational day 19 fetuses and postnatal day 21 female offspring and total cholesterol was elevated in postnatal day 7 (males) and 21 (female) offspring. LDL levels were noticeably elevated in postnatal day 7 mice and in females, AST levels were significantly increased suggesting damage to the liver. Histological examination revealed clustering of monocytes, indicative of inflammation, in postnatal day 7 females and hepatic lipid droplets in hepatocytes of the offspring mice, with effects more pronounced in males (Ren et al. 2019). Overall, offspring mice exhibited hepatic steatosis and excessive lipid droplets formation within hepatocytes suggesting glyphosate alters lipid metabolism (Ren et al. 2019).
Other developmental endpoints evaluated include developmental neurotoxicity. Frank et al. (2017) conducted in vitro assays at concentrations ranging between 0.03 to 30 µM of glyphosate to examine whether it disrupts normal cortical development. Glyphosate was not found to exert neurodevelopmental toxicity *in vitro*.

2.18 OTHER NONCANCER

No associations were found between glyphosate exposure and increased risks of diabetes (Montgomery et al. 2008) or gestational diabetes (Saldana et al. 2007) in epidemiology studies (see Table 2-5). Metabolic acidosis (Kim et al. 2014; Lee et al. 2008; Moon and Chun 2010; Tominack et al. 1991), hyperkalemia (Kim et al. 2014; Lee et al. 2008; Moon and Chun 2010), and acute pancreatitis (Hsiao et al. 2008; Kim et al. 2014; Moon and Chun 2010) have been reported in case series of individuals ingesting glyphosate; metabolic acidosis was typically reported in >35% of the cases.

Hypothermia was reported among rats following single gavage dosing of glyphosate technical at 2,000 mg/kg (EPA 2013c).

2.19 CANCER

Meta-Analyses of Epidemiological Studies

Lymphohematopoietic Cancers. From 2014 to 2016, several meta-analyses were conducted for lymphohematopoietic cancers. The results of these analyses are presented in Table 2-6. The primary literature used in these meta-analyses is discussed later in this section.

Schinasi and Leon (2014) conducted a systematic review and meta-analysis of 21 pesticide active ingredients and chemical groups including glyphosate. The authors reported a positive association between glyphosate use and B-cell lymphoma based on two studies (meta-relative risk [RR] 2.0; 95% confidence interval [CI] 1.1–3.6) and a positive association between glyphosate use and non-Hodgkin's lymphoma (NHL) based on six studies (meta RR 1.5; 95% CI 1.1–2.0).

Chang and Delzell (2016) performed meta-analyses for NHL subtypes (diffuse large B-cell lymphoma, B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic leukemia [CLL/SLL], and hairy-cell leukemia), as well as other types of lymphohematopoietic cancers (leukemia, multiple myeloma, and Hodgkin's lymphoma). The authors reported a positive association between glyphosate use and the risk of NHL (meta RR 1.3; 95% CI 1.0–1.6; six studies), multiple myeloma (meta RR 1.4; 95% CI 1.0–1.9; four studies), and the NHL subtype B-cell lymphoma (meta RR 2.0; 95% CI 1.1–3.6; two studies). The authors concluded that associations were statistically null for Hodgkin's lymphoma (meta RR 1.1; 95% CI 0.7–1.6; two studies), leukemia (meta RR 1.0; 95% CI 0.6–1.5; three studies); and the NHL subtypes diffuse large B-cell lymphoma (meta RR 1.1; 95% CI 0.5–2.3; two studies), CLL/SLL (meta RR 1.3; 95% CI 0.2–10; two studies), follicular lymphoma (meta RR 1.7; 95% CI 0.7–3.9; two studies), and hairy cell leukemia (meta RR 2.5; 95% CI 0.9–7.3; two studies). Some of the RR CIs were wide, indicating uncertainty in the point estimate.

The IARC Working Group conducted a meta-analysis for NHL using the same six studies as Schinasi and Leon (2014) and Chang and Delzell (2016). The Working Group reanalyzed the data, but used the most fully adjusted risk estimates for the studies by Hardell et al. (2002) and Eriksson et al. (2008) and estimated a slightly lower meta-analysis relative risk (meta RR 1.3; 95% CI 1.03–1.65) (IARC 2017).

Zhang et al. (2019a) conducted a meta-analysis of the association between glyphosate exposure and NHL based on five case-control studies and the 2018 update of the Agricultural Health Study. The most highly exposed individuals had a 41% higher risk of NHL as compared to unexposed controls (meta RR 1.41; 95% CI 1.13–1.75).

Table 2-6. Summary of Meta-Analyses of Results from Studies Examining Possible Association Between Self-Reported Use of Glyphosate and Lymphohematopoietic Cancers

Outcome	Studies included in analysis	Number of participants	Number reporting glyphosate use	Meta-analysis[a] relative risk or hazard ratio (95% CI)	Reference
Non-Hodgkin's lymphoma	De Roos et al. 2003 De Roos 2005a Eriksson et al. 2008 Hardell et al. 2002 McDuffie et al. 2001 Orsi et al. 2009	650 cases/1,933 controls 54,315 1,163 cases/1,016 controls 515 cases/1,141 controls 517 cases/1,506 controls 244 cases/436 controls	36 cases/61 controls 71 cases 29 cases/18 controls 8 cases/8 controls 51 cases/133 controls 12 cases/24 controls	1.5 (1.1–2.0) I^2=32.7%	Schinasi and Leon 2014
Non-Hodgkin's lymphoma	De Roos et al. 2003 De Roos 2005a Eriksson et al. 2008 Hardell et al. 2002 McDuffie et al. 2001 Orsi et al. 2009	Not stated 54,315 910 cases/1,016 controls 404 cases/741 controls 517 cases/1,506 controls 244 cases/436 controls	Not stated Not stated 29 cases 8 cases 51 cases 12 cases	1.3 (1.03–1.65) I^2=0.0%, p=0.589 for heterogeneity	IARC 2017
Non-Hodgkin's lymphoma	De Roos et al. 2003 De Roos 2005a Eriksson et al. 2008 Hardell et al. 2002 McDuffie et al. 2001 Orsi et al. 2009	650 cases/1,933 controls 49,211 995 cases/1,016 controls 515 cases/1,141 controls 517 cases/1,506 controls 244 cases/436 controls	36 cases/61 controls 71 cases 29 cases/18 controls 8 cases/8 controls 51 cases/133 controls 12 cases/24 controls	1.3 (1.0–1.6) I^2=0.0%, p=0.84 for heterogeneity	Chang and Delzell 2016
Non-Hodgkin's lymphoma	Leveque-Morlais et al. 2015 Kristensen et al. 1996 Alavanja et al. 1996	127,282 137,821 51,167	Estimated 36% Estimated 38% Estimated 83%	mHR 0.95 (0.77–1.18) I^2=57.0%, p=0.10 for heterogeneity	Leon et al. 2019
Non-Hodgkin's lymphoma	McDuffie et al. 2001 Cantor et al. 1992 Hoar et al. 1986 Zahm et al. 1990	517 cases/1,506 controls 622 cases/1,245 controls 200 cases/1,005 controls 201 cases/725 controls		mOR 1.43 (1.11–1.83) I^2= not reported	Pahwa et al. 2019
Non-Hodgkin's lymphoma	Andreotti et al.2018 De Roos 2003 De Roos 2005a Eriksson et al. 2008 Hardell et al. 2002	54,251 650 cases/1,933 controls 54,315 910 cases/1,016 controls 515 cases/1,141 controls	Estimated 83% 36 cases Estimated 76% Estimated 2% 8 cases	1.41 (1.13–1.75) p=0.14 for heterogeneity	Zhang et al. 2019a

Table 2-6. Summary of Meta-Analyses of Results from Studies Examining Possible Association Between Self-Reported Use of Glyphosate and Lymphohematopoietic Cancers

Outcome	Studies included in analysis	Number of participants	Number reporting glyphosate use	Meta-analysis[a] relative risk or hazard ratio (95% CI)	Reference
	McDuffie et al. 2001	517 cases/1,506 controls	51 cases		
	Orsi et al. 2009	244 cases/435 controls	12 cases		
B-cell lymphoma	Cocco et al. 2013	2,348 cases/2,462 controls	4 cases/2 controls	2.0 (1.1–3.6)	Chang and Delzell 2016; Schinasi and Leon 2014
	Eriksson et al. 2008	1,163 cases/1,016 controls	Not stated	I^2=0.0%, p=0.58 for heterogeneity	
Leukemia	Brown et al. 1990	578 cases/1,245 controls	15 cases/49 controls	1.0 (0.6–1.5)	Chang and Delzell 2016
	De Roos et al. 2005a	49,211	43 cases	I^2=0.0%[a], p=0.92 for heterogeneity	
	Kaufman et al. 2009	180 cases/756 controls	1 case/3 controls		
Multiple myeloma	Brown et al. 1993	173 cases/650 controls	11 cases/40 controls	1.4 (1.0–1.9)	Chang and Delzell 2016
	De Roos et al. 2005a	19 cases	Not stated	I^2=0.0%, p=0.63 for heterogeneity	
	Kachuri et al. 2013	342 cases/1,357 controls	32 cases/131 controls		
	Orsi et al. 2009	56 cases/456 controls	5 cases/24 controls		
	Pahwa et al. 2012	32 cases/133 controls	Not stated		
	Sorahan 2015	40,719	24 cases		
Multiple myeloma	Leveque-Morlais et al. 2015	127,282	Estimated 36%	mHR 0.87 (0.66–1.15) I^2=0.0%, p=0.95 for heterogeneity	Leon et al. 2019
	Kristensen et al. 1996	137,821	Estimated 38%		
	Alavanja et al. 1996	51,167	Estimated 83%		
Hodgkin's lymphoma	Karunanayake et al. 2012	316 cases/1,506 controls	38 cases/133 controls	1.1 (0.7–1.6)	Chang and Delzell 2016
	Orsi et al. 2009	87 cases/496 controls	6 cases/24 controls	I^2=0.0%, p=0.36 for heterogeneity	
Diffuse large B-cell lymphoma	Eriksson et al. 2008	955 cases/1,016 controls	Not stated	1.1 (0.5–2.3)	Chang and Delzell 2016
	Orsi et al. 2009	456 controls	5 cases/24 controls	I^2=0.0%, p=0.79 for heterogeneity	
Diffuse large B-cell lymphoma	Leveque-Morlais et al. 2015	127,282	Estimated 36%	mHR 1.36 (1.00–1.82) I^2=0.0%, p=0.48 for heterogeneity	Leon et al. 2019
	Kristensen et al. 1996	137,821	Estimated 38%		
	Alavanja et al. 1996	51,167	Estimated 83%		

Table 2-6. Summary of Meta-Analyses of Results from Studies Examining Possible Association Between Self-Reported Use of Glyphosate and Lymphohematopoietic Cancers

Outcome	Studies included in analysis	Number of participants	Number reporting glyphosate use	Meta-analysis[a] relative risk or hazard ratio (95% CI)	Reference
Diffuse large B-cell lymphoma	McDuffie et al. 2001 Cantor et al. 1992 Hoar et al. 1986 Zahm et al. 1990	517 cases/1,506 controls 622 cases/1,245 controls 200 cases/1,005 controls 201 cases/725 controls	51 cases/133 controls 26 cases/49 controls Not stated Undetermined	mOR 1.60 (1.12–2.29) I^2 not reported; p=0.08 for heterogeneity	Pahwa et al. 2019
CLL/SLL	Eriksson et al. 2008 Orsi et al. 2009	955 cases/1,016 controls 456 controls	Not stated 2 cases/18 controls	1.3 (0.2–10) I^2=83.7%, p=0.01 for heterogeneity	Chang and Delzell 2016
CLL/SLL	Leveque-Morlais et al. 2015 Kristensen et al. 1996 Alavanja et al. 1996	127,282 137,821 51,167	Estimated 36% Estimated 38% Estimated 83%	mHR 0.92 (0.69–1.24) I^2=0.0%, p=0.38 for heterogeneity	Leon et al. 2019
CLL/SLL	McDuffie et al. 2001 Cantor et al. 1992 Hoar et al. 1986 Zahm et al. 1990	517 cases/1,506 controls 622 cases/1,245 controls 200 cases/1,005 controls 201 cases/725 controls	51 cases/133 controls 26 cases/49 controls Not stated Undetermined	mOR 1.77 (0.98–3.22) I^2 not reported; p=0.04 for heterogeneity	Pahwa et al. 2019
Follicular lymphoma	Eriksson et al. 2008 Orsi et al. 2009	955 cases/1,016 controls 456 controls	Not stated 3 cases/24 controls	1.7 (0.7–3.9) I^2=0.0%, p=0.73 for heterogeneity	Chang and Delzell 2016
Follicular lymphoma	Leveque-Morlais et al. 2015 Kristensen et al. 1996 Alavanja et al. 1996	127,282 137,821 51,167	Estimated 36% Estimated 38% Estimated 83%	mHR 0.79 (0.52–1.21) I^2=0.0%, p=0.56 for heterogeneity	Leon et al. 2019
Follicular lymphoma	McDuffie et al. 2001 Cantor et al. 1992 Hoar et al. 1986 Zahm et al. 1990	517 cases/1,506 controls 622 cases/1,245 controls 200 cases/1,005 controls 201 cases/725 controls	51 cases/133 controls 26 cases/49 controls Not stated Undetermined	mOR 1.00 (0.65–1.54) I^2 not reported; p=0.04 for heterogeneity	Pahwa et al. 2019
Hairy cell leukemia	Orsi et al. 2009 Nordstrom et al. 1998	456 controls 111 cases/400 controls	2 cases/18 controls 4 cases/5 controls	2.5 (0.9–7.3) I^2=0.0%, p=0.63 for heterogeneity	Chang and Delzell 2016

Table 2-6. Summary of Meta-Analyses of Results from Studies Examining Possible Association Between Self-Reported Use of Glyphosate and Lymphohematopoietic Cancers

Outcome	Studies included in analysis	Number of participants	Number reporting glyphosate use	Meta-analysis[a] relative risk or hazard ratio (95% CI)	Reference

[a]I^2 is a measure of total variance explained by study heterogeneity and measure of inconsistency in results; higher values indicate greater inconsistency.

CI = confidence interval; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma

Leon et al. (2019) performed meta-analyses for exposure to glyphosate with NHL, diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL), multiple myeloma, Hodgkin's lymphoma, and follicular lymphoma based on three cohort studies included in the AGRICOH consortium; this includes agricultural workers in France, Norway, and the US. Of these, a significant association was observed between diffuse B-cell lymphoma and glyphosate (meta hazard ratio [HR] 1.36; 95% CI 1.00–1.85; $I^2 = 0\%$). The authors concluded that associations were statistically null for NHL (meta HR 0.95' 95% CI: 0.77-1.18), multiple myeloma (meta HR 0.87; 95% CI: 0.66-1.15), CLL/SLL (meta HR 0.92; 95% CI: 0.69-1.24), and follicular lymphoma (meta HR 0.79;95% CI: 0.52-1.21). Findings for other cancer types are listed in Table 2-6.

Pahwa et al. (2019) conducted meta-analyses for exposure to glyphosate with NHL, diffuse large B-cell lymphoma, CLL/SLL, and follicular lymphoma based on four case-control studies in the US and Canada. The authors reported a positive association between glyphosate use and NHL (meta odds ratio [OR] 1.43; 95% CI: 1.11, 1.83) and diffuse large B-cell lymphoma (meta OR 1.60; 95% CI: 1.12-2.29). The authors concluded that associations were statistically null for CLL/SLL (meta OR 1.77; 95% CI: 0.98-3.22) and follicular lymphoma (meta OR 1.00; 95% CI: 0.65, 1.54).

Epidemiological Studies

A number of case-control and prospective cohort epidemiology studies have examined possible associations between use of glyphosate-containing compounds and increased cancer risks. Detailed overviews—including a description of the exposure metric used, the results, and the conclusions and limitations as reported by the study authors—are presented in Table 2-7 for solid tumor types and Table 2-8 for lymphohematopoietic cancers.

The majority of the studies examined individuals who were occupationally exposed to pesticides and used self-reported or proxy-reported (ever/never use of glyphosate-containing compounds) use as the marker of exposure. A few studies examined potential cancer risk among family members (i.e., wife and children) of pesticide applicators. The cohort studies utilized data on participants from the Agricultural Health Study, a prospective study of cancer and other health outcomes. The cohort consisted of >89,000 licensed pesticide applicators and their spouses (52,394 applicators and 32,345 spouses) who were recruited between 1993 and 1997 from Iowa and North Carolina. Study limitations included self-reported exposure information, few cases for many of the cancer subtypes, limited information regarding the timing and duration of exposure, and recall bias.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Andreotti et al. 2018 Prospective cohort study of 54,251 licensed pesticide applicators (97% white, 97% male) recruited between 1993 and 1997 in Iowa and North Carolina from the Agricultural Health Study to evaluate agricultural exposure to 50 pesticides (including glyphosate) and cancer incidence cases. 44,932 participants reported ever use of glyphosate, including 5,779 participants with incident cancer cases.	Exposure: Self-reported ever/never use of any glyphosate pesticides, lifetime days of glyphosate use (days per year x number of years), and intensity-weighted lifetime days (lifetime days x intensity score) at enrollment (1993–1997) or follow-up (1999–2005). Intensity-weighted lifetime days of glyphosate use was categorized into quartiles, tertiles, or the median, such that there were at least five exposed cases in each category. Outcome: Incident cancer diagnoses ascertained via linkage to cancer registries in Iowa (enrollment through 2013) and North Carolina (enrollment through 2012). Data analysis: Poisson regression Adjustments: Age, cigarette smoking status, alcohol drinks per month, family history of any cancer, state of recruitment, and the five pesticides (atrazine, alachlor, metolachlor, trifluralin, and 2,4-D). Confounders considered included BMI and pack-years of cigarettes smoked.	Oral cavity: Q4: RR 0.84 (0.48–1.46) p-trend: 0.54 Colon: Q4: RR 1.01 (0.74–1.38) p-trend: 1.00 Rectum: Q4: RR 0.84 (0.52–1.34) p-trend: 0.43 Pancreas: Q4: RR 1.06 (0.57–1.97) p-trend: 0.14 Lung: Q4: RR 1.00 (0.76–1.33) p-trend: 0.78 Melanoma: Q4: RR 1.17 (0.78–1.74) p-trend: 0.53 Prostate: Q4: RR 0.99 (0.86–1.13) p-trend: 0.89 Testicular: T3: RR 0.57 (0.20–1.67) p-trend: 0.07 Bladder: Q4: RR 1.26 (0.87–1.82) p-trend: 0.42	Conclusions: The authors observed no associations between glyphosate use and overall cancer risk or risk of cancer of the oral cavity, colon, rectum, pancreas, lung, skin, prostate, testes, bladder or kidney. Risk estimates were similar in magnitude between the unlagged and lagged (5 or 20 years) exposure analyses for all sites evaluated. Limitations: Some misclassification of exposure undoubtedly occurred; because many cancer sites were evaluated, there is the possibility that results were observed by chance, and should be interpreted with caution. However, 37% of the participants did not respond to follow-up, which may have resulted in an underestimation of glyphosate exposure though imputation procedures were used in an attempt to mitigate this issue.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
		Kidney: Q4: RR 1.03 (0.66–1.61) p-trend: 0.95	
De Roos et al. 2005a Prospective cohort study of 54,315 certified pesticide applicators (97% male, 97% Caucasian) in Iowa and North Carolina (Agricultural Health Study) to evaluate agricultural exposure to glyphosate and cancer incidence. Among 54,315 subjects included in age-adjusted analyses, 41,035 subjects reported exposure to glyphosate and 13,280 reported no exposure. Number cases (exposed percent) for different cancer sites: All cancers: 2,088 (73.0%) Lung: 204 (72.1%) Oral cavity: 59 (76.3%) Colon: 174 (75.3%) Rectum: 76 (77.6%) Pancreas: 38 (76.3%) Kidney: 63 (73.0%) Bladder: 79 (76.0%) Prostate: 825 (72.5%) Melanoma: 75 (84.0%)	Exposure: Self-reported never/ever use of glyphosate. Cumulative exposure days (CEDs): 1–20 (reference), 21–56, and 57–2,678 days. Intensity weighted exposure days (IWEDs) of 0.1–79.5 (reference), 79.6–337.1, and 337.2–18,241 units. Outcomes/endpoints: Cancer registry files in Iowa and North Carolina for case identification. Incident cases were identified from enrollment to 2001 (median follow-up time: 6.7 years). Data analysis: Poisson regression analyses for all cancers combined and 12 specific cancer sites (with at least 30 cases). Adjustments: Age at enrollment, education, pack-years of cigarette smoking, alcohol consumption, family history of cancer, state of residency, and co-exposure to 10 other pesticides (2,4-D, alachlor, atrazine, metolachlor, trifluralin, benomyl, maneb, paraquat, carbaryl, and diazinon).	All cancers: Ever used: RR 1.0 (0.9–1.2) CED T3: RR 1.0 (0.9–1.1) p-trend: 0.57 IWED T3: RR 0.9 (0.8–1.1) p-trend: 0.35 Lung: Ever used: RR 0.9 (0.6–1.3) CED T3: RR 0.7 (0.4–1.2) p-trend: 0.21 IWED T3: RR 0.6 (0.3–1.0) p-trend: 0.02 Oral cavity: Ever used: RR 1.0 (0.5–1.8) CED T3: RR 0.8 (0.4–1.7) p-trend: 0.66 IWED T3: RR 1.0 (0.5–2.3) p-trend: 0.95 Colon: Ever used: RR 1.4 (0.8–2.2) CED T3: RR 0.9 (0.4–1.7) p-trend: 0.54 IWED T3: RR 1.4 (0.8–2.5) p-trend: 0.10 Rectum: Ever used: RR 1.3 (0.7–2.3)	Conclusions: No association between glyphosate exposure and all cancer incidence or most of the specific cancer subtypes, including NHL. A small number of cases suggested a positive association between multiple myeloma and glyphosate exposure. Limitations: Self-reported exposure information, few cases for many of the cancer subtypes, most applicators were male, there is no information on timing of pesticide use in relation to disease.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
		CED T3: RR 1.1 (0.6–2.3) p-trend: 0.70 IWED T3: RR 0.9 (0.5–1.9) p-trend: 0.82 Pancreas: Ever used: RR 0.7 (0.3–2.0) CED T3: RR 1.3 (0.5–3.6) p-trend: 0.83 IWED T3: RR 0.5 (0.1–1.9) p-trend: 0.06 Kidney: Ever used: RR 1.6 (0.7–3.8) CED T3: RR 0.7 (0.3–1.6) p-trend: 0.34 IWED T3: RR 0.5 (0.2–1.0) p-trend: 0.15 Bladder: Ever used: RR 1.5 (0.7–3.2) CED T3: RR 1.2 (0.6–2.2) p-trend: 0.53 IWED T3: RR 0.8 (0.3–1.8) p-trend: 0.88 Prostate: Ever used: RR 1.1 (0.9–1.3) CED T3: RR 1.1 (0.9–1.3) p-trend: 0.69 IWED T3: RR 1.1 (0.9–1.3) p-trend: 0.60 Melanoma: Ever used: RR 1.6 (0.8–3.0)	

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
		CED T3: RR 0.9 (0.5–1.8) p-trend: 0.77 IWED T3: RR 0.7 (0.3–1.2) p-trend: 0.44	
Engel et al. 2005 Prospective cohort study of 30,454 wives (98% Caucasian) of private pesticide applicators (largely farmers) in Iowa and North Carolina (Agricultural Health Study) to evaluate breast cancer risk in relation to use of individual pesticides by the women themselves or by their husbands. Glyphosate analysis for wife's pesticide use among all wives in the cohort included 82 exposed and 227 unexposed cases (n= 309) and 10,016 exposed and 20,129 (n= 30,145) unexposed controls. Further analysis of husband's pesticide use among wives who reported never having used pesticides themselves included 109 "exposed" (husband used pesticide) and 43 "unexposed" cases and 9,304 "exposed" and 3,993 "unexposed" controls.	Exposure: Self-reported ever/never use of any glyphosate products at enrollment (1993–1997). Husband's information was used as a measure of possible indirect pesticide exposure for their wives. Outcomes/endpoints: Breast cancer incident cases identified through state cancer registries from enrollment to 2000 (mean follow-up period: 4.8 years). Data analysis: Poisson regression Adjustments: Age, race, and state of residence. Confounders considered included BMI, age at menarche, parity, age at first birth, menopausal status, age at menopause, family history of breast cancer, physical activity, smoking, alcohol consumption, fruit and vegetable consumption, and education.	Breast cancer: Wife's pesticide use among all wives in cohort: RR 0.9 (0.7–1.1) Husband's pesticide use among wives who never used pesticides: RR 1.3 (0.8–1.9)	Conclusions: No specific conclusion was given on glyphosate exposure and breast cancer. Limitations: Some associations may have occurred by chance, data on pesticide-specific exposure-response relations were only available for the husband, lack of information on how long each woman had been married to her current partner, limited power to assess associations for less commonly used pesticides, pesticide use was based on self-reporting.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Flower et al. 2004 Prospective and retrospective cohort study of 17,280 children (52% male, 96% Caucasian) of pesticide applicators in Iowa (Agricultural Health Study) to evaluate parental exposure to 50 pesticides (including glyphosate) and childhood cancer risk. Glyphosate analysis included 6,075 children (13 cases) with maternal use and 3,231 children (6 cases) with paternal use of glyphosate.	Exposure: Self-reported parental ever/never use of any glyphosate product by both applicators and spouses at enrollment (1993–1997). Outcomes/endpoints: Childhood cancer cases were both retrospectively and prospectively identified after parental enrollment through Iowa Cancer registries from 1975 to 1998. Data analysis: Multiple logistic regression. Adjustments: Child's age at parent's enrollment. Confounders considered included parental age at child's birth, child's sex, child's birth weight, history of parental smoking, paternal history of cancer, and maternal history of miscarriage.	Childhood cancers: Maternal use (ever): OR 0.61 (0.32–1.16) Paternal use (prenatal): OR 0.84 (0.35–2.34)	Conclusions: No significant associations were observed between maternal (or paternal) pesticide (including glyphosate) application, including increased frequency of application, and risk of childhood cancer risk. Limitations: Small number of cases limits statistical power, maternal use is limited by lack of data on timing of exposure in relation to child's birth, paternal prenatal use constitutes a broad window of exposure and not necessarily just prenatal.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Koutros et al. 2013a, 2013b Prospective cohort study of 54,412 certified pesticide applicators in Iowa and North Carolina (Agricultural Health Study) to evaluate agricultural exposure to 50 pesticides (including glyphosate) and prostate cancer risk. There were 1,962 incident prostate cancer cases, 919 of whom had aggressive prostate cancer. Glyphosate analysis included 1,464 exposed and 498 unexposed cases (n=1,962) and 42,420 exposed and 10,015 unexposed controls (n=52,435).	Exposure: Self-reported ever/never glyphosate use, lifetime days of glyphosate use (years of use x days/year used), intensity-weighted lifetime days of glyphosate use (lifetime days x exposure intensity) at enrollment (1993–1997). Exposure was categorized into non-exposed and quartiles exposure on the basis of the distribution of exposed cases. Outcomes/endpoints: Prostate cancer incidences determined through state cancer registries from enrollment to 2007. Data analysis: Poisson regression. Adjustments: Age at enrollment, race, state, family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity in the winter. Separate glyphosate analyses were conducted by disease aggressiveness and family history of prostate cancer (yes, no).	Cumulative lifetime exposure based on intensity-weighted days: Total prostate cancer: Q4: RR 0.99 (0.86–1.15) Aggressive prostate cancer: Q4: RR 0.94 (0.75–1.18) Total prostate cancer, no family history: Q4: RR 1.02 (0.86–1.21) p-trend: 0.27 Total prostate cancer, with family history: Q4: RR 0.95 (0.64–1.40) p-trend: 0.71	Conclusions: No significant association was found between any specific pesticide (including glyphosate) and risk of total prostate cancer. Limitations: Information on Gleason score of severity was missing for some and not standardized, which most likely led to an underestimation of advanced cases; use of take-home questionnaire could introduce selection bias and exposure misclassification; large number of pesticides investigated so cannot rule out the possibility that some findings may be due to chance.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Koutros et al. 2016 Prospective cohort study of 54,344 male pesticide applicators in Iowa and North Carolina (Agricultural Health Study) to evaluate agricultural exposure to 65 pesticides (including glyphosate) and bladder cancer risk (n=321 incident cases identified). Glyphosate analysis included 248 exposed and 73 unexposed cases (n=321) and 54,023 controls.	Exposure: Self-reported ever/never glyphosate use, lifetime days of glyphosate use (years of use x days/year used), intensity-weighted lifetime days of glyphosate use (lifetime days x exposure intensity) at enrollment (1993–1997). Outcomes/endpoints: Bladder cancer incidences determined through state-based cancer registries from enrollment through 2010 in North Carolina and 2011 in Iowa. Data analysis: Poisson regression. Adjustments: Age, race, state, cigarette smoking, and pipe smoking.	Bladder cancer: Ever use: RR 1.17 (0.78–1.77) Cumulative lifetime exposure based on intensity-weighted days: Overall Q4: RR 1.07 (0.73–1.56) p-trend: 0.99 Stratification by smoking status Never smoker: Q4: RR 1.93 (0.95–3.91) p-trend: 0.03 Former smoker: Q4: RR 1.00 (0.58–1.72) p-trend: 0.67 Current smoker: Q4: RR 0.58 (0.25–1.34) p-trend: 0.17	Conclusions: No specific conclusion given on glyphosate exposure and bladder cancer. Never smokers who were heavy users of the glyphosate had increased risk of bladder cancer. Limitations: Potential for exposure misclassification, findings may be due to chance, due to small number of cases.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Lee et al. 2007 Prospective cohort study of 56,813 certified pesticide applicators (97% male, 97% Caucasian) in Iowa and North Carolina (Agricultural Health Study) to evaluate agricultural exposure to 50 pesticides (including glyphosate) and colorectal cancer risk. Glyphosate analysis included 225 exposed and 67 unexposed for colorectal cancer cases (n=305), 151 exposed and 49 unexposed for colon cancer cases (n=212), and 74 exposed and 18 unexposed for rectal cancers (n=93).	Exposure: Self-reported ever use of any glyphosate pesticides at enrollment (1993–1997). Outcomes/endpoints: Colorectal cancer incidences determined through cancer registries from enrollment to 2002 (mean follow-up period: 7.3 years). Data analysis: Unconditional multivariate logistic regressions. Adjustments: Age, state of residence, smoking history, total pesticide application days to any pesticide. Confounders considered included BMI, race, license type, education level, aspirin intake, family history of colorectal cancer, physical activity, smoking, and intakes of meat, fruits, vegetables, and alcohol.	Colorectal cancer: OR 1.2 (0.9–1.6) Colon cancer: OR 1.0 (0.7–1.5) Rectal cancer: OR 1.6 (0.9–2.9)	Conclusions: No specific conclusion was given on glyphosate exposure and colorectal cancers. Limitations: Since the study examined risks for 50 pesticides, it is possible that some significant findings might occur by chance alone due to the multiple comparisons. Potential recall bias and thus exposure misclassification associated with subjects recalling pesticide use from many years ago.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Andreotti et al. 2009 Nested case-control study of 93 cases of pancreatic cancer (64 applicators and 29 spouses) and 82,503 controls (52,721 applicators and 29,782 spouses) from the Agricultural Health Study, conducted in Iowa and North Carolina, to evaluate the association of pancreatic cancer and use of 24 pesticides (including glyphosate). Glyphosate analysis included 55 exposed and 35 unexposed cases (n= 90) and 48,461 exposed and 31,282 unexposed controls (n= 79,743).	Exposure: Self-reported ever/never use of any glyphosate product for applicators and spouses and intensity-weighted lifetime exposure days for applicators at enrollment (1993–1997). Outcomes/endpoints: Pancreatic cancer incidences identified through state cancer registries from enrollment to 2004 (over 9 years of follow-up time). Data analysis: Unconditional logistic regression. Adjustments: Age, cigarette smoking, diabetes, and subject type for ever/never pesticide exposure (applicator versus spouse).	Pancreatic cancer: Ever/never among applicators and spouses: OR 1.1 (0.6–1.7) Intensity weighted pesticide exposure among applicators: Never: 1.0 (reference) ≤184: 1.9 (0.9–3.8) ≥185: 1.2 (0.6–2.6) p-trend: 0.85	Conclusions: No specific conclusion given on glyphosate exposure and pancreatic cancer. Limitations: There was a limited number of exposed cases and limited in generalizability due to predominantly white male study population.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Band et al. 2011 Case-control study on male cancer patients (96.8% Caucasian) in British Columbia, Canada, to evaluate exposure to 139 specific active compounds in pesticides (including glyphosate) and prostate cancer risk. Glyphosate analysis included 25 exposed and 1,128 unexposed cases (n=1,153) and 60 exposed and 3,939 age-matched internal controls (patients with cancer of other primary site) controls (n=3,999).	Exposure: Self-reported ever/never use of glyphosate pesticides from questionnaire. Agricultural job exposure matrix (JEM) was developed for farm workers in British Columbia for the period of 1950–1998. Outcomes/endpoints: Prostate cancer cases identified through British Columbia Cancer Registry for 1983–1990 and histologically confirmed. Data analysis: Conditional logistic regression on age-matched sets of cases and controls. Adjustments: Alcohol consumption, cigarette years, education level, p-years, and respondent. Confounders considered included marital status, smoking (age started smoking, average number of cigarettes, pipe or cigars smoked per day, total years smoked), and ethnicity.	Prostate cancer: OR 1.36 (0.83–2.25)	Conclusions: No specific conclusion given on glyphosate exposure and prostate cancer. JEM likely to result in non-differential misclassification and may underestimate the true association; thus, negative findings should be regarded as inconclusive. Limitations: Lack of information on familial history, potential for misclassification of exposure due to use of JEM, use of cancer controls may result in selection bias, statistically significant associations could have occurred by chance as a result of multiple comparisons since 142 active chemicals were examined.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Lee et al. 2004b Case control study of white men and women (ages ≥21 years) diagnosed with stomach adenocarcinoma (n=170) or esophagus adenocarcinoma (n=137) and 502 controls in eastern Nebraska to evaluate the risk of the stomach and esophageal adenocarcinomas associated with farming and agricultural use of 16 insecticides and 14 herbicides (including glyphosate). Glyphosate analysis included 12 cases of stomach cancer and 12 cases of esophageal cancer among farmers, and 46 controls compared to non-farmers (59 stomach cancer, 62 esophageal cancer cases and 184 controls). Controls were randomly selected from a group of controls interviewed in 1986–1987 for a previous population-based case-control study. Controls were frequency-matched by sex and age to the combined distribution of the stomach and esophagus cases.	Exposure: Self- or proxy-reported ever use of glyphosate pesticide at enrollment (1992–1994). Outcomes: Stomach and esophageal cancer cases were identified from the Nebraska Cancer Registry (1988–1990) or by review of discharge diagnosis and pathology records at 14 hospitals (1991–1993). Data analysis: Unconditional logistic regression. Adjustments: Age, sex. Confounders considered included BMI, smoking, alcohol consumption, educational level, family history of stomach or esophageal cancer, respondent type, dietary intake of vitamin A and C, b-cryptoxanthin, riboflavin, folate, zinc, dietary fiber, protein, and carbohydrate.	Stomach cancer: OR 0.8 (0.4–1.5) Esophageal cancer: OR 0.7 (0.3–1.4)	Conclusions: “No significant associations were found between specific agricultural pesticide exposures (including glyphosate) and the risk of stomach or esophageal adenocarcinomas among Nebraska farmers.” Limitations: Possible misclassification of pesticide exposure and generally small number of farmers exposed to some of the individual pesticides.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Lee et al. 2005 Case control study of 251 white men and women (ages ≥21 years) diagnosed with gliomas and 498 controls in eastern Nebraska (Nebraska Health Study II) to evaluate adult glioma associated with farming and agricultural use of 20 insecticides and 17 herbicides (including glyphosate). Glyphosate analysis (only conducted among male farmers) included 17 cases and 32 controls among farmers compared to non-farmers (49 cases and 112 controls). Among these, self-reported respondents included 4 cases/17 controls for glyphosate users and 20 cases/40 controls for reference non-farmers; proxy-reported respondents included 13 cases/15 controls for glyphosate users and 29 cases/ 72 controls for reference non-farmers. Controls were randomly selected from a group of controls interviewed in 1986–1987 for a previous population-based case-control study. Controls were frequency-matched by sex, age, and vital status to the combined distribution of the cases.	Exposure: Self- or proxy-reported ever use of glyphosate pesticide at enrollment (1992–1994). Outcomes: Incident primary adult glioma cases diagnosed between 1988 and 1993 were identified from the Nebraska Cancer Registry or from 11 hospitals. Data analysis: Unconditional logistic regression. Separate analyses by sex and respondent type (self- versus proxy-reported) were also conducted. Adjustments: Age, sex, and respondent type. Confounders considered included history of head injury, marital status, education level, alcohol consumption, medical history of diabetes mellitus, dietary intake of a- and b-carotene, and dietary fiber.	Glioma among male farmers: OR 1.5 (0.7–3.1), all reported glyphosate use OR 0.4 (0.1–1.6), self-reported glyphosate use OR 3.1 (1.2–8.2), proxy-reported glyphosate use	Conclusions: "Glioma risk was also significantly increased among men who used specific pesticides (including glyphosate) and pesticide chemical classes; however, the positive results were mostly limited to proxy respondents." Limitations: The major limitation was the large proportion of proxy respondents. Most of the associations observed were limited to proxy respondents.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Pahwa et al. 2011 Case control study of 357 soft tissue sarcoma cases and 1,506 controls in Canada (all males, ≥19 years of age) to investigate the putative associations of pesticides (including glyphosate) with soft-tissue sarcoma (STS). Glyphosate analysis included 36 exposed and 321 unexposed cases and 147 exposed and 1,359 unexposed controls. Potential controls were selected randomly within age constrains (±2 years) from provincial health records, comprehensive telephone lists, or voters' lists.	Exposure: Self-reported ever use of glyphosate herbicides collected through self-administered postal questionnaire and telephone interviews. Outcomes: STS cases (first diagnosed in 1991–1994) ascertained from provincial cancer registries, except in Quebec, where hospital ascertainment was used. Data analysis: Conditional logistic regression. Adjustments: Age, province of residence, medical history.	Soft tissue sarcoma: OR 0.93 (0.60–1.42), stratified by age group and province of residence OR 0.90 (0.58–1.40), adjusted for medical history and with strata for age group and province of residence	Conclusions: "No association between herbicides (individual compound or major chemical class) (including glyphosate) and STS." Limitations: Limitations common to epidemiological case-control studies.

Table 2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Yiin et al. 2012 Case control study of 798 cases of glioma and 1,175 controls (98% white, aged 18–80 years) in Iowa, Michigan, Minnesota, and Wisconsin (Upper Midwest Health Study) to investigate association between exposure to pesticides (including glyphosate) and risk of glioma in male and female participants. Pesticide use in non-farm jobs: Glyphosate analysis included 12 exposed and 786 unexposed cases and 147 exposed and 1,359 unexposed controls. Analysis included 8 exposed and 430 unexposed cases and 19 exposed and 1,122 unexposed controls excluding proxy respondents. House and garden pesticide use: Glyphosate analysis included 51 exposed and 747 unexposed cases and 76 exposed and 1,099 unexposed controls. Analysis included 28 exposed and 410 unexposed cases and 75 exposed and 1,066 unexposed controls excluding proxy respondents. Randomly-selected, population-based controls were frequency-matched within a state.	Exposure: Self- or proxy-reported ever/never use of glyphosate pesticide through 1992. Outcomes: Cases with a histologically confirmed primary intracranial glioma were identified through medical facilities, oncologists, neurosurgeons, and cancer registries (1995–1997). Data analysis: Unconditional logistic regression. Analyses were separately conducted with or without proxy respondents. Adjustments: Age, sex, education.	Glioma Non-farm job use: OR 0.83 (0.39–1.73) including proxy respondents; OR 0.79 (0.33–1.86) excluding proxy respondents. House and garden use: OR 0.98 (0.67–1.43) including proxy respondents; OR 0.84 (0.52–1.33) excluding proxy respondents	Conclusions: “No individual pesticides (including glyphosate) or broader category of pesticides, with or without proxy respondent, was associated with a statistically significant decrease or elevation in glioma risk.” Limitations: A limitation of this study is the high proportion (45%) of proxy interviews for case participants compared to 2.9% control interviews that were with proxies. The accuracy and completeness of information given by proxy respondents varies by many factors. Another concern is the validity and reliability of the pesticide exposure assessment.

BMI = body mass index; CED = cumulative exposure day; CI = confidence interval; IWED = intensity weighted exposure day; JEM = job exposure matrix; NHL = non-Hodgkin’s lymphoma; OR = odds ratio; RR = relative risk; Q = quartile; STS = soft tissue sarcoma; T = tertile

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Andreotti et al. 2018 Prospective cohort study of 54,251 licensed pesticide applicators (97% white, 97% male) recruited between 1993 and 1997 in Iowa and North Carolina from the Agricultural Health Study to evaluate agricultural exposure to 50 pesticides (including glyphosate) and cancer incidence cases. 44,932 participants reported ever use of glyphosate, including 5,779 participants with incident cancer cases.	Exposure: Self-reported ever/never use of any glyphosate pesticides, lifetime days of glyphosate use (days per year x number of years), and intensity-weighted lifetime days (lifetime days x intensity score) at enrollment (1993–1997) or follow-up (1999–2005). Intensity-weighted lifetime days of glyphosate use was categorized into quartiles, tertiles, or the median, such that there were at least five exposed cases in each category. Outcome: Incident cancer diagnoses ascertained via linkage to cancer registries in Iowa (enrollment through 2013) and North Carolina (enrollment through 2012). Data analysis: Poisson regression Adjustments: Age, cigarette smoking status, alcohol drinks per month, family history of any cancer, state of recruitment, and the five pesticides (atrazine, alachlor, metolachlor, trifluralin, and 2,4-D). Confounders considered included BMI and pack-years of cigarettes smoked.	Lymphohematopoietic: Q4: RR 1.00 (0.74–1.34) p-trend: 0.43 Hodgkin's lymphoma: M2: RR 0.90 (0.25–3.24) p-trend: 0.94 NHL: Q4: RR 0.87 (0.64–1.20) p-trend: 0.95 B-cell: Q4: RR 0.86 (0.62–1.19) p-trend: 0.86 CLL/SLL: Q4: RR 0.87 (0.48–1.58) p-trend: 0.71 Diffuse large B-cell lymphoma: Q4: RR 0.97 (0.51–1.85) p-trend: 0.83 Marginal-zone lymphoma: M2: RR 0.44 (0.09–2.17) p-trend: 0.67 Follicular lymphoma: T3: RR 0.85 (0.36–2.03) p-trend: 0.95 Multiple myeloma: Q4: RR 0.87 (0.45–1.69) p-trend: 0.84	Conclusions: The authors observed no associations between glyphosate use and overall cancer risk or with total lymphohematopoietic cancers, including NHL, multiple myeloma, and any other NHL subtypes. There was some evidence of an increased risk of acute myeloid leukemia for applicators, particularly in the highest category of glyphosate exposure compared with never users of glyphosate. Risk estimates were similar in magnitude between the unlagged and lagged (5 or 20 years) exposure analyses for all sites evaluated. Limitations: Some misclassification of exposure undoubtedly occurred; because the authors evaluated many cancer sites, there is the possibility that results were observed by chance and should therefore be interpreted with caution; the fact that no other studies have reported an association with acute myeloid leukemia also calls for cautious interpretation. However, 37% of the participants did not respond to follow-up, which may have resulted in an underestimation of

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
		NHL T-cell: M2: RR 1.53 (0.23–10.38) p-trend: 0.31 Acute myeloid leukemia: Q4: RR 2.44 (0.94–6.32) p-trend: 0.11 Chronic myeloid leukemia: M2: RR 0.82 (0.23–2.98) p-trend: 0.36	glyphosate exposure though imputation procedures were used in an attempt to mitigate this issue.
De Roos et al. 2005a A prospective cohort study in 57,311 licensed pesticide applicators (>97% males) recruited between 1993 and 1997 in Iowa and North Carolina from the Agricultural Health Study to study cancer incidence associated with glyphosate use. All lymphohematopoietic: 190 (75.3%) NHL: 92 (77.2%) Leukemia: 57 (75.4) Multiple myeloma: 32 (75.0%)	Exposure: Self-reported never/ever use of glyphosate. Cumulative exposure days (CEDs): 1–20 (reference), 21–56, and 57–2,678 days. Intensity weighted exposure days (IWEDs) of 0.1–79.5 (reference), 79.6–337.1, and 337.2–18,241 units. Outcomes: Incident cases identified between enrollment and Dec 31st of 2001 from cancer registry files. Data analysis: Poisson regression adjusted for age, education, smoking status, alcohol consumption, family history of cancer in 1st degree relative, state of residence.	All lymphohematopoietic cancers: Ever use: RR 1.1 (0.8–1.6) CED T3: RR 1.2 (0.8–1.8) p-trend: 0.69 IWED T3: RR 1.0 (0.7–1.6) p-trend: 0.90 NHL cancers: Ever use: RR 1.1 (0.7–1.9) CED T3: RR 0.9 (0.5–1.8) p-trend: 0.73 IWED T3: RR 0.8 (0.5–1.4) p-trend: 0.99 Leukemia: Ever use: RR 1.0 (0.5–1.9) CED T3: RR 1.0 (0.4–2.9) p-trend: 0.61 IWED T3: RR 0.7 (0.2–2.1) p-trend: 0.11	Conclusions: Glyphosate exposure was not associated with overall cancer incidence or with most cancer subtypes, but there was a suggested association of glyphosate exposure with multiple myeloma incidence. Limitations: Small number of specific cancers cases, only males included in the analysis, no information on timing of pesticide use.

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
		Multiple myeloma: Ever use: RR 2.6 (0.7–9.4) CED T3: RR 1.9 (0.6–6.3) p-trend: 0.27 IWED T3: RR 2.1 (0.6–7.0) p-trend: 0.17	
Sorahan 2015 Cohort study of 55,934 licensed pesticide applicators in Iowa and North Carolina (Agricultural Health Study). Set 1: 54,315 applicators, excluded those with cancer diagnosis before enrollment, those lost to follow-up, those who had missing data for age at enrollment, those who did not provide information on glyphosate use. ("Not known/missing" data included as a separate category for each variable.) n=32 cases. Set 2: 49,211 applicators, additionally excluded those with missing data on education, smoking history, or alcohol used. n=26 cases. Set 3: 40,719 applicators, additionally excluded those missing data on additional pesticide use. n=22 cases. Set 4: 55,934 applicators, excluding those with any cancer diagnosis prior to enrollment, those lost to follow up, and	Exposure: Self-reported never/ever use of glyphosate. CEDs: 1–20 (reference), 21–56, and 57–2,678 days. IWEDs of 0.1–79.5, 79.6–337.1, and 337.2–18,241 units. Outcomes: Incident cases identified between enrollment and December 31st from 2001 cancer registry files. Data analysis: Poisson regression adjusted for the following: Set 2: Age at enrollment, cigarette use, alcohol use, education. Set 4: Age at enrollment, cigarette use, alcohol use, education, family history of cancer. Sets 1 and 3: Age at enrollment, cigarette use, alcohol use, education, family history of cancer, use of some pesticides (2,4-D, alachlor, atrazine, metolachlor, trifluralin), ever use of other	Multiple myeloma: Set 1: Ever use: RR 1.24 (0.52–2.94) CED Q4: RR 1.38 (0.42–4.45) p-trend: 0.48 IWED Q4: RR 1.87 (0.67–5.27) p-trend: 0.22 Set 2: Ever use: RR 2.07 (0.71–6.04) Set 3: Ever use: RR 2.79 (0.78, 9.96) Set 4: Ever use: RR 1.18 (0.53–2.65) CED Q4: RR 1.17 (0.40–3.41) p-trend: >0.50 IWED Q4: RR 1.58 (0.62–4.05) p-trend: 0.30	Conclusions: Glyphosate is not a risk factor for multiple myeloma. Limitations: The small number of cases, absence of information on timing of pesticide exposure, unable to adjust for state of residence.

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
those missing data for age at enrollment. n=34 cases. Re-analysis of data reported by De Roos et al. (2005a).	pesticides (maneb, paraquat, carbaryl, diazinon, benomyl).		
Brown et al. 1990 Case-control study of 578 cases of leukemia and 1,245 controls (all white males, ages ≥30 years) in Iowa and Minnesota to investigate agricultural exposure to 24 animal insecticides, 34 crop insecticides, 38 herbicides, and 16 fungicides (including glyphosate) and risk of leukemia. Glyphosate analysis included 15 cases and 49 controls who used glyphosate herbicide compared to never-farmers (243 cases and 547 controls). Controls were a population-based, stratified sample of white men frequency-matched to the cases by 5-year age group, vital status at interview, and state of residence.	Exposure: Self-reported ever mixing/handling/applying glyphosate herbicides at enrollment (1981–1984). Outcomes: Leukemia cases ascertained from Iowa Tumor Registry or hospital records in Minnesota from 1 year before (retrospectively) to 2 years after the start of the study (prospectively). Data analysis: Unconditional logistic regression. Adjustments: Vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk non-farming occupations, high risk exposures (benzene, naphtha, hair dyes).	Leukemia OR 0.9 (0.5–1.6)	Conclusions: “Risks for all leukemia were not significantly increased among subjects who personally mixed, handled, or applied specific herbicides (including glyphosate).” Limitations: With the case-control study design, the associations found or failure to find an association could be due to bias. Potential inaccuracies in the evaluation of pesticide exposure could lead to exposure misclassification. Multiple statistical comparisons make it difficult to separate real association from chance findings.

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Brown et al. 1993 Case control study to evaluate the association between multiple myeloma, agricultural risk factors, and exposure to individual pesticides in 823 white males aged ≥30 years in Iowa. 173 cases and 650 frequency-matched controls from random digit dialing, Medicare records, and death certificate files. Glyphosate analysis included 11 exposed and 162 unexposed cases (n=173) for multiple myeloma and 40 exposed and 610 unexposed controls (n=650).	Exposure: Self-reporting never/ever mixing, handling, or applying glyphosate. Outcomes: Multiple myeloma cases from the Iowa Health Registry from 1981 to 1984. Data analysis: Logistic models adjusted for vital status and age. Other confounders considered included smoking and education.	Multiple myeloma: OR 1.7 (0.8–3.6)	Conclusions: Little evidence of an association between risk of multiple myeloma and exposure to pesticides (including glyphosate). Limitations: Small number of cases and controls, multiple statistical comparisons, and possibility of recall bias or chance.
Cocco et al. 2013 Case control study of 4,810 in the EPILYMPH study from six European countries to investigate the role of occupational exposure to agrochemicals (including glyphosate) in etiology of lymphoma, B cell lymphoma and subtypes. 2,348 incident lymphoma cases and 2,462 controls (n=4,810). Glyphosate analysis included four exposed B cell lymphoma cases and two exposed controls.	Exposure: Self-reported questionnaires: never/ever glyphosate exposure. Outcomes: First diagnosis according to 2001 WHO classification of lymphoma between 1998 and 2004; patients referred from centers within referral area. Data analysis: Unconditional logistic regressions. Adjustments for age, gender, education, center.	B cell lymphoma: OR 3.1 (0.6–17.1)	Conclusions: No support to the role of occupation exposure to agrochemicals (including glyphosate) in etiology of B cell lymphoma. Limitations: Low response rate may have resulted in selection bias.

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
De Roos et al. 2003 Pooled data from three case-control studies conducted by the National Cancer Institute to investigate exposure to multiple pesticides in farming as risk factors for NHL among 3,417 white males from Nebraska, Iowa, Minnesota, and Kansas. Glyphosate analysis included 36 exposed and 614 unexposed cases (n=650) and 61 exposed and 1,872 unexposed population based matched controls (n=1,933).	Exposure: Interview self-reported never/ever glyphosate exposure. Outcomes: In Nebraska, cases were identified through Nebraska Lymphoma Study Group and area hospitals among males aged ≥21 years from July 1983 to June 1986. In Iowa, cases were ascertained from Iowa State Health Registry from 1981 to 1983 from males ≥30 years of age. In Minnesota, cases were ascertained from a surveillance system of Minnesota hospitals and pathology laboratories from 1980 to 1982 in males ≥30 years of age. In Kansas, cases were randomly selected from statewide cancer registry from males ≥21 years of age. Data analysis: Two models were used: (1) standard logistic regression and (2) hierarchical regression adjusted for age and study site.	Logistic regression: NHL: OR 2.1 (1.1–4.0) Hierarchical regression: NHL: OR 1.6 (0.9–2.8)	Conclusions: No specific conclusions for glyphosate and NHL. Limitations: Crude exposure metric, no information on timing of exposure versus NHL onset or timing of use of pesticides to each other. Potential bias for missing data exclusion.

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Eriksson et al. 2008 Case control study of 1,926 male and female subjects aged 18–74 years were recruited between December 1, 1999 and April 30, 2002 in Sweden to evaluate pesticides (including glyphosate) as a risk factor for NHL. Glyphosate analysis included 29 exposed and 881 unexposed cases (n=910) and 18 exposed and 998 unexposed frequency-match controls (n=1,016).	Exposure: Self-reporting questionnaires; never/ever exposed and days of exposure. Outcomes: Newly diagnosed NHL, identified through physicians and pathologists recruited between December 1, 1999 and April 30, 2002. Subtypes divided according to WHO classification. Data analysis: Unconditional logistic regression analysis adjusted for age, sex, year of diagnosis/enrollment.	NHL: Ever: OR 2.02 (1.10–3.71) Ever (adjusted for other pesticides): OR 1.51 (0.77–2.94) Ever (1–10-year latency): OR 1.11 (0.24–5.08) Ever (>10-year latency): OR 2.26 (1.16–4.40) ≤10 days: OR 1.69 (0.70–4.07) ≥10 days: OR 2.36 (1.04–5.37) B-cell lymphomas: Ever: OR 1.87 (0.998–3.51) Lymphocytic lymphoma: Ever: OR 3.35 (1.42–7.89) Follicular, grade I-III: Ever: OR 1.89 (0.62–5.79) Diffuse large B-cell lymphoma: Ever: OR 1.22 (0.44–3.35) Other specified B-cell lymphoma: Ever: OR 1.63 (0.53–4.96) Unspecified B-cell lymphoma: Ever: OR 1.47 (0.33–6.61) T-cell lymphoma: Ever: OR 2.29 (0.51–10.4) Unspecified NHL: Ever: OR 5.63 (1.44–22.0)	Conclusions: The association of NHL with glyphosate was strengthened by the study. Limitations: No registries of pesticide use kept in Sweden, possible misclassification of pesticide exposure, no information gathered on protective equipment use.

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Hardell et al. 2002 Pooled analysis of two case-control studies of 1,656 male and female subjects from Sweden to investigate pesticides in etiology of NHL and HCL. Glyphosate analysis included 8 exposed and 507 unexposed cases (n=515) and 8 exposed and 1,133 unexposed county-matched controls (n=1,141).	Exposure: Self-reporting questionnaires; never/ever glyphosate exposure. Outcomes: Histopathologically verified NHL cases from regional cancer registries in males age ≥25 years from 1987 to 1990. HCL diagnosed cases from the national Swedish Cancer Registry in males from 1987 to 1992. Data analysis: Conditional logistic regression analysis adjusted for both univariate and multivariate.	NHL and HCL (pooled): Ever (univariate analysis): OR 3.04 (1.08–8.52) Ever (multivariate analysis): OR 1.85 (0.55–6.20)	Conclusions: Glyphosate is a risk factor for developing NHL. Limitations: Possible recall bias. Correlation of pesticides.
Kachuri et al. 2013 A population-based, case-control study in 1,506 males from six Canadian provinces to investigate the association between lifetime use of multiple pesticides and multiple myeloma. Glyphosate analysis included 32 exposed cases and 310 unexposed cases (n=342) and 121 exposed and 1,236 unexposed frequency-matched controls (n=1,357). Excluding proxy respondents, analysis included 23 exposed cases and 108 exposed frequency-matched controls.	Exposure: Self-reporting questionnaires; ever/never, days/year glyphosate use. Outcomes: Incident multiple myeloma cases among men aged ≥19 years who were diagnosed between September 1, 1991 and December 31, 1994 ascertained from provincial cancer registries. Cases in Quebec were ascertained from hospitals. Data analysis: Logistic regression. Adjusted for age, province of residence, use of proxy responders, smoking, and selected medical history.	Multiple myeloma: Ever: OR 1.19 (0.76–1.87) Ever (exclude proxies): OR 1.11 (0.66–1.86) >0 and ≤2 days/year: OR 0.72 (0.39–1.32) >0 and ≤2 days/year (exclude proxies): OR 0.70 (0.35–1.40) >2 days/year: OR 2.04 (0.98–4.23) >2 days/year (exclude proxies): OR 2.11 (0.95–4.70)	Conclusions: No specific conclusions for glyphosate and multiple myeloma. Limitations: Low response rates observed for cases and controls, possibility of recall bias.

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Karunanayake et al. 2012 Case-control study of 1,822 men to evaluate exposure to pesticides and incidence of Hodgkin lymphoma in six Canadian provinces. Glyphosate analysis included 38 exposed and 278 unexposed Hodgkin lymphoma cases (n=316) and 133 exposed and 1,373 unexposed age-matched controls (n=1,506).	Exposure: Any self-reported glyphosate use. Outcomes: Hodgkin lymphoma incidences determined using Internal Classification of Diseases for Oncology, 2nd Edition (ICD-O-2) from September 1, 1991 to December 31, 1994. Data analysis: Conditional logistic regression. Adjustments for age, province of residence, personal and family medical history.	Hodgkin lymphoma: OR 0.99 (0.62–1.56)	Conclusions: This study shows a lack of association between Hodgkin lymphoma and glyphosate. Limitations: Inability to ascertain Epstein-Barr virus exposure. Potential for recall bias and for misclassification of exposure to pesticides, as well as misclassification of exposure duration. Low response rates resulted in inability to evaluate dose-response relationship and women were not included in the study.
Lee et al. 2004a Case control study of 3,253 in Iowa, Minnesota, and Nebraska to evaluate if asthma modifies risk associated with pesticide exposure. 872 cases of NHL and 2,381 frequency-matched controls. Glyphosate analyses, 259 cases and 684 controls for non-asthmatic non-farmers (reference), 53 cases and 91 controls for non-asthmatic farmers, and 6 cases and 12 controls for asthmatic farmers. These data were used in the pooled analysis by De Roos et al. (2003).	Exposure: Self-reported ever/never glyphosate use. Self-reported asthma from physician diagnosis. Outcomes: Cases identified through Iowa State Health Registry and Minnesota's surveillance system of hospital and pathology laboratories from 1980 to 1983 (n=530). Cases identified through Nebraska Lymphoma Study group and area hospitals between July 1983 and June 1986 (n=346). Data analysis: Unconditional logistic regression adjusted for age, state, vital status.	NHL(non-asthmatic farmers): OR 1.4 (0.98–2.1) NHL (asthmatic farmers): OR 1.2 (0.4–3.3)	Conclusions: No specific conclusion concerning exposure to glyphosate, asthma, and NHL. Limitations: Self-reported exposure and asthma diagnosis may be subject to misclassification bias.

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
McDuffie et al. 2001 Case-control study to investigate the association between non-occupational exposure to pesticides (including glyphosate) and NHL among 2,023 men in six Canadian provinces. Glyphosate analysis included 51 exposed and 466 unexposed NHL cases (n=517) and 133 exposed and 1,373 unexposed age-matched controls (n=1,506).	Exposure: Self-reported ever/never use of any glyphosate use and number days/year use. Outcomes: First diagnosis of NHL between September 1, 1991 and December 31, 1991 from cancer registries for five providences, in Quebec where hospital records were used. Data analysis: Conditional logistic regression adjusted for age, province of residence, medical history (measles, mumps, cancer, allergy desensitization shots, positive family history of cancer in 1st-degree relative).	NHL: Ever use: OR 1.20 (0.83–1.74) Exposure >0 and ≤2 days/year: OR 1.00 (0.63–1.57) Exposure >2 days/year: OR 2.12 (1.20–3.73)	Conclusions: No conclusions stated for glyphosate ever use. When stratified by average number of days per year of exposure, glyphosate was not significantly associated with NHL for exposure, but demonstrated a dose-response relationship. Limitations: Potential for recall bias and misclassification of pesticide exposure. Inclusion of occupational groups without extensive validations studies could bias findings towards null. Less-than-optimal response rates. Due to multiple comparison, a small number of statistically significant results may be attributable to chance. Because of limited statistical power, analysis was restricted to exposure that at least 1% of respondents ever used.

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Nordström et al. 1998 Case-control study of 511 Swedish adult males to evaluate occupational exposures (including glyphosate) as risk factors for HCL. Glyphosate analysis included 4 exposed and 107 unexposed cases (n=111) of HCL and 5 exposed and 395 controls (n=400) in Sweden. These data were used in pooled analysis by De Roos et al. (2003).	Exposure: Self-reported never/ever glyphosate exposure determined by at least 1 working day (8 hours) and induction of at least 1 year. Outcomes: HCL reported to Swedish Cancer Registry from 1987 to 1992. One case diagnosed in 1993 included in analysis. Data analysis: Logistic regression adjusted for age.	HCL: OR 3.1 (0.8–12)	Conclusions: No specific conclusions were given for glyphosate and HCL. Limitations: Possible correlation of occupational exposures resulting in confounding. Multiple comparisons may result in some correlations to occur by chance. Possibility of elevated OR due to recall bias.

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Orsi et al. 2009 Case-control study to investigate the relationship between occupational exposure to pesticides and lymphoid neoplasms in 947 18–75-year-old males from six hospitals in France from 2000 to 2004. Glyphosate analysis included: 12 exposed and 232 unexposed NHL cases (n=244) and 24 exposed and 412 unexposed center, age, sex-matched controls (n=436). 6 exposed and 81 unexposed cases of Hodgkin's lymphoma (n=87) and 15 exposed and 250 unexposed center, age, sex-matched controls (n=265). 5 exposed and 51 unexposed cases of multiple myeloma (n=56) and 18 exposed and 295 unexposed center, age, sex-matched controls (n=313). 27 exposed and 464 unexposed cases of lymphoid neoplasms (n=491) and 24 exposed and 432 unexposed center, age, sex-matched controls (n=456).	Exposure: Self-reported none and probable/definite glyphosate exposure, after expert review of pesticide use questionnaire. Outcomes: Cases determined using ICD-O-3 code diagnosis from September 2000 to December 2004. Data analysis: Unconditional logistic regression, adjusted for age, center, socioeconomic category (white collar/blue collar).	Lymphoid neoplasms: OR 1.2 (0.6–2.1) NHL: OR 1.0 (0.5–2.2), all subtypes OR 1.0 (0.3–2.7) for diffuse large cell lymphoma OR 1.4 (0.4–5.2) for follicular lymphoma Hodgkin's lymphoma: OR 1.7 (0.6–5.0) Lymphoproliferative syndrome: OR 0.6 (0.2–2.1), all subtypes OR 0.4 (0.1–1.8) for chronic lymphocytic leukemia OR 1.8 (0.3–9.3) for HCL Multiple myeloma: OR 2.4 (0.8–7.3)	Conclusions: No specific conclusions for glyphosate and development of lymphoid neoplasms. Limitations: Potential non-differential misclassification resulting in reduced power.

Table 2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products

Reference and study overview	Methods and outcomes	Results (with 95% CI)	Study author conclusions and limitations
Pahwa et al. 2012 Case-control study to investigate the association between non-occupational exposure to pesticides (including glyphosate) and multiple myeloma among 1,848 men in six Canadian provinces. Glyphosate analysis included 32 exposed and 310 unexposed cases (n=342) and 133 exposed and 1,373 unexposed controls (n=1,506).	Exposure: Self-reported glyphosate never/ever use. Outcomes: First diagnosis of multiple myeloma between September 1, 1991 and December 31, 1994 from cancer registries for five providences, in Quebec where hospital records were used. Data analysis: Conditional logistic regression adjusted for age, province of residence, medical history (measles, mumps, cancer, allergy desensitization shots, positive family history of cancer in 1st degree relative).	Multiple myeloma: OR 1.22 (0.77–1.93)	Conclusions: No specific conclusion for glyphosate and multiple myeloma. Limitations: Low response rates, potential for selection bias, recall bias, and misclassification of pesticide exposure.

BMI = body mass index; CED = cumulative exposure day; CI = confidence interval; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL = diffuse large B-cell lymphoma; HCL = hairy cell leukemia; IWED = intensity weighted exposure day; M = median; NHL = non-Hodgkin's lymphoma; OR = odds ratio; Q = quartile; RR = relative risk; T = tertile; WHO = World Health Organization

Solid Tumors. The epidemiological studies on the association between glyphosate use and solid-type tumors are presented in Table 2-7. Overall, these studies did not detect a statistically significant association between glyphosate use and all cancer types studied, including melanoma, childhood cancers, soft tissue sarcoma, colorectal cancer, and cancers of the lung, oral cavity, colon, rectum, pancreas, kidney, prostate (including total prostate and aggressive prostate cancers), testes, breast, bladder, stomach, and esophagus. A statistically significant association with glyphosate use and solid tumors was reported in one study. Lee et al. (2005) reported an association between proxy-reported glyphosate use and glioma cancer (odds ratio [OR] 3.1; 95% CI 1.2–8.2). However, when using self-reported glyphosate use or combined self- and proxy-reported glyphosate use, no association with glioma was observed (OR 0.4; 95% CI 0.1–1.6 and OR 1.5; 95% CI 0.7–3.1, respectively).

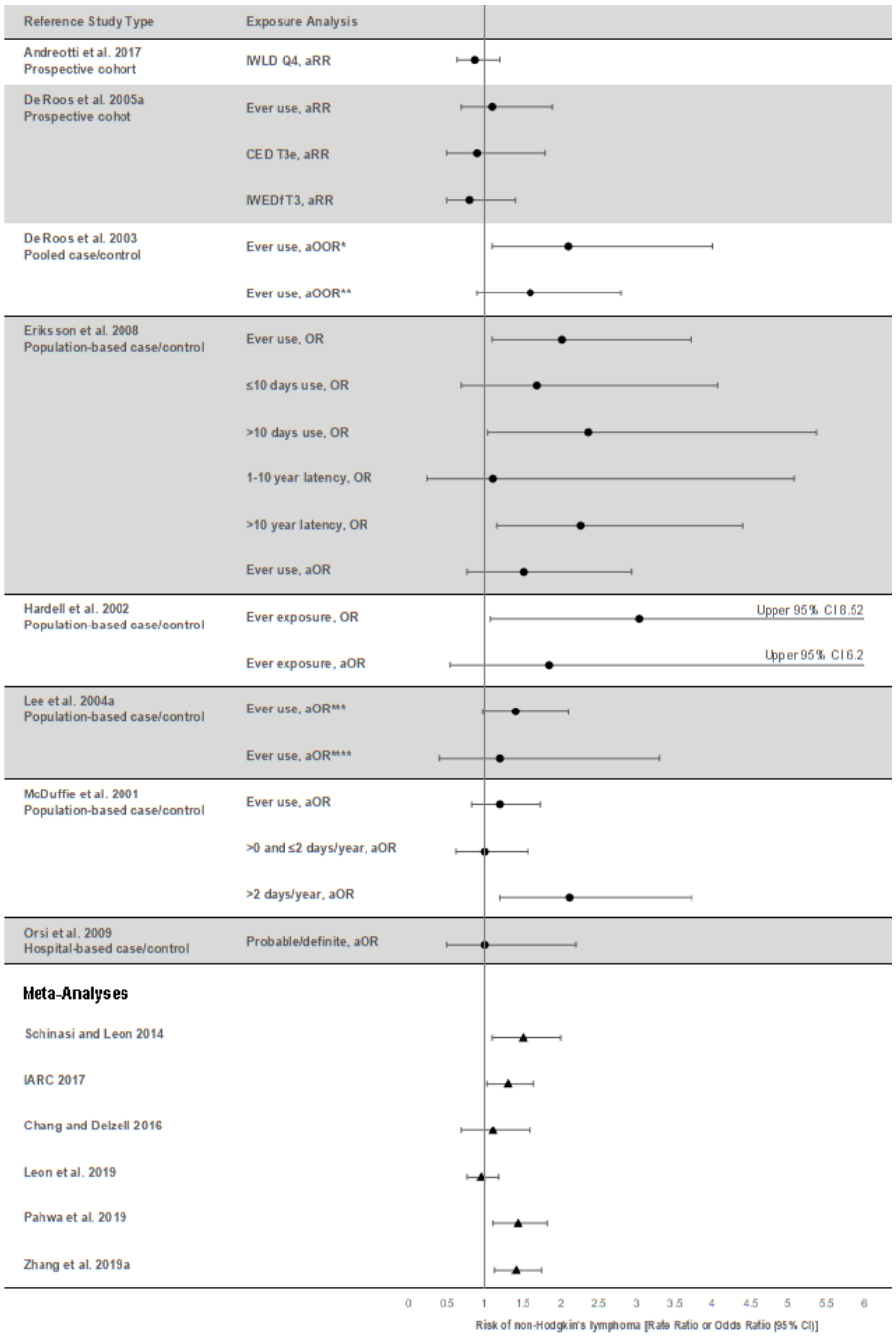
Lymphohematopoietic Cancers. Overviews of epidemiological studies that focused on the association between glyphosate use and lymphohematopoietic cancers are presented in Table 2-8. A majority of the studies did not report statistically significant associations between glyphosate use and many of the lymphohematopoietic cancer subtypes. These statistically null associations were reported for the following subtypes: all lymphohematopoietic cancers (Andreotti et al. 2018; De Roos et al. 2005a); NHL (Andreotti et al. 2018; De Roos et al. 2005a; Lee et al. 2004a; Orsi et al. 2009); leukemia (Brown et al. 1990; De Roos et al. 2005a); multiple myeloma (Andreotti et al. 2018; Brown et al. 1993; De Roos et al. 2005a; Kachuri et al. 2013; Orsi et al. 2009; Pahwa et al. 2012; Sorahan 2015); B-cell lymphoma (Andreotti et al. 2018; Cocco et al. 2013; Eriksson et al. 2008); follicular lymphoma (Andreotti et al. 2018; Eriksson et al. 2008; Orsi et al. 2009); diffuse large B-cell lymphoma (Andreotti et al. 2018; Eriksson et al. 2008; Orsi et al. 2009); other specified B-cell lymphoma (Eriksson et al. 2008); unspecified B-cell lymphoma (Eriksson et al. 2008); T-cell lymphoma (Andreotti et al. 2018; Eriksson et al. 2008); Hodgkin's lymphoma (Andreotti et al. 2018; Karunanayake et al. 2012; Orsi et al. 2009); hairy cell leukemia (Nordström et al. 1998; Orsi et al. 2009); lymphoid neoplasms (Orsi et al. 2009); marginal-zone lymphoma (Andreotti et al. 2018); chronic myeloid leukemia (Andreotti et al. 2018); and lymphoproliferative syndrome, all subtypes and chronic lymphocytic leukemia (Andreotti et al. 2018; Orsi et al. 2009). Andreotti et al. (2018) reported an increased risk of acute myeloid leukemia among applicators in the highest exposure quartile, compared with never users (RR 2.44; 95% CI 0.94–6.32), although the authors noted that this association was not statistically significant. However, in a letter to the editor, Sheppard and Shaffer (2018) argued that the statistical procedure used by Andreotti et al. (2019) to account for the 37% loss to follow-up was not sufficient given health outcomes were not included in their imputations. Therefore, the results of the analysis may have been biased towards the null (Sheppard and Shafer 2019). Andreotti et al (2019) responded to this comment stating that although the argument in

Sheppard and Shafer (2019) is theoretically possible, however based on a sensitivity analysis, Andreotti et al. argue their imputation likely did not impact risk estimates.

In contrast, Eriksson et al. (2008) reported positive associations between glyphosate use and lymphocytic lymphoma (OR 2.56; 95% CI 1.17–5.60) and unspecified NHL (OR 5.29; 95% CI 1.60–17.50). Several other studies reported significant associations between glyphosate use and NHL, but these studies reported conflicting results depending on the statistical methods used, adjustment for confounders, or inclusion criteria. De Roos et al. (2003) reported a positive association between glyphosate use and NHL using logistic regression (OR 2.1; 95% CI 1.1–4.0); however, analysis using hierarchical regression did not find an association (OR 1.6; 95% CI 0.9–2.8). Similarly, Eriksson et al. (2008) reported a positive association with NHL (OR 2.02; 95% CI 1.10–3.71); when this analysis further adjusted for other pesticide use, the reported OR was 1.51 (95% CI 0.7–2.94). Hardell et al. (2002) investigated the association between glyphosate use and combined cases of NHL and hairy cell leukemia. The authors reported an OR of 3.04 (95% CI 1.08–8.52) in unadjusted models, but after adjusting for potential confounders, the reported OR was 1.85 (95% CI 0.55–6.20). McDuffie et al. (2001) reported that glyphosate use was not associated with NHL (OR 1.20; 95% CI 0.83–1.74); however, after restricting analyses to individuals who reported using glyphosate >2 days a year, there was a positive association with NHL (OR 2.12; 95% CI 1.20–3.73).

Results for risk of non-Hodgkin's lymphoma and self-reported glyphosate use or exposure from individual studies summarized in Table 2-8 and meta-analyses summarized in Table 2-6 are plotted in Figure 2-4. Results for risk of multiple myeloma and self-reported glyphosate use or exposure from individual studies summarized in Table 2-8 and the meta-analysis summarized in Table 2-6 are plotted in Figure 2-5.

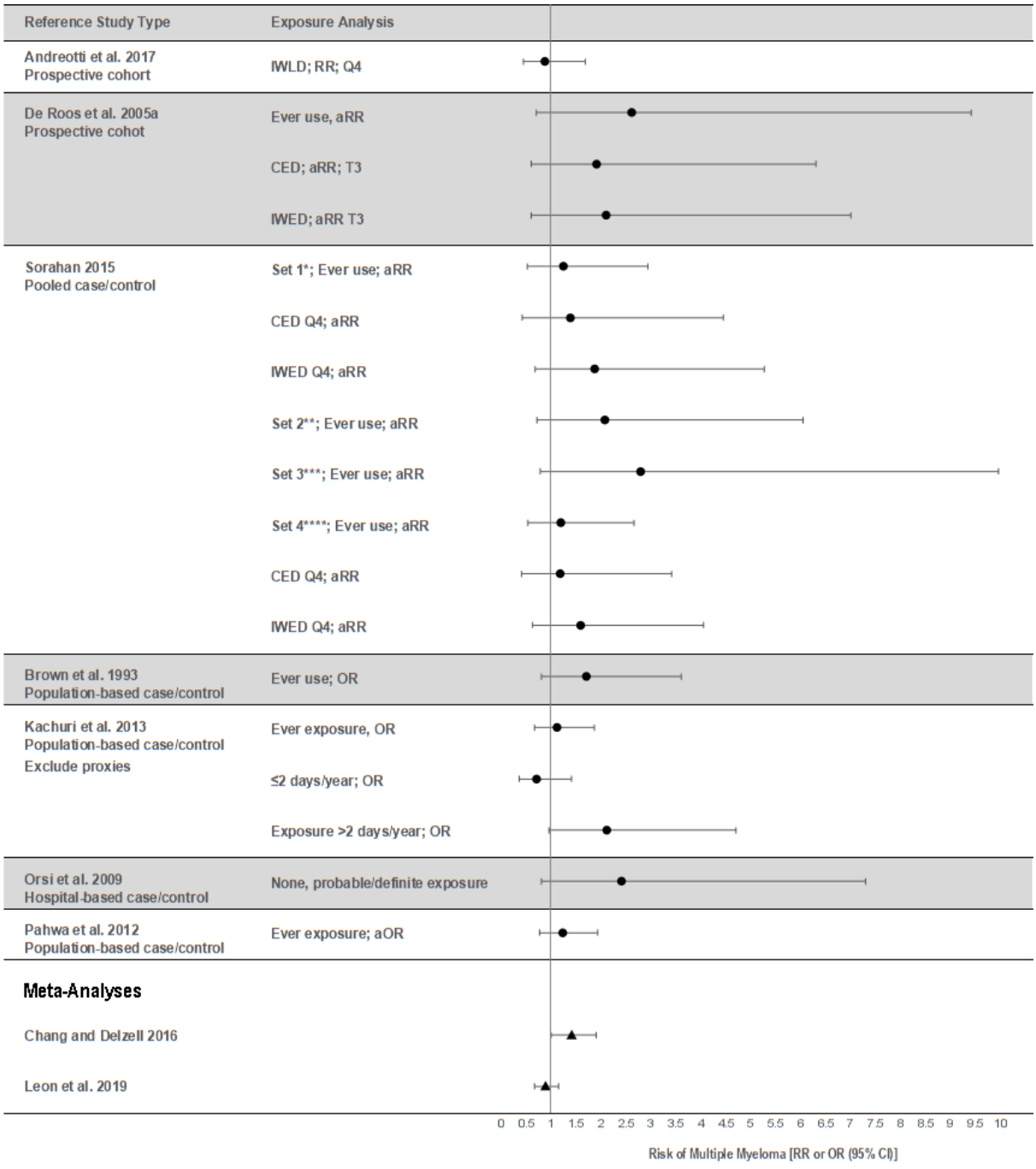
Figure 2-4. Risk of non-Hodgkin's Lymphoma Relative to Self-Reported Glyphosate Use or Exposure



*Logistic Regression; **Hierarchical regression; ***Non-Asthmatic farmers; ****Asthmatic farmers

a = adjusted; CED = cumulative exposure; IWED = intensity-weighted exposure days; IWLD = intensity-weighted lifetime days; OR = odds ratio; Q4 = 4th quartile; RR = rate ratio; T3 = 3rd tertile

Figure 2-5. Risk of Multiple Myeloma Relative to Self-Reported Glyphosate Use or Exposure



*Set 1 included 54,315 applicators; **Set 2 included 49,211 applicators; ***Set 3 included 40,719 applicators; ****Set 4 included 55,934 applicators

a = adjusted; CED = cumulative exposure; IWED = intensity-weighted exposure days; IWLD = intensity-weighted lifetime days; IRED = intensity-rated exposure days; OR = odds ratio; Q4 = 4th quartile; RR = rate ratio; T3 = 3rd tertile

Laboratory Animal Studies

EPA evaluated results from four unpublished rat studies in which the carcinogenicity of glyphosate technical was assessed; EPA summarized the findings in publicly available DERs (EPA 1991a, 1991b, 1992d, 2015c).

Groups of weanling Sprague-Dawley rats (50/sex/group) were administered glyphosate technical (98.7% purity) in the diet for up to 26 months at initial concentrations of 0, 30, 100, or 300 ppm (EPA 1992d). Based on body weight and food consumption data, concentrations of glyphosate technical were adjusted to achieve oral doses of 0, 3.05, 10.30, and 31.49 mg/kg/day, respectively, for males and 0, 3.37, 11.22, and 34.02 mg/kg/day, respectively, for females. Incidences of testicular interstitial cell tumors in the control, low-, mid-, and high-dose male rats were 0/50 (0%), 3/50 (6%), 1/50 (2%), and 6/50 (12%), respectively (Table 2-9). The incidence in the high-dose males was statistically significant (p=0.013) in pairwise comparison to the control incidence. Although the incidence in the mid-dose group was less than that in the low-dose group, trend analysis revealed a significant trend (p=0.009) for increasing incidence of testicular interstitial cell tumors with increasing dose. Evaluation of historical control incidences resulted in testicular interstitial cell tumor incidences in the range of 0–12%, with a mean incidence of 4.5% (range: 3.4–6.7%) among lifetime studies that employed the same rat strain and were conducted concurrently with the 26-month study.

Incidences of thyroid c-cell tumors (adenoma, carcinoma, combined adenoma or carcinoma) in the female rats are presented in Table 2-9. An increased incidence of thyroid c-cell carcinomas in female rats approached statistical significance (p=0.055) at the highest dose (6/47 versus 1/47 for controls) (EPA 1992d). The combined incidence of combined c-cell carcinomas or adenomas was not significantly increased (9/47 high-dose females versus 6/47 controls), and time-to-tumor analysis revealed no sign of a treatment-related effect. Historical control incidences of spontaneous thyroid c-cell tumors in female Sprague-Dawley rats were as high as 17%.

Table 2-9. Incidences of Selected Tumors in Sprague-Dawley Rats Administered Technical Glyphosate (98.7% purity) in the Diet for up to 26 Months

	Glyphosate dose (mg/kg/day)				Historical control incidence
	0	3.05	10.3	31.49	
Male rats					
Testes interstitial cell tumors					
Interstitial cell tumors	0/50 (0%)	3/50 (6%)	1/50 (2%)	6/50[a] (12%)	0–12%
Female rats					
Thyroid c-cell tumors					
Adenoma	5/47 (11%)	3/49 (6%)	6/50 (14%)	3/47 (6%)	0–17%
Carcinoma	1/47 (2%)	0/49 (0%)	2/50 (4%)	6/47 (13%)	0–5%
Adenoma or carcinoma (combined)	6/47 (13%)	3/49 (6%)	8/50 (16%)	9/47 (19%)	0–17%

[a]Significantly different from concurrent control according to Fisher's Exact Test ($p<0.05$).

NA = not applicable; NS = not specified

Sources: EPA 1992d

Groups of albino Sprague-Dawley rats (60/sex/group) were administered technical glyphosate (96.5% purity) in the diet at target concentrations of 0, 2,000, 8,000, or 20,000 ppm (mean measured concentrations of 0, 1,900, 7,600, and 19,000 ppm, respectively) for up to 24 months (EPA 1991a, 1991b). Based on mean body weight and food consumption data, estimated glyphosate doses to controls and low-, mid-, and high-dose groups were 0, 89, 362, and 940 mg/kg/day, respectively, for the males and 0, 113, 457, and 1,183 mg/kg/day, respectively, for the females.

As shown in Table 2-10, low-dose (but not mid- or high-dose) males exhibited significantly increased incidences of pancreatic islet cell adenoma ($p=0.015$) in pairwise comparison to control incidence (EPA 1991a, 1991b). Incidences of pancreatic islet cell carcinoma in low-, mid-, and high-dose males were not significantly different from control incidences. Incidences of combined adenoma or carcinoma among mid-, and high-dose males were not significantly different from control incidences. After excluding those male rats that died or were sacrificed prior to treatment week 55 (before the first adenoma or carcinoma were observed), incidences of pancreatic islet cell adenoma in the low-dose group remained significantly ($p=0.018$) higher than controls. However, exclusion of the early deaths resulted in only borderline significantly increased incidence of combined adenoma or carcinoma ($p=0.052$) in the low-dose group. Historical control incidences for pancreatic islet cell adenoma in male rats from 2-year studies conducted at the same testing facility ranged from 1.8 to 8.5%. In the female rats, no significant differences were

observed between controls and treated rats regarding pancreatic islet cell tumor incidences in pairwise comparisons with controls.

Table 2-10. Incidences of Selected Tumors in Albino Sprague-Dawley Rats Administered Technical Glyphosate (96.5% Purity) in the Diet for 2 Years

	Glyphosate dose (mg/kg/day)				Historical control incidence
	0	89	362	940	
Male rats					
Pancreatic islet cell tumors					
All deaths considered					
Adenoma	1/58 (2%)	8/57[a] (14%)	5/60 (8%)	7/59 (12%)	1.8–8.5%
Carcinoma	1/58 (2%)	0/57 (0%)	0/60 (0%)	0/59 (0%)	NS
Adenoma or carcinoma (combined)	2/58 (3%)	8/57 (14%)	5/60 (8%)	7/59 (12%)	NA
Excluding deaths prior to treatment week 55 (first adenoma at week 81; first carcinoma at week 105)					
Adenoma	1/43 (2%)	8/45[a] (18%)	5/49 (8%)	7/48[a] (15%)	NA
Carcinoma	1/43 (2%)	0/45 (0%)	0/49 (0%)	0/48 (0%)	NA
Adenoma or carcinoma (combined)	2/43 (2%)	8/45 (18%)	5/49 (10%)	7/48 (15%)	NA
Thyroid c-cell tumors					
All deaths considered					
Adenoma	2/60 (3%)	4/58 (7%)	8/58[b] (14%)	7/60 (12%)	1.8–10.6%
Carcinoma	0/60 (0%)	2/58 (3%)	0/58 (0%)	1/60 (2%)	NS
Excluding deaths prior to treatment week 55 (first adenoma at week 54; first carcinoma at week 93)					
Adenoma	2/54 (4%)	4/55 (7%)	8/58 (14%)	7/58 (12%)	NA
Carcinoma	0/54 (0%)	2/55 (4%)	0/58 (0%)	1/58 (1%)	NA
Adenoma or carcinoma (combined)	2/54 (4%)	6/55 (11%)	8/58 (14%)	8/58 (14%)	NA
Liver tumors					
All deaths considered					
Adenoma	2/60 (3%)	2/60 (3%)	3/60 (5%)	7/60 (12%)	1.4–18.3%
Carcinoma	3/60 (5%)	2/60 (3%)	1/60 (2%)	2/60 (3%)	0–6.7%
Excluding deaths prior to treatment week 55 (first adenoma at week 88; first carcinoma at week 85)					
Adenoma	2/44 (5%)	2/45 (4%)	3/49 (6%)	7/48 (15%)	NA
Carcinoma	3/44 (7%)	2/45 (4%)	1/49 (2%)	2/48 (4%)	NA
Adenoma or carcinoma (combined)	5/44 (11%)	4/45 (9%)	4/49 (8%)	9/48 (19%)	NA

Table 2-10. Incidences of Selected Tumors in Albino Sprague-Dawley Rats Administered Technical Glyphosate (96.5% Purity) in the Diet for 2 Years

	Glyphosate dose (mg/kg/day)				Historical control incidence
	0	89	362	940	
Female rats					
Pancreatic islet cell tumors					
All deaths considered					
Adenoma	5/60 (8%)	1/60 (2%)	4/60 (7%)	0/59 (0%)	NS
Carcinoma	0/60 (0%)	0/60 (0%)	0/60 (0%)	0/59 (0%)	NS
Adenoma or carcinoma (combined)	5/60 (8%)	1/60 (2%)	4/60 (7%)	0/59 (0%)	NA
Thyroid c-cell tumors					
All deaths considered					
Adenoma	2/60 (3%)	2/60 (3%)	6/60 (10%)	7/60 (10%)	3.3–10%
Carcinoma	0/60 (0%)	0/60 (0%)	1/60 (2%)	0/60 (0%)	0–2.9%
Adenoma or carcinoma (combined)					
Excluding deaths prior to treatment week 55 (first adenoma at week 72; first carcinoma at week 93)					
Adenoma	2/57[c] (4%)	2/60 (3%)	6/59 (10%)	6/55 (11%)	NS
Carcinoma	0/57 (0%)	0/60 (0%)	1/59 (2%)	0/55 (0%)	NS
Adenoma or carcinoma (combined)	2/57[c] (4%)	2/60 (3%)	7/59 (12%)	6/55 (11%)	NA

[a]Significantly different from concurrent control according to Fisher's Exact Test ($p<0.05$).
[b]Marginally significantly different from concurrent control according to Fisher's Exact Test ($p=0.051$).
[c]Significant trend ($p<0.05$) for increasing incidence of adenoma and adenoma/carcinoma combined, excluding deaths prior to treatment week 55.

NA = not applicable; NS = not specified

Sources: EPA 1991a, 1991b

As shown in Table 2-10, the incidence of thyroid c-cell adenoma in mid-dose (but not low- or high-dose) male rats was marginally significantly ($p=0.051$) greater than that of controls. Historical control incidences for thyroid c-cell adenoma in male rats ranged from 1.8 to 10.6%. Pairwise comparison with concurrent controls revealed no significant difference between controls and low-, mid-, or high-dose groups regarding incidences of thyroid c-cell adenoma or carcinoma. There were no significant differences between controls and low-, mid-, or high-dose groups regarding incidences of thyroid c-cell adenoma after excluding those male rats that died prior to week 54 (EPA 1991a, 1991b). In the female rats, no significant differences were observed between controls and treated rats regarding thyroid c-cell tumor incidences in pairwise comparisons with controls. Significant trends ($p<0.05$) for increasing

incidence of adenoma and adenoma/carcinoma combined were noted after excluding those female rats that died prior to week 55 (EPA 1991a, 1991b).

As shown in Table 2-10, incidences of liver tumors in the glyphosate-treated male rats were not significantly different from incidences among controls. Lack of statistical significance remained after excluding those rats that died or were sacrificed prior to study week 55 and upon combining incidences of adenoma or carcinoma combined.

EPA summarized results from two unpublished rat studies in which the carcinogenicity of glyphosate technical was assessed. In one study, groups of Alpk:AP$_f$SD Wistar rats (64/sex/group) received glyphosate (97.6% purity) from the diet for up to 2 years at 0, 121, 361, or 1,214 mg/kg/day (males) and 0, 145, 437, or 1,498 mg/kg/day (females) (EPA 2015c). An interim sacrifice was performed on 12 rats/sex/group after 1 year. Incidences of hepatocellular adenoma among controls, low-, mid-, and high-dose male rats were reported as 0/52 (0%), 2/52 (4%), 0/52 (0%), and 5/52 (10%), respectively. The incidence in the high-dose group was significantly greater than that of controls (p=0.028 by Fisher's exact test). EPA (2015c) noted a range of 0–11.5% for this tumor type among historical controls reported by Greim et al. (2015). In the other study, there were no treatment-related increased incidences of any tumor type among Sprague-Dawley rats (50/sex/group) that received glyphosate (98.9 purity) from the diet for up to 104 weeks at 0, 100, 300, or 1,000 mg/kg/day (EPA 2015c).

In a combined chronic toxicity/carcinogenicity study, groups of Sprague-Dawley rats (50/sex/group for the carcinogenicity portion) received glyphosate (98.9 purity) from the diet for up to 104 weeks at 0, 100, 300, or 1,000 mg/kg/day (EPA 2015c). There were no treatment-related increased incidences of any tumor type.

EPA also evaluated results from two unpublished mouse studies in which the carcinogenicity of glyphosate technical was assessed; EPA summarized the findings in publicly-available DERs.

In one study, groups of CD-1 mice (50/sex/group) were administered technical glyphosate (99.78% purity) for 24 months at doses of 0, 161, 835, or 4,945 mg/kg/day to the males and 0, 195, 968, or 6,069 mg/kg/day to the females (EPA 2015a; selected results also available in EPA 1985a, 1985b, 1986b, 1989, and 1993). Guidelines for testing of chemicals for carcinogenicity generally consider 1,000 mg/kg/day as an upper limit for oral dosing (e.g., OECD Test Guideline 451, available at: http://www.oecd.org/chemicalsafety/testing/41753121.pdf). The highest dose tested in the mouse study

far exceeds the upper limit and the mid-dose level approached the upper limit. There were no treatment-related effects on tumor incidences in the female mice. Table 2-11 shows incidence data for renal tubular cell tumors in the male mice summarized by EPA (2015a). There were no statistically significant trends for increased incidence of renal tubule adenoma, carcinoma, or combined carcinoma or adenoma and no statistically significant differences between groups upon pairwise analyses.

Table 2-11. Incidences of Renal Tubular Cell Tumors in Male CD-1 Mice Administered Technical Glyphosate (99.78% Purity) in the Diet for up to 24 Months

	Dose (mg/kg/day)			
	0	161	835	4,945
Adenoma	1/49 (2%)	0/49 (0%)	0/50 (0%)	1/50 (2%)
Carcinoma	0/49 (0%)	0/49 (0%)	1/50 (2%)	2/50 (4%)
Adenoma or carcinoma (combined)	1/49 (2%)	0/49 (0%)	1/50 (2%)	3/50 (6%)

Source: EPA 2015a

In the other study, groups of CD-1 mice (50/sex/group) received glyphosate (≥97.5% purity) from the diet at 0, 100, 300, or 1,000 mg/kg/day for 104 weeks (EPA 2015c). Incidence data for tumors reported by EPA are summarized in Table 2-12. Compared to controls, the incidence of hemangiosarcoma in the high-dose males approached the level of statistical significance (p=0.056 according to Fishers exact test). A significant trend (p=0.00296) was noted for increased incidence of hemangiosarcoma with increasing dose. All tumors were malignant and were located in the liver and spleen of one mouse; liver of another mouse; spleen of a third mouse; and liver, spleen, and prostate of the fourth mouse. Hemangiosarcoma incidences among glyphosate-treated female mice were not significantly increased relative to controls. All tumors were malignant and were located in the uterus of one low-dose female, spleen of another low-dose female, and liver of the high-dose female.

Table 2-12. Incidences of Tumors in Male and Female CD-1 Mice Administered Glyphosate (≥97.5% Purity) in the Diet for up to 104 Weeks

	Dose (mg/kg/day)			
	0	100	300	1,000
Males				
Hemangiosarcoma	0/50[a] (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Histiocytic sarcoma	0/50 (0%)	2/50 (4%)	0/50 (0%)	2/50 (4%)
Females				

Table 2-12. Incidences of Tumors in Male and Female CD-1 Mice Administered Glyphosate (≥97.5% Purity) in the Diet for up to 104 Weeks

	Dose (mg/kg/day)			
	0	100	300	1,000
Hemangiosarcoma	0/50 (0%)	2/50 (4%)	0/50 (0%)	1/50 (2%)
Histiocytic sarcoma	0/50 (0%)	3/50 (6%)	3/50 (6%)	1/50 (2%)

[a]Significant trend (p=0.00296) for increasing incidence of hemangiosarcoma

Source: EPA 2015c

Additional studies were conducted evaluating the potential carcinogenicity and pathogenic role of glyphosate or glyphosate formulation in cancer, specifically multiple myeloma. George et al. (2010) evaluated the potential carcinogenicity of Roundup Original® using the 2-stage mouse skin carcinogenesis model. The study included groups of male Swiss albino mice (20/group) receiving the glyphosate formulation topically 3 days/week for 32 weeks, single topical application of dimethylbenz[a]anthracene (DMBA; a tumor initiator) followed by repeated dermal applications of 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA; a tumor promoter), single or multiple topical application of the glyphosate formulation followed by dermal applications of TPA (test for initiation potential of the glyphosate formulation), single application of DMBA followed by repeated dermal application of the glyphosate formulation (test for promotion potential of the glyphosate formulation), single DMBA application, repeated TPA application, and untreated controls. Skin tumors were observed in 100% of the DMBA + TPA treatment group; the first tumor appeared at 52 days. Tumors were noted in 40% of the DMBA + glyphosate formulation treatment group; the first tumor appeared at 130 days. No tumors were observed in other groups. The results indicate that the glyphosate formulation functioned as a tumor promoter, but not a tumor initiator or complete carcinogen.

In an effort to understand whether glyphosate is involved in the pathogenesis of multiple myeloma, Wang et al. (2019) treated wild type and multiple myeloma model mice (C57b1/b strain) with drinking water containing up to 30 g/L glyphosate for 7 days or 1.0 g/L of glyphosate for 72 weeks. Vk*MYC mice with sporadic MYC activation in germinal B cells have been found to be the best available animal model for multiple myeloma (MM); this model follows the biological and clinical progression of human multiple myeloma. In the acute study, neither spleen, body weight nor serum creatinine levels were altered, however, plasma cells in bone marrow, spleen and lymph nodes were elevated (Wang et al. 2019). In the chronic study of 72 weeks, Wang et al. (2019) observed glyphosate to damage the liver and kidney and induce splenomegaly and benign monoclonal gammopathy in wildtype (WT) mice, an early indicator of

MM in humans; in MM model mice, glyphosate was seen to cause splenomegaly and organ dysfunction including lytic bone lesions, renal, liver, lung and kidney damage. Glyphosate also promoted the progression of multiple myeloma in Vk*MYC mice as shown by the development of plasma cell neoplasms. Upregulation of activation-induced cytidine deaminase (AID), a B-cell genome mutator, in bone marrow and spleen was exhibited in wild type and MM model mice in both acute and chronic study duration (Wang et al. 2019).

Assessment of Carcinogenicity. Several national and international agencies and organizations have assessed the carcinogenicity of glyphosate (Table 2-13). These evaluations provide different types of determinations—some focused on hazard identification, or whether there is evidence that a chemical can cause an effect, and others focused on carcinogenic risk, or the likelihood of cancer effects at levels of exposure typically experienced by humans. In addition, there are large numbers of unpublished guideline studies on glyphosate and the inclusion or exclusion of these may account for the differences in the conclusions reached by these various agencies. For additional discussion regarding the carcinogenicity of glyphosate, refer to the following sources: Acquavella et al. 2016; Greim et al. 2015; McClellan 2016; Portier et al. 2016; Samsel and Seneff 2015; Tarazona et al. 2017; Williams et al. 2016.

Table 2-13. Carcinogenicity Classification

Organization	Reference	Classification	Justification
Domestic organizations			
U.S. Environmental Protection Agency	EPA 2017c, EPA 2017d, EPA 2020	Not likely to be carcinogenic to humans	EPA's January 2020 Glyphosate Interim Registration Review Decision finalized the Glyphosate Draft Human Health Risk Assessment in Support of Registration Review. Based on a weight of evidence analysis of animal, human, and genotoxicity studies, EPA concluded glyphosate is "not likely to be carcinogenic to humans." EPA (2017c) concluded "there is not strong support for the 'suggestive evidence of carcinogenic potential' cancer classification descriptor based on the weight-of-evidence, which includes the fact that even small, non-statistically significant changes observed in animal carcinogenicity and epidemiological studies were contradicted by studies of equal or higher quality."
International organizations			
Australian Pesticides and Veterinary Medicines Authority	APVMA 2017	Exposure does not pose a carcinogenic risk to humans	Concluded "that the scientific weight-of-evidence indicates that exposure to glyphosate does not pose a carcinogenic risk to humans".
European Chemical Agency	ECHA 2016	No hazard classification for carcinogenicity is warranted	Conclusion is "based on epidemiological data as well as on data from long-term studies in rats and mice, taking a weight of evidence approach, no hazard classification for carcinogenicity is warranted for glyphosate according to the CLP criteria"
European Food Safety Authority	EFSA 2015	Unlikely to pose a carcinogenic hazard to humans	Conclusion is based on very limited evidence for an association between glyphosate-based formulations and non-Hodgkin lymphoma, overall inconclusive for a causal or clear associative relationship between glyphosate and cancer in human studies, "no evidence of carcinogenicity" in rats or mice, and "unlikely to be genotoxic".
Food and Agricultural Organization/World Health Organization Joint Meeting on Pesticide Residues	FAO and WHO 2016	Unlikely to pose a carcinogenic risk to humans from dietary exposure	Conclusions were "in view of the absence of carcinogenic potential in rodents at human-relevant doses and the absence of genotoxicity by the oral route in mammals, and considering the epidemiological evidence from occupational exposures."
Health Canada	Health Canada 2015, 2017	Unlikely to pose a human cancer risk	In consideration of the strength and limitations of the large body of information on glyphosate, which included multiple short- and long-term (lifetime) animal toxicity studies and numerous *in vivo* and *in vitro* genotoxicity assays, as well as the large body of epidemiological information.

Table 2-13. Carcinogenicity Classification

Organization	Reference	Classification	Justification
International Agency for Research on Cancer	IARC 2017	Group 2A (*probably carcinogenic to humans)*	This classification is based on IARC's conclusions that there is "*limited evidence*" in humans, "*sufficient evidence*" in animals, and evidence that glyphosate and glyphosate-based formulations are genotoxic and capable of inducing oxidative stress.
New Zealand Environmental Protection Agency	NZ EPA 2016	Unlikely to be genotoxic or carcinogenic to humans	This conclusion is "based on a weight of evidence approach, and taking into account the quality and reliability of the available data – glyphosate is unlikely to be genotoxic or carcinogenic to humans."

2.20 GENOTOXICITY

The potential genotoxicity of glyphosate technical and glyphosate formulations has been extensively evaluated. The intent of this section of the Toxicological Profile for Glyphosate is to present representative results from available sources of information on glyphosate technical and glyphosate formulations. Results from selected *in vitro* and *in vivo* genotoxicity tests for glyphosate technical are presented in Table 2-14 and Table 2-15, respectively. Results from selected *in vitro* and *in vivo* genotoxicity tests for glyphosate formulations are presented in Table 2-16 and Table 2-17, respectively.

Table 2-14. Genotoxicity of Glyphosate Technical *In Vitro*

Species (test system)	Test substance purity	Endpoint	Result		Reference
			Activation		
			With	Without	
Salmonella typhimurium TA98, TA100, TA1535, TA1537	NS	Gene mutation	–	–	EPA 1992i
S. typhimurium TA98, TA100	NS	Gene mutation	–	–	Kubo et al. 2002
S. typhimurium TA97a, TA98, TA100, TA102	NS	Gene mutation	–	–	Chruscielska et al. 2000
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	98%	Gene mutation	–	–	Li and Long 1988
S. typhimurium TA97, TA98, TA100, TA1535	98.6%	Gene mutation	–	–	NTP 1992
Escherichia coli WP2 *hcr*	98%	Gene mutation	–	–	Li and Long 1988
Chinese hamster ovary cells	98%	Gene mutation	–	–	Li and Long 1988
Bacillus subtilis rec+, *rec*-	98%	*rec* assay	NT	–	Li and Long 1988
Human peripheral blood lymphocytes	>98%	Chromosomal aberrations	NT	+	Lioi et al. 1998a
Bovine peripheral blood lymphocytes	≥98%	Chromosomal aberrations	NT	+	Lioi et al. 1998b
Human peripheral blood lymphocytes	>96%	Chromosomal aberrations	NT	–	Mañas et al. 2009
Human peripheral blood lymphocytes	>98%	Sister chromatid exchange	NT	(+)	Lioi et al. 1998a
Human peripheral blood lymphocytes	99.9%	Sister chromatid exchange	NT	+	Bolognesi et al. 1997
Bovine peripheral blood lymphocytes	≥98%	Sister chromatid exchange	NT	(+)	Lioi et al. 1998b

Table 2-14. Genotoxicity of Glyphosate Technical *In Vitro*

Species (test system)	Test substance purity	Endpoint	Result		Reference
			Activation		
			With	Without	
Human-derived buccal epithelial cells	95%	Micronuclei	NT	+	Koller et al. 2012
Chinese hamster CHO-K1 cells	NS	Micronuclei	–	+	Roustan et al. 2014
Rat hepatocytes	98%	Unscheduled DNA synthesis	NT	–	Li and Long 1988
Human fibroblast CM5757 cells	96%	DNA damage	NT	+	Alvarez-Moya et al. 2014
Human fibroblasts	98.4%	DNA damage	NT	+	Lueken et al. 2004
Human peripheral blood lymphocytes	96%	DNA damage	NT	+	Mañas et al. 2009
Human GM38 cells	Technical grade	DNA damage	NT	+	Monroy et al. 2005
Human HT1080 (fibrosarcoma) cells	Technical grade	DNA damage	NT	+	Monroy et al. 2004, 2005
Chinese hamster ovary cells	Technical grade	DNA damage	NT	+	Monroy et al. 2004
Raji cells	95%	DNA damage	NT	+	Townsend et al. 2017
Human lymphocytes	NS	DNA damage	NT	+	Suarez-Larios et al. 2017
Human lymphocytes	NS	Chromosomal aberrations	NT	+	Santovito et al. 2018
Human lymphocytes	NS	Micronuclei	NT	+	Santovito et al. 2018
Peripheral blood mononuclear cells	NS	DNA damage	NT	+	Kwiatkowska et al. 2017
HEPG2	Standard purity <100%	DNA damage	NT	+	Kasuba et al. 2017
HEPG2	Standard purity <100%	Micronuclei	NT	+	Kasuba et al. 2017
HEC1A	99.5%	DNA damage	NT	+	De Almeida et al. 2018
MDA MB 231	99.5%	DNA damage	NT	+	De Almeida et al. 2018
MCF7	99.5%	DNA damage	NT	-	De Almeida et al. 2018
Mouse (oocytes)	NS	DNA Damage	NT	+	Zhang et al. 2019b
Mouse (oocytes)	NS	Abnormal chromosome spindle		+	Zhang et al. 2019b

– = negative result; + = positive result; (+) = weakly positive result; +/– = equivocal result; DNA = deoxyribonucleic acid; NS = not specified; NT = not tested

Table 2-15. Genotoxicity of Glyphosate Technical *In Vivo*

Species (test system)	Test substance purity	Endpoint	Result	Reference
		Oral exposure		
Mouse (bone marrow)	98.6%	Micronuclei	–	NTP 1992
Mouse (male germ cells)	98.7%	Dominant lethal mutation	–	EPA 1992j
		Intraperitoneal injection		
Rat (bone marrow)	98%	Chromosomal aberrations	–	Li and Long 1988
Mouse (bone marrow)	99.9%	Micronuclei	+	Bolognesi et al. 1997
Mouse (bone marrow)	96%	Micronuclei	+	Mañas et al. 2009
Mouse (bone marrow)	NS[a]	Micronuclei	–	Rank et al. 1993
Mouse (liver DNA)	99.9%	DNA damage	+	Bolognesi et al. 1997
Mouse (kidney DNA)	99.9%	DNA damage	+	Bolognesi et al. 1997
Mouse (liver DNA)	99.9%	Oxidative DNA damage	+	Bolognesi et al. 1997
Mouse (kidney DNA)	99.9%	Oxidative DNA damage	–	Bolognesi et al. 1997
Mouse (liver, kidney DNA)	NS[a]	DNA adducts	–	Peluso et al. 1998
Rats (leukocytes, liver DNA)	≤100 %	DNA damage	+	Milic et al. 2018

[a]Test substance: glyphosate isopropylamine salt.

– = negative result; + = positive result; DNA = deoxyribonucleic acid; NS = not specified

Table 2-16. Genotoxicity of Glyphosate Formulations *In Vitro*

Test system	Glyphosate formulation	End point	Result: Activation: With	Result: Activation: Without	Reference
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Roundup® (composition NS)	Gene mutation	–	–	Moriya et al. 1983
S. typhimurium TA98	Roundup® (48% glyphosate isopropylamine salt)	Gene mutation	–	(+)[a]	Rank et al. 1993
S. typhimurium TA100	Roundup® (48% glyphosate isopropylamine salt)	Gene mutation	(+)[b]	–	Rank et al. 1993
S. typhimurium TA98, TA100	Glyphosate (Unspecified commercial formulation)	Gene mutation	–	–	Wildeman and Nazar 1982
Escherichia coli WP2 *hcr*	Roundup® (composition NS)	Gene mutation	–	–	Moriya et al. 1983

Table 2-16. Genotoxicity of Glyphosate Formulations *In Vitro*

Test system	Glyphosate formulation	End point	Result		Reference
			Activation		
			With	Without	
Bovine peripheral blood lymphocytes	Glyphosate (62% w/w isopropylamine salt; 38% unspecified inerts)	Chromosomal aberrations	NT	–	Holečková 2006
Bovine peripheral blood lymphocytes	Glyphosate (62% isopropylamine salt; 38% unspecified inerts)	Chromosomal aberrations	NT	–	Šiviková and Dianovskỳ 2006
Human peripheral blood lymphocytes	Roundup® (not otherwise described)	Sister chromatid exchange	NT	(+)	Vigfusson and Vyse 1980
Human peripheral blood lymphocytes	Roundup® (30.4% glyphosate)	Sister chromatid exchange	NT	+	Bolognesi et al. 1997
Bovine peripheral blood lymphocytes	Glyphosate (62% isopropylamine salt; 38% unspecified inerts)	Sister chromatid exchange	+	+	Šiviková and Dianovskỳ 2006
Human-derived buccal epithelial cells	Roundup Ultra Max® (45% glyphosate)	Micronuclei	NT	+	Koller et al. 2012
Bovine peripheral blood lymphocytes	Glyphosate (62% isopropylamine salt; 38% unspecified inerts)	Micronuclei	NT	(+)	Piešová 2004
Bovine peripheral blood lymphocytes	Glyphosate (62% isopropylamine salt; 38% unspecified inerts)	Micronuclei	NT	(+)	Piešová 2005
Human liver HepG2 cells	Grands Travaux® (40% glyphosate)	DNA damage	NT	(+)	Gasnier et al. 2009
E. coli PQ37	Roundup BIO® (NS)	DNA damage	NT	+	Raipulis et al. 2009
HEC1A	Roundup	DNA damage	NT	+	De Almeida et al. 2018
MDA MB 231	Roundup	DNA damage	NT	+	De Almeida et al. 2018
MCF7	Roundup	DNA damage	NT	-	De Almeida et al. 2018
HEC1A	Wipeout	DNA damage	NT	+	De Almeida et al. 2018
MDA MB 231	Wipeout	DNA damage	NT	+	De Almeida et al. 2018
MCF7	Wipeout	DNA damage	NT	-	De Almeida et al. 2018
peripheral blood mononuclear cells	Roundup	DNA damage	NT	+	Wozniak et al. 2018

Table 2-16. Genotoxicity of Glyphosate Formulations *In Vitro*

Test system	Glyphosate formulation	End point	Result		Reference
			Activation		
			With	Without	

[a]Weakly positive at 360 µg/plate in one test (4-fold increase in revertants/plate) but not in another test; cytotoxicity at concentrations ≥360 µg/plate.
[b]Weakly positive at 720 µg/plate (3.3-fold increase in revertants/plate); cytotoxicity at concentrations ≥360 µg/plate.

– = negative result; + = positive result; (+) = weakly positive result; NS = not specified; NT = not tested

Table 2-17. Genotoxicity of Glyphosate Formulations *In Vivo*

Species (test system)	Test substance (purity)	End point	Result	Reference
Drosophila (sex-linked recessive lethal mutation assay)[a]	Roundup® (glyphosate isopropylamine salt; purity NS)	Gene mutation	+	Kale et al. 1995
		Oral		
Mouse (bone marrow)	Roundup® (9.8% active ingredient)	Chromosomal aberrations	–	Dimitrov et al. 2006
		Intraperitoneal injection		
Mouse (bone marrow)	Roundup® (>41% glyphosate isopropylamine salt)	Chromosomal aberrations	+	Prasad et al. 2009
Mouse (bone marrow)	Roundup® (48% glyphosate isopropylamine salt)	Micronuclei	–	Rank et al. 1993
Mouse (bone marrow)	Roundup® (30.4% glyphosate)	Micronuclei	+	Bolognesi et al. 1997
Mouse (bone marrow)	Roundup® (9.8% glyphosate)	Micronuclei	–	Dimitrov et al. 2006
Mouse (bone marrow)	Roundup® (>41% glyphosate isopropylamine salt)	Micronuclei	+	Prasad et al. 2009
Mouse (bone marrow)	Roundup® (48% glyphosate isopropylammonium salt; 12% inerts including POEA)	Micronuclei	–	Grisolia 2002
Mouse (liver DNA)	Roundup® (30.4% glyphosate)	DNA damage	+	Bolognesi et al. 1997
Mouse (kidney DNA)	Roundup® (30.4% glyphosate)	DNA damage	+	Bolognesi et al. 1997
Mouse (liver DNA	Roundup® (30.4% glyphosate)	Oxidative DNA damage	–	Bolognesi et al. 1997
Mouse (kidney DNA)	Roundup® (30.4% glyphosate)	Oxidative DNA damage	+	Bolognesi et al. 1997

Table 2-17. Genotoxicity of Glyphosate Formulations *In Vivo*

Species (test system)	Test substance (purity)	End point	Result	Reference
Mouse (liver, kidney DNA)	Roundup® (30.4% glyphosate isopropylammonium salt)	DNA adducts	+	Peluso et al. 1998

[a]*Drosophila* larvae were exposed to test substance in growing medium.

+ = positive result; – = negative result; DNA = deoxyribonucleic acid; NS = not specified

Glyphosate Technical. Glyphosate did not induce gene mutations either with or without exogenous metabolic activation in numerous bacterial assays, or in assays using mammalian cells (Chruscielska et al. 2000; EPA 1992i, Kubo et al. 2002; Li and Long 1988; NTP 1992). Lioi et al. (1998a, 1998b) reported concentration-related significant increases in chromosomal aberrations in human and bovine peripheral blood lymphocytes exposed to glyphosate, although concomitant decreases in mitotic index were indicative of some degree of cytotoxicity at least at the highest glyphosate concentrations. Mañas et al. (2009) found no evidence of glyphosate-induced chromosomal aberrations in human peripheral blood lymphocytes. Glyphosate was positive for induction of sister chromatid exchange in one assay using human peripheral blood lymphocytes (Bolognesi et al. 1997); weakly positive responses were obtained in other assays using human lymphocytes (Lioi et al. 1998a) and bovine lymphocytes (Lioi et al. 1998b). There was some evidence of cytotoxicity in the assays of Lioi et al. (1998a, 1998b). The result was considered equivocal due to significant apoptosis at concentrations resulting in significantly increased micronuclei frequency. Koller et al. (2012) reported significantly increased frequency of micronuclei in an assay using human-derived buccal epithelial cells exposed to glyphosate. Roustan et al. (2014) reported significantly increased micronuclei frequency in Chinese hamster ovary K1 cells exposed to glyphosate without (but not with) exogenous metabolic activation. Negative results were obtained in an assay that evaluated the potential for glyphosate to induce unscheduled DNA synthesis in rat hepatocytes (Li and Long 1988). Mañas et al. (2009) and Lueken et al. (2004) reported positive results for DNA damage in glyphosate-exposed human fibroblasts. Alvarez-Moya et al. (2014) reported DNA damage in human fibroblast CM5757 cells exposed to glyphosate technical. Exposure-related DNA damage was observed in assays of human GM38 cells (Monroy et al. 2005), human HT1080 (fibrosarcoma) cells (Monroy et al. 2004, 2005), and Chinese hamster ovary cells (Monroy et al. 2004) exposed to glyphosate technical.

Townsend et al (2017) evaluated DNA damage in human Raji cells exposed to various concentrations of glyphosate. Significant DNA damage occurred after exposure to concentrations of 1 or 5 mM for 30 to 60 minutes. However, after two hours, DNA damage was no longer apparent. One hour after the initial exposure, cells were again exposed to the same concentrations for the same length of time. DNA repair was not observed in any cells after two exposures (Townsend et al. 2017). Suarez-Larios et al (2017) also reported DNA damage in the form of double strand breaks in human lymphocytes after exposure to glyphosate. Santovito et al (2018) reported increases in chromosomal aberrations, micronuclei, and nuclear microplasmic bridges with increasing doses of glyphosate in human lymphocytes. Kwiatkowska et al (2017) also reported DNA damage in the form of single and double stand breaks in human lymphocytes after exposure to glyphosate. However, after two hours, significant repair of the DNA had occurred. The authors also reported a significant decrease in DNA methylation levels.

DNA damage was also reported in HEPG2 cells after 4 hours of exposure but not after 24 hours of exposure (Kasuba et al. 2017). Kasuba et al (2017) also report statistically significant increases in micronuclei and nuclear buds after four hours of exposure. Increases were also reported for nucleoplasmic bridges, but not at statistically significant levels after four hours of exposure. After 24 hours of exposure, decreases in micronuclei and nucleoplasmic bridges were noted (Kasuba et al. 2017). De Almeida et al (2018) also reported DNA damage in two of three cell lines assessed: HEC1A and MDA MB 231. No significant damage was reported for the MCF7 cell line. Wozniak et al (2018) reported DNA damage for human peripheral blood mononuclear cells after exposure to glyphosate for 24 hours. Elie-Caille et al. (2010) examined the effects of glyphosate on human keratinocyte cell lines and found alterations in cell morphology and size that were indicative of apoptosis.

Koureas et al. (2014) investigated the effects of occupational exposures to pesticides on oxidative DNA damage. Use of herbicides (defined as glyphosate, ammonium or glufosinate) was significantly associated with increased risk of oxidative damage, as measured by levels of 8-hydroxy-2-deoxyguanosine in whole blood (RR = 2.60; 95% CI: 1.35-5.04). However, no significant associations were found between levels of this marker and glyphosate exposure specifically (RR = 1.47; 95% CI: 0.78-2.77).

Zhang et al. (2019b) reported DNA damage in the form of double strand breaks as well as abnormal spindly morphology in mouse oocytes after exposure to up to 500 μM glyphosate for 14h. See section 2.16 for a discussion of non-genotoxic reproductive effects associated with glyphosate exposure.

The genotoxicity of glyphosate technical has been evaluated in a number of *in vivo* tests; results are mixed across a variety of cell types. Glyphosate did not induce dominant lethal mutations following oral dosing of male CD-1 mice once by gavage at up to 2,000 mg/kg (EPA 1992j). Glyphosate did not increase the frequency of micronuclei in bone marrow cells from B6C3F1 mice administered glyphosate in the diet for 13 weeks at concentrations resulting in estimated doses as high as 10,780–11,977 mg/kg/day (NTP 1992). Glyphosate did not increase the frequency of micronuclei in bone marrow cells from C3H mice administered glyphosate technical via single intraperitoneal injection (Chruscielska et al. 2000) or NMRI-bom mice administered glyphosate (as isopropylammonium salt) via two intraperitoneal injections 24 hours apart (Rank et al. 1993). Glyphosate did not induce chromosomal aberrations in bone marrow cells from rats administered glyphosate via intraperitoneal injection at 1,000 mg/kg (Li and Long 1988). Kier and Kirkland (2013) summarized results from 10 industry studies that evaluated frequency of micronuclei in bone marrow cells from mice or rats administered glyphosate orally or via intraperitoneal injection; results were consistently negative for glyphosate-induced micronuclei, although an inconclusive result was determined for one study.

However, other investigators reported positive results for micronuclei induction in bone marrow cells from mice administered glyphosate via intraperitoneal injection by single 300 mg/kg dose (Bolognesi et al. 1997) or two 200 mg/kg doses 24 hours apart (Mañas et al. 2009). Bolognesi et al. (1997) reported significantly increased frequency of DNA damage (single strand breaks) in liver and kidney and significantly increased frequency of oxidative DNA damage in liver (but not kidney) from mice administered glyphosate via single intraperitoneal injection at 300 mg/kg. Peluso et al. (1998) found no evidence of the formation of DNA adducts in liver or kidney from mice following intraperitoneal injection of glyphosate (as isopropylammonium salt) at up to 270 mg/kg. It should be noted that intraperitoneal injection studies typically employed lethal dose levels; a positive result at such high dose levels does not necessarily indicate potential for genotoxicity at doses relevant to human exposure. Rats exposed up to 10 mg/kg bw/day glyphosate orally for 28 days were reported to have DNA damage in leukocytes and liver cells compared to controls (Milic et al. 2018). Furthermore, liver cell DNA damage was greatest in the lowest (0.1 mg/kg bw/day) and highest (10 mg/kg bw/day) exposure groups (Milic et al. 2018).

DNA damage in human fibroblast cells and peripheral blood lymphocytes were the most frequently reported clearly positive results from available *in vitro* assays that employed glyphosate technical. From available *in vivo* assays that employed glyphosate technical, DNA damage in mouse kidney and liver was

the most frequent positive result. Summaries should be interpreted with caution because the genotoxicity of glyphosate technical was assessed based on a limited number of primary results available to ATSDR.

Glyphosate Formulations. Glyphosate formulations (active ingredient typically ranging from approximately 30 to 62% of the formulation) were not mutagenic to bacterial test systems in available published studies (Chruscielska et al. 2000; Moriya et al. 1983; Wildeman and Nazar 1982), numerous unpublished industry studies summarized by Kier and Kirkland (2013), or several other studies summarized by Williams et al. (2000). Weakly positive results were obtained for *Salmonella typhimurium* strain TA98 in the absence (but not presence) of exogenous metabolic activation and strain TA100 in the presence (but not absence) of exogenous metabolic activation (Rank et al. 1993); however, the positive responses were observed at concentrations exhibiting cytotoxicity and in only one of two tests in strain TA98. Glyphosate formulations did not induce chromosomal aberrations in bovine peripheral blood lymphocytes in two assays that employed 24-hour exposures (Holečková 2006; Šiviková and Dianovskỳ 2006); however, a significant increase in sister chromatid exchange was noted both with and without exogenous metabolic activation (Šiviková and Dianovskỳ 2006). A slight, (statistically significant) 1.1–1.3-fold increase in frequency of sister chromatid exchange was observed in human peripheral blood lymphocytes exposed to Roundup® (Vigfusson and Vyse 1980). Bolognesi et al. (1997) reported significantly increased sister chromatid exchange (1.3–1.5-fold greater than that of controls) in human peripheral blood lymphocytes exposed to Roundup® for 72 hours at concentrations of 0.1 and 0.33 mg/mL. The magnitude of this effect was comparable to that obtained using analytical-grade glyphosate at 10 times the concentration of the Roundup® formulation, indicating that other substances in the Roundup® formulation may have been at least partly responsible for the effect. In two assays, unspecified glyphosate formulations induced micronuclei in cultured bovine peripheral blood lymphocytes at noncytotoxic concentrations (Piešová 2004, 2005). Koller et al. (2012) reported significantly increased numbers of micronuclei in human-derived buccal epithelial cells exposed to Roundup Ultra Max® for 20 minutes, including concentrations that were noncytotoxic; this effect was more pronounced than that resulting from similar treatment using analytical grade glyphosate. A weakly positive result for DNA damage was reported for human liver HepG2 cells exposed to Roundup Grands Travaux® (Gasnier et al. 2009). Roundup® induced dose-dependent increases in DNA damage and the proportion of apoptotic cells in human alveolar carcinoma cells (Hao et al. 2019). In the same study, DNA single-strand and double-strand breaks, and the collapse of mitochondrial membrane were induced by RoundUp® concentrations ranging from 50 to 125 µg/mL (Hao et al. 2019). Exposure to non-specified concentrations of glyphosate resulted in treatment-related DNA damage in *Escherichia coli* PQ37 cells (Raipulis et al. 2009). Wozniak et al (2018) reported DNA damage for human peripheral blood

mononuclear cells after exposure to Roundup 360 plus for 24 hours at a dose two orders of magnitude lower than glyphosate. De Almeida et al (2018) also reported DNA damage in two of three cell lines exposed to Roundup and Wipeout: HEC1A and MDA MB 231. No significant damage was reported for the MCF7 cell line.

Several studies were designed to evaluate the genotoxicity of selected glyphosate formulations *in vivo*; similar to findings from *in vivo* studies using glyphosate technical, mixed results were obtained from *in vivo* exposure to glyphosate-containing products. Roundup® induced mutations in *Drosophila* in a sex-linked recessive lethal mutation assay (Kale et al. 1995). Roundup® did not induce chromosomal aberrations or micronuclei in mice administered the test chemical orally at a 1,080 mg/kg dose, reported by the study authors as one-half the LD_{50} (Dimitrov et al. 2006). The potential for Roundup® to induce chromosomal aberrations and/or micronuclei in bone marrow cells has been assessed in several studies in which the test chemical was administered to mice via intraperitoneal injection. Although intraperitoneal administration of Roundup® at 25 and 50 mg/kg resulted in significantly increased frequencies of chromosomal aberrations and micronuclei, both doses appeared to be cytotoxic, as indicated by time- and dose-related significant decreases in mitotic indices (Prasad et al. 2009). Roundup® induced micronuclei in bone marrow from mice administered the chemical via intraperitoneal injection at 300 mg/kg (expressed as glyphosate) (Bolognesi et al. 1997). Negative results were reported in two other studies that evaluated micronucleus induction in bone marrow cells from mice treated by intraperitoneal injection of Roundup® (Grisolia 2002; Rank et al. 1993). In the study of Grisolia (2002), polyoxyethylene amine surfactant accounted for 12% of the formulation. Negative results were also reported for micronucleus induction in bone marrow cells from mice treated by intraperitoneal injection of a commercial formulation identified only as Perzocyd 10 SL (Chruscielska et al. 2000). Roundup® induced single-strand breaks in DNA from liver and kidney of mice administered the chemical via intraperitoneal injection at 300 mg/kg (expressed as glyphosate) and oxidative DNA damage in kidney (but not liver) cells (Bolognesi et al. 1997). However, Heydens et al. (2008) repeated the study design of Bolognesi et al. (1997) and found a 300 mg/kg intraperitoneally-injected dose to be highly toxic to liver and kidney. It was suggested that the genotoxic effects observed by Bolognesi et al. (1997) might have been secondary effects mediated by local toxicity. Peluso et al. (1998) reported the formation of DNA adducts in liver and kidney from mice following intraperitoneal injection of Roundup® at doses in the range of 122–182 mg active ingredient/kg. The DNA adduct formation was considered likely related to other components of the Roundup® formulation because DNA adduct formation was not observed in mice similarly treated with analytical-grade glyphosate at 270 mg/kg.

Exposure to glyphosate-containing products and evidence of genetic damage was reported in limited human studies that did not measure specific exposure levels. Paz-y-Miño et al. (2007) evaluated prevalence of DNA strand breaks in blood samples from 24 residents of an area in northern Ecuador at 2 weeks to 2 months following aerial applications of Roundup-Ultra®; the study included 21 unexposed control individuals. The exposed individuals exhibited a higher degree of DNA damage (comet length 35.5±6.4 µm) than the unexposed controls (comet length 25.94±0.6 µm). There was no evidence of exposure-related chromosomal damage among 92 individuals from 10 communities near the northern Ecuador border evaluated at 2 years following the last aerial applications of glyphosate-containing herbicides (Paz-y-Miño et al. 2011). Bolognesi et al. (2009) reported increases in micronuclei in peripheral blood lymphocytes from nearby residents following aerial spraying of glyphosate-based formulation with adjuvant to coca and poppy crops, or without adjuvant on sugar-cane plantations. These residents were evaluated both prior to and following aerial spraying.

DNA damage in human cells was the most frequently reported clearly positive results from available *in vitro* assays that employed glyphosate formulations. However, comparison of results across available studies was precluded due to lack of information regarding the composition of the various formulations tested. From available *in vivo* assays that employed glyphosate formulations, DNA damage in mouse kidney and liver was the most frequent positive result. Summaries should be interpreted with caution because the genotoxicity of glyphosate technical was assessed based on a limited number of primary results available to ATSDR.

Additional unpublished genotoxicity assays were submitted to EPA and/or the European Commission (EC) during re-registration of products containing glyphosate. Many agencies, organizations, and/or expert panels have reviewed available genotoxicity data and concluded that the data do not support a genotoxicity role for glyphosate, at least at concentrations relevant to human exposure (e.g., APVMA 2017; Brusick et al. 2016; EFSA 2015; EPA 2017c; FAO and WHO 2016; Health Canada 2017; Kier and Kirkland 2013; NZ EPA 2016; Williams et al. 2016). In contrast, IARC (2017) concluded that there is strong evidence for the genotoxicity of glyphosate. For more detailed information regarding genotoxicity evaluations and conclusions of these agencies, organizations, and/or expert panels, consult corresponding references.

2.21 MECHANISMS OF ACTION

Mechanism of Action in Plants. Glyphosate-based herbicides act on the shikimate pathway in plants by blocking the activity of the enzyme, 5-enolpyruvylshikimate-3-phosphate synthetase (EPSPS), thereby inhibiting the biosynthesis of essential aromatic amino acids in plants (see Funke et al. 2006; Martinez et al. 2018; Pollegioni et al. 2011 for more specific information regarding mechanisms of action). The action of glyphosate on the shikimate pathway is not of direct human concern because this pathway does not exist in mammals. However, animal exposures to glyphosate could impact the shikimate pathway of gut bacteria, thereby affecting the gut microbiome (Aitbali et al. 2018; Deschartres et al. 2019; Lozano et al. 2018). The implications of microbiome effects are further discussed in Section 3.1.3.

Some crop plants have been genetically modified to resist the action of glyphosate by the addition of a glyphosate-insensitive form of EPSPS (CP4 EPSPS) obtained from *Agrobacterium* sp. strain CP4 (Funke et al. 2006). Some transgenic plants have been genetically altered to express N-acetyltransferase proteins (e.g., glyphosate acetyltransferase [GAT4601] from *Bacillus licheniformis*), which acetylate glyphosate to a non-phytotoxic metabolite (N-acetylglyphosate) (Pioneer 2006).

Proposed Mechanisms of Action with Human Relevance. Although glyphosate is generally considered to be of relatively low toxicity to mammals, the following mechanisms of action have been proposed:

Hepatotoxicity. Ford et al. (2017) administered glyphosate to male C57BL/6 mice by intraperitoneal injection at 200 mg/kg/day for 7 days, after which livers were evaluated for levels of glyphosate, aminomethylphosphonic acid (AMPA), and glyoxylate (a reactive substance produced endogenously). Glyphosate treatment at this high dose level resulted in measurable levels of AMPA, indicating some degree of glyphosate metabolism. Glyphosate treatment also resulted in an approximately 2-fold increase in glyoxylate. Because glyoxylate is formed endogenously, the increase in glyoxylate level in the liver may be a result of glyphosate acting on mechanisms responsible for endogenous production of glyoxylate. The study authors demonstrated that glyoxylate inhibited liver fatty acid oxidation enzymes in mice and that glyphosate treatment increased triglycerides and cholesteryl esters, which was considered a likely result of the diversion of fatty acids toward lipid pathways other than oxidation. In another study, Astiz et al. 2009 exposed rats to 10 mg/kg/bw of glyphosate three times a week for five weeks via injection and measured oxidative stress and cell damage. In the liver, lipid peroxidation as measured by thiobarbituric acid-reactive substances (TBARS) was two times greater than control; antioxidant (alpha-Tocopherol) and SOD levels were significantly decreased suggestive of oxidative damage induced by glyphosate.

Enzyme levels of γ-glutamyl transpeptidase, a sensitive biomarker for hepato-cellular damage, increased by 125% compared to controls indicating glyphosate induces cell damage. No clinical signs of animal toxicity were observed during the experiment. An *in vitro* assessment of Roundup® cytotoxicity on human L-02 hepatocytes determined that exposure induced structural and morphological changes in cell membranes, mitochondria and nuclei, in addition to cell shrinkage, nuclear fragmentation, and mitochondrial vacuolar degenerations (Luo et al. 2017). Study authors determined that the Roundup-induced overproduction of reactive oxygen species led to oxidative stress responses affecting normal cell function.

Renal toxicity. Mohamed et al. (2016) observed increases in serum and urinary cystatin C and urinary interleukin-18, cytochrome C, and neutrophil gelatinase-associated protein (NGAL) in patients presenting with poisoning from glyphosate-based formulations. The study authors noted that the increases in cystatin C and interleukin-18 suggest that glyphosate-based formulations might induce apoptosis and mitochondrial toxicity.

Astiz et al. 2009 reported increases in oxidative stress in the kidney tissues of rats exposed to 10 mg/kg/bw day glyphosate as measured by TBARS and a decrease in superoxide dismutase activity (SOD) level. Dedeke et al. (2018) administered glyphosate alone or a glyphosate-based formulation to rats by daily gavage for 12 weeks at dose levels of 3.6, 50.4, or 248.8 mg glyphosate/kg/day. The rats administered the glyphosate-based formulation exhibited significantly altered markers of kidney changes (serum urea and creatinine, plasma cystatin-C, NGAL), oxidative stress, and activities of selected membrane-bound enzymes compared to the rats treated with glyphosate alone. Those rats administered glyphosate-based formulation were the only ones to exhibit severe histopathologic kidney lesions. The study authors suggested that these results did not support a nephrotoxic role for glyphosate alone.

Dermal Toxicity. George and Shukla (2013) examined whether the mechanism of action for glyphosate and its potentially tumor-promoting properties could be elucidated; previously the research group found glyphosate to cause tumor promotion in mouse skin carcinogenesis (George et al. 2010). In an in-vitro model, human skin keratinocyte, or HaCaT cells, were exposed to up to 1 mM of glyphosate for 72 hours. Glyphosate was observed to induce proliferation, decrease Ca+2 and increase reactive oxygen species (ROS) generation in HaCaT cells. Taken together, these suggest glyphosate may possibly have a proliferative effect on HaCaT cells by disturbing the homeostasis levels of Ca+2 and decrease SOD1 to increase ROS generation potentially leading to neoplastic growth in the mammalian skin system.

Gehin et al. (2005) evaluated the cytotoxic effect of glyphosate or glyphosate formulation (Roundup 3® plus) in relation to antioxidants such as Vitamin C and E, glyphosate formulation was found to be more toxic than glyphosate after epidermal HaCaT cells were exposed to the herbicide for 24 hours. Taken together, glyphosate-based formulations, and comparatively to a lesser degree, glyphosate, are implicated in generating oxidative damage, which in turn may lead to dermal toxicity. The interaction between glyphosate and other chemicals (e.g. surfactants) may explain this observation; Section 3.4 discusses this further.

Neurotoxicity. Astiz et al. 2009 reported increases in oxidative stress in the brain of rats exposed to 10 mg/kg/bw day glyphosate as measured by increased concentrations of TBARS, altered levels of antioxidant enzymes (decrease in superoxide dismutase and increase in catalase activity), and nitric oxide metabolites.

Cattani et al. (2014) added 1% Roundup® (0.38% glyphosate) to the drinking water of rat dams from gestation day 5 through lactation day 15. Hippocampal slices from 15-day-old pups were exposed to Roundup® (0.00005–0.1%) for 30 minutes. The study authors reported that Roundup® treatment resulted in increased Ca^{2+} influx via activation of NMDA receptors and voltage-dependent Ca^{2+} channels, activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and extracellular signal-regulated kinase (ERK), increased glutamate release into the synaptic cleft, decreased glutathione content, increased lipoperoxidation, decreased glutamate uptake and metabolism, and induced Ca^{2+} uptake and methyl-amino-isobutyric acid accumulation. The study authors suggested that exposure to Roundup® might lead to excessive extracellular glutamate levels and resulting glutamate excitotoxicity and oxidative stress in rat hippocampus.

Martinez and Al-Ahmad (2019) examined the effects of glyphosate on the blood brain barrier in vitro on induced pluripotent stem cells (iPSCs) after a single exposure. The study used a range of concentrations similar to levels found in patients and occupational exposures. Following treatment of 1 to 10 µM glyphosate for 24 hours, there was increased blood brain barrier permeability to fluorescein (dye) indicating disruption of the barrier function. Glyphosate permeated across the blood brain barrier via a transcellular mechanism. Subsequently, neuronal cell metabolic activity and glucose uptake in brain microvascular endothelial cells was observed. Study authors suggest that exposure to glyphosate may lead to increased blood brain barrier permeability and alteration of glucose metabolism resulting in neurological damage.

Reproductive/endocrine effects. Perego et al. (2017) reported results from an *in vitro* study designed to evaluate the effects of glyphosate treatment (up to 5 µg/mL) on bovine granulosa cells and theca cells. Granulosa cell proliferation and estradiol production were impaired, but no effects were observed on theca cell proliferation or steroidogenesis. The results suggest that glyphosate may affect the reproductive system in cattle via direct action on ovarian function. EPA evaluated results from the battery of *in vitro* assays and relevant laboratory mammalian and wildlife studies. Using this approach, EPA determined that there is no convincing evidence of potential interaction between glyphosate and estrogen or androgen.

Zhang et al. (2019b) evaluated the effects of glyphosate on mice oocytes, and found reduced rates of germinal vesicle breakdown (GVBD) and first polar body extrusion (PBE), indicating disruption of nuclear oocyte maturation after treatment with 500 µm glyphosate. In response to glyphosate exposure, cells produced excess reactive oxygen species, displayed abnormal spindle morphology, DNA double strand breaks, aggregated distribution of mitochondria and decrease in membrane potential of oocytes. Genes related to oxidative-stress (cat, sod2, gpx) were found expressed at greater levels than the control group; on the other hand, expression of apoptosis related genes including Bcl-2 (inhibits apoptosis) decreased, while Bax (pro-apoptosis gene), increased. Zhang et al. (2019b) suggests these changes led to the generation of oxidative stress and early apoptosis that result in the interference of mouse oocyte maturation and development.

Romano et al. (2010) reported decreased serum testosterone in young male rats gavaged with Roundup Transorb®. Romano et al. (2012) implicated disruption of gonadotropin expression as a mechanism of action.

Vanlaeys et al. (2018) evaluated the effects of Roundup Bioforce® and Glyphogan on cultured mice TM4 Sertoli cell lines. These formulations induced dose-dependent cell death, and induced cell mitochondrial dysfunction, lipid droplet accumulation, and disruption of cell detoxification systems. Additionally, the penetration and accumulation of glyphosate formulants in cells led to cell death. Vanlaeys et al. (2018) suggests these mechanisms can lead to disruption of reproductive function in pre-pubertal mammals.

Carcinogenicity. As stated in Section 2.20 (Genotoxicity), IARC (2017) concluded that there is strong evidence for the genotoxicity of glyphosate, although other agencies, organizations, and/or expert panels have concluded that the data do not support a genotoxicity role for glyphosate (e.g., APVMA 2017; Brusick et al. 2016; EFSA 2015; EPA 2017c; FAO and WHO 2016; Health Canada 2017; Kier and

Kirkland 2013; NZ EPA 2016; Williams et al. 2016). IARC (2017) also concluded that there is strong evidence for glyphosate-induced oxidative stress based on results from studies of animal models *in vivo* and human cells *in vitro*.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Toxicokinetic data for glyphosate are summarized below.

- Glyphosate is readily absorbed from the gastrointestinal tract; very little glyphosate is absorbed through the skin; it is assumed that glyphosate is readily absorbed from the respiratory tract.
- Absorbed glyphosate is readily distributed via the blood, but does not accumulate in any particular organ or tissue.
- Glyphosate does not undergo significant metabolism in mammals; <1% is metabolized to aminomethylphosphonic acid (AMPA).
- Approximately two-thirds of an oral dose of glyphosate is excreted in the feces as unabsorbed parent compound. Most absorbed glyphosate is rapidly excreted in the urine as parent compound.

3.1.1 Absorption

3.1.1.1 Inhalation Exposure

Limited information is available regarding the toxicokinetics of inhaled glyphosate. Observations of increased urinary glyphosate levels among 48 farmer-applicators following application of glyphosate-containing products is evidence that inhaled glyphosate can be absorbed (Acquavella et al. 2004). However, dermal absorption was likely involved in some cases because mean urinary glyphosate was higher among those farmers (14/48) who did not use rubber gloves. Detectable levels of urinary glyphosate were also measured in children of the farmers who were present during mixing, loading, or application of the herbicide; exposures among the children may have involved inhalation and/or dermal routes. No information was located regarding the toxicokinetics of inhaled glyphosate in laboratory animals.

3.1.1.2 Oral Exposure

Information regarding the toxicokinetics of ingested glyphosate in humans is limited. The detection of glyphosate in serum and/or urine samples from individuals who had intentionally or unintentionally

ingested glyphosate-containing products is confirmation of absorption from the gastrointestinal tract (e.g., Hiraiwa et al. 1990; Hori et al. 2003; Sribanditmongikol et al. 2012; Zouaoui et al. 2013). Numerous reports of systemic effects following intentional or unintentional ingestion of glyphosate-containing products serve as additional evidence that ingested glyphosate is absorbed (e.g., Chang and Chang 2009; Chen et al. 2009; Hsiao et al. 2008; Kim et al. 2014; Lee et al. 2000; Menkes et al. 1991; Moon and Chun 2010; Roberts et al. 2010; Sato et al. 2011; Sawada et al. 1988; Sørenson and Gregersen 1999; Stella and Ryan 2004; Talbot et al. 1991; Tominack et al. 1991).

Several groups of investigators have evaluated the absorption of glyphosate following oral exposure in laboratory animals, particularly rats. In one study (NTP 1992), male F344/N rats were administered a single gavage dose of ^{14}C-glyphosate (purity 99%) in distilled water at 5.6 or 56 mg/kg. Other rats were administered a single dose of glyphosate at 5.6 mg/kg via intravenous injection, intraperitoneal injection, or oral (gavage) to compare 24-hour urinary and fecal elimination by these administration routes. Results from comparative studies of oral, intravenous, and intraperitoneal administration of glyphosate indicated that urinary radioactivity represented the amount of glyphosate absorbed and fecal radioactivity represented the amount of unabsorbed glyphosate following oral exposure. Although quantitative data were not included in the study report, the study authors estimated that 30% of the 5.6 mg/kg dose of ^{14}C-glyphosate was absorbed and that a slightly higher percentage (34%) of the 56 mg/kg dose was absorbed. In another study, male Sprague-Dawley rats received a single gavage dose of ^{12}C- and ^{14}C-glyphosate at 10 mg/kg (Brewster et al. 1991). Based on urinary radioactivity, it was estimated that 35–40% of the oral dose had been absorbed from the gastrointestinal tract. Anadón et al. (2009) reported an absorption half-life of 2.29 hours following administration of an oral dose of 400 mg glyphosate/kg to rats; an estimated peak plasma glyphosate of 4.62 μg/mL was reached at 5.16 hours postdosing. Results from a number of unpublished industry studies cited in EPA (1993), FAO and WHO (2016), IPCS (1994), and/or Williams et al. (2000), but not available to ATSDR, demonstrate that single or repeated oral dosing of glyphosate to rats at doses in the range of 10–1,000 mg/kg/day result in urinary excretion of 7–36% of the administered dose during ≤7 days of posttreatment, which presumably represents the proportion of absorbed glyphosate.

3.1.1.3 Dermal Exposure

Limited human data are available regarding the toxicokinetics of glyphosate following dermal exposure. Increased urinary glyphosate levels among 48 farmer-applicators following application of glyphosate-containing products is evidence that glyphosate can be absorbed (Acquavella et al. 2004). Dermal

absorption was likely involved in some cases because mean urinary glyphosate was higher among those farmers (14/48) who did not use rubber gloves.

In vitro studies using human skin samples indicate that dermal penetration of glyphosate is very low. Wester et al. (1996) applied 300 µL of a 1% aqueous dilution of analytical-grade ^{14}C-labeled glyphosate to human cadaver skin (0.8 cm^2 of available skin area). The study authors reported a permeability constant of $4.59x10^{-4}$ cm/hour, with a lag time of 10.48 hours, which resulted in a calculated flux of 4.12 µg glyphosate/hour. Wester et al. (1991) used a ^{14}C-labeled Roundup® formulation to evaluate dermal absorption of glyphosate through human skin (*in vitro*) and abdominal skin of Rhesus monkeys (*in vivo*). Undiluted application to human skin samples at doses ranging from 15.4 to 154 µg/cm^2 resulted in 0–0.4% dermal absorption over 8 hours postapplication; dermal absorption of glyphosate from aqueous dilutions of test substance (1:20 or 1:32 test substance:water, v/v) during 16 hours postapplication was ≤2.2%. Twelve-hour *in vivo* application of the test substance diluted 1:29 with water at concentrations of 25 or 270 µg/cm^2 resulted in 7-day recovery of 0.8 and 2.2% of the applied dose, respectively, in the urine and 3.6 and 0.7%, respectively, in the feces. These results indicate that approximately 3–4% of the applied dose had been absorbed. An *in vitro* study using rat skin membranes, applied glyphosate formulations, concentration and field diluted, for 8 hours at concentrations of 6.249 and 0.08 mg/cm^2 for MON 35012 and 6.343 and 0.08 mg/cm^2 for MON 0139 (van Burgsteden 2002). Over a period of 48 hours, penetration of concentrates was higher, with 10% penetration of MON 35012 concentrate through rat skin membrane and 1.3% penetration of MON 0139 concentrate.

3.1.2 Distribution

3.1.2.1 Inhalation Exposure

No human or animal data were located regarding distribution of glyphosate following absorption via the inhalation exposure route.

3.1.2.2 Oral Exposure

Limited human data were located regarding distribution of glyphosate following absorption via the oral exposure route. Menkes et al. (1991) reported measurable glyphosate in kidney, liver, blood, and brain in postmortem examination of an individual who had ingested 200–250 mL of Roundup®.

Following oral administration, absorbed glyphosate is readily distributed and rapidly eliminated without significant accumulation in any particular tissue. In male F344/N rats administered a single gavage dose of ^{14}C-glyphosate (purity 99%) in distilled water at 5.6 or 56 mg/kg, peak blood radioactivity occurred at 1 and 2 hours postdosing, respectively, mean peak blood concentration was 30-fold higher in the high-dose group (NTP 1992). Among rats gavaged at 5.6 mg radiolabeled glyphosate/kg and evaluated for tissue distribution, total tissue radioactivity amounted to approximately 12, 11.7, 5.5, 0.9, and 0.1% of the administered dose at 3, 6, 12, 24, and 96 hours postdosing, respectively. The highest radioactivity level was found in the small intestine, reaching a peak level of approximately 10% of the administered dose at 6 hours postdosing; radioactivity in the large intestine peaked at approximately 1.2% at 3 hours postdosing. Liver, kidney, skin, and blood each accounted for <1% of the administered dose at each time point. By 24 hours postdosing, <1% of the administered dose remained in all tissues combined. Brewster et al. (1991) administered ^{12}C- and ^{14}C-glyphosate by a single gavage dose at 10 mg/kg to male Sprague-Dawley rats and found approximately 34% of the administered dose in the small intestine (not associated with intestinal content) at 2 hours postdosing, decreasing to 0.05% of the administered dose by 96 hours postdosing. Radioactivity levels in most other tissues (blood, colon, kidney, liver, stomach, abdominal fat, testicular fat) peaked at 2–6 hours postdosing; each of these tissues accounted for ≤1.3% of the administered dose at peak and ≤0.06% by 96 hours postdosing. Radioactivity in bone peaked at 6 hours postdosing (4.7% of the administered dose) and remained at 1.7% at 96 hours postdosing. The tissue to blood ratio for bone increased with time suggesting a slower elimination from bone compared to blood. Anadón et al. (2009) reported an absorption half-life of 2.29 hours following administration of an oral dose of 400 mg glyphosate/kg to rats; an estimated peak plasma glyphosate level of 4.62 μg/mL was reached at 5.16 hours postdosing.

3.1.2.3 Dermal Exposure

No human data were located regarding distribution following dermal exposure to glyphosate.

Limited animal data are available. The observation of radioactivity in urine and feces collected from rhesus monkeys following dermal application of a ^{14}C-labeled Roundup® formulation is demonstration of systemic distribution following dermal absorption (Wester et al. 1991). However, at sacrifice 7 days posttreatment, no radioactivity was detected in spleen, ovaries, kidney, brain, abdominal fat, bone marrow, upper spinal column, or central nervous system fluid.

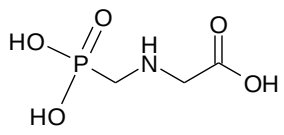
3.1.2.4 Other Routes of Exposure

Limited data are available regarding the distribution of parenterally administered glyphosate. Male and female Sprague-Dawley rats were administered ^{14}C-glyphosate via intraperitoneal injection at 1,150 mg/kg (EPA 1992h). Radioactivity measured in bone marrow samples taken 30 minutes postinjection amounted to approximately 0.0044 and 0.0075% of the administered activity for the males and females, respectively. Anadón et al. (2009) administered glyphosate (95% purity) to male Wistar rats via intravenous injection at 100 mg/kg. Plasma levels of glyphosate and its metabolite, AMPA, were measured using high-performance liquid chromatography (HPLC). Reported fast plasma distribution (half-life of 0.345 hours) and high volume of distribution at steady state (2.99 L/kg) were interpreted to indicate that glyphosate was extensively distributed to extravascular tissues.

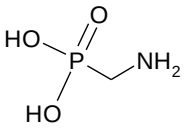
3.1.3 Metabolism

Glyphosate does not undergo significant metabolism in mammals. Available data are limited to the oral exposure route and indicate that ingested glyphosate is eliminated mostly as parent compound; only a small amount may be metabolized to AMPA. Figure 3-1 depicts the chemical structures of glyphosate and AMPA. In one human case of intentional ingestion of an herbicide in a suicide attempt, glyphosate and its metabolite, AMPA, were detected in serum and urine (Hori et al. 2003). At 16 hours postingestion, serum levels of glyphosate and AMPA were 4.4 and 0.03 μg/mL, respectively (147:1, glyphosate:AMPA). Total urinary excretion of glyphosate and its metabolite during 4 days postingestion was 3.7 g and 25 mg, respectively (148:1, glyphosate:AMPA).

Figure 3-1. Chemical Structures of Glyphosate and Aminomethylphosphonic Acid (AMPA)



Glyphosate



Aminomethylphosphonic acid (AMPA)

Results from available animal studies also indicate that very little ingested glyphosate is metabolized. Anadón et al. (2009) administered glyphosate (95% purity) to male Wistar rats by gavage at 400 mg glyphosate/kg. Plasma glyphosate peaked at 5.16 hours postdosing and measured 4.62 μg/mL; plasma AMPA peaked at 2.42 hours postdosing and measured 0.416 μg/mL. Based on the ratios between the

area under the curve (AUC) for AMPA and the AUC for glyphosate, it was estimated that the metabolite represented 6.49% of the parent compound plasma concentration. In an unpublished study summarized by EPA (1993) and Williams et al. (2000), following oral administration of radiolabeled glyphosate (>99% purity) to Sprague-Dawley rats at 10 mg/kg, the glyphosate metabolite (AMPA) was detected in the urine (0.2–0.3% of the administered dose) and feces (0.2–0.4% of the administered dose). The formation of AMPA was thought to have occurred in the gastrointestinal tract (possibly by microflora) because AMPA was not detected in other rats administered glyphosate via intravenous injection. Following a single gavage dose of administered radiolabeled glyphosate (>99% purity) to Sprague-Dawley rats, expired air accounted for <0.27% of the administered radioactivity at 24 hours postdosing, indicating that glyphosate metabolism had occurred to a slight extent (EPA 1993).

In addition to its potential role in glyphosate metabolism, gut microflora can also be impacted by exposure to glyphosate and glyphosate-based herbicides. Though the shikimate pathway is absent in mammals, the shikimate pathway in animal gut microbes synthesizes amino acids (Aitbali et al. 2018; Nielsen et al. 2018). Rodents orally exposed to doses of glyphosate-based herbicides ranging from 5 to 500 mg/kg/d showed a significant decrease in bacteria count and changes in community composition (Aitbali et al. 2018; Dechartres et al. 2019). A study using fecal samples from Roundup®-exposed Sprague-Dawley rats also found changes in bacterial community composition (Lozano et al. 2018). Decreases in bacteria count were also observed in rodents orally exposed to 5 mg/kg/d of glyphosate technical (Aitbali et al. 2018). However, fecal samples from Sprague-Dawley rats orally exposed to doses of glyphosate or Glyfonova® found that while minimal changes in bacteria composition were observed, exposure to the glyphosate formulation appeared to have a more pronounced effect than exposure to glyphosate technical (Nielsen et al. 2018). While the implications of alterations in the gut microbiome are unclear, some animal studies suggest neurologic and behavioral changes (Aitbali et al. 2018; Dechartres et al. 2019; Lozano et al. 2018) and greater susceptibility to infection may be associated with loss of microbiome diversity, especially in cases of malnutrition (Nielsen et al. 2018; Shehata et al. 2013).

Ford et al. (2017) administered glyphosate to male C57BL/6 mice by intraperitoneal injection at 200 mg/kg/day for 7 days. Glyphosate treatment at this high dose level resulted in measurable levels of AMPA (approximately 4% of the dose of glyphosate) and an approximately 2-fold increase in hepatic glyoxylate (a reactive substance produced endogenously). Because glyoxylate is formed endogenously, the increase in glyoxylate level in the liver may be a result of glyphosate acting on mechanisms responsible for endogenous production of glyoxylate.

3.1.4 Excretion

3.1.4.1 Inhalation Exposure

Limited information is available regarding elimination and excretion of glyphosate in humans following inhalation exposure. In one study, urinary glyphosate levels were evaluated in 48 farmer-applicators prior to application of glyphosate-containing products, immediately following application, and for 3 days thereafter (Acquavella et al. 2004). Urinary glyphosate was detectable in 15% (7/47) of the farmers prior to application, in 60% (29/48) of the farmers immediately following application, and in only 27% (13/48) of the farmers on postapplication day 3. No information was located regarding elimination or excretion following inhalation exposure of laboratory animals to glyphosate.

3.1.4.2 Oral Exposure

Roberts et al. (2010) estimated a half-life of 3–4 hours for elimination of glyphosate from the blood of patients who had intentionally ingested large amounts of glyphosate-containing herbicide products. In other cases of poisoning victims, plasma glyphosate levels dropped rapidly (within 2–3 days) following the onset of observation (e.g., Talbot et al. 1991). Glyphosate has been detected in feces and urine of individuals who intentionally or accidentally ingested relatively large amounts of glyphosate.

Results from animal studies identify the feces and urine as major routes of elimination following oral exposure to glyphosate. For example, among male and female Sprague-Dawley rats administered ^{14}C-glyphosate (99% purity) via a single gavage dose at 10 mg/kg, during 7 days posttreatment, radioactivity recovered in the feces averaged 62.4 and 69.4% of the administered dose (males and females, respectively); another 28.6 and 22.5% of the administered dose (males and females, respectively) was recovered in the urine (IPCS 1994). Thus, feces and urine accounted for approximately 88–91% of the administered dose. HPLC analysis revealed that parent compound accounted for 98.5–99.3% of the radioactivity in feces and urine. There were no significant differences in fecal and urinary excretion among rats dosed with unlabeled glyphosate for 14 days followed by a single oral dose of radiolabeled glyphosate. Following a single gavage dosing of ^{14}C-glyphosate (>96% purity) to male and female Sprague-Dawley rats at 30 mg/kg, the feces accounted for 57–59% of the administered radioactivity and the urine accounted for 27–29% during the first 36 hours posttreatment; indicating that fecal and urinary excretion occur relatively rapidly following oral exposure to glyphosate (IPCS 1994). In male F344/N rats administered a single gavage dose of ^{14}C-glyphosate (purity 99%) in distilled water at 5.6 or 56 mg/kg, 72-hour collection of feces and urine resulted in the recovery of 91–92% of the administered

radioactivity; 74 and 19%, respectively, at the low dose and 58 and 34%, respectively, at the high dose (NTP 1992). In one study (NTP 1992), male F344/N rats were administered a single dose of glyphosate at 5.6 mg/kg via intravenous injection, intraperitoneal injection, or oral (gavage) to compare 24-hour urinary and fecal elimination by these administration routes. Results from comparative studies of oral, intravenous, and intraperitoneal administration of glyphosate indicated that urinary radioactivity represented the amount of glyphosate absorbed and fecal radioactivity represented the amount of unabsorbed glyphosate following oral exposure. Although quantitative data were not included in the study report, the study authors estimated that 30–34% of the oral doses of ^{14}C-glyphosate was absorbed and excreted in the urine. Therefore, approximately 66–70% was unabsorbed and eliminated in the feces.

Very little ingested glyphosate is eliminated via routes other than feces and urine. Among Sprague-Dawley rats administered radiolabeled glyphosate (>99% purity) by a single gavage dose, <0.27% of the administered radioactivity was recovered in expired air at 24 hours postdosing (EPA 1993).

3.1.4.3 Dermal Exposure

No information was located regarding elimination or excretion following known dermal exposure to glyphosate in humans. However, in a study that evaluated urinary glyphosate levels in 48 farmer-applicators involved in application of glyphosate-containing products, mean urinary glyphosate was higher among those farmers (14/48) who did not use rubber gloves, indicating that some glyphosate had been absorbed through the skin (Acquavella et al. 2004). Limited information is available for laboratory animals. Wester et al. (1991) applied a ^{14}C-labeled Roundup® formulation to the abdominal skin of Rhesus monkeys (*in vivo*) to evaluate dermal absorption of glyphosate. Twelve-hour application of the test substance at concentrations of 25 or 270 μg/cm^2 resulted in 7-day recovery of 0.8 and 2.2% of the applied dose, respectively, in the urine and 3.6 and 0.7%, respectively, in the feces.

3.1.4.4 Other Routes of Exposure

Male and female Sprague-Dawley rats were administered ^{14}C-glyphosate via intraperitoneal injection at 1,150 mg/kg (EPA 1993). Assuming first-order kinetics, the half-life of elimination from the bone marrow was estimated at 7.6 and 4.2 hours for males and females, respectively. A half-life for elimination of radioactivity from plasma was approximately 1 hour for both sexes. These results indicate that glyphosate reaching the blood was rapidly eliminated and that the small fraction reaching bone marrow was rapidly eliminated. Anadón et al. (2009) reported a half-time of 9.99 hours for elimination of

glyphosate from the blood of male Wistar rats administered glyphosate (95% purity) via intravenous injection at 100 mg/kg.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

PBPK models for glyphosate were not located.

3.1.6 Animal-to-Human Extrapolations

No information was located to suggest significant differences between animals and humans regarding the toxicokinetics of glyphosate.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at risk of exposure to glyphosate at unusually high levels are discussed in Section 5.7, Populations with Potentially High Exposures.

Limited information was located regarding possible age- or gender-related differences in susceptibility to toxic effects from glyphosate technical or glyphosate formulations. Mao et al. (2018) added glyphosate or Roundup Bioflow® to the drinking water of rat dams from GD 6 through lactation and to their offspring up to postpartum day 125 at a concentration resulting in a dose of 1.25 mg glyphosate/kg/day. Microbiome profiling of the gut resulted in significant changes in overall bacterial composition in the pups only (particularly apparent prior to puberty); this effect was noted for glyphosate and for Roundup Bioflow®. Romano et al. (2010) employed Roundup Transorb® as a test substance and found decreased serum testosterone in young male rats gavaged at a dose as low as 5 mg/kg/day; however, the effect may have been caused, at least in part, by other ingredients in the glyphosate formulation.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to glyphosate are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for glyphosate from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung

capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts formed by covalent bonding of a chemical to DNA, the formation of which can induce abnormal replication, mutation, and/or prevent proper DNA repair). Biomarkers of effect caused by glyphosate are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Glyphosate and the metabolite, AMPA, have been measured in blood and urine (e.g., Connolly et al. 2018; Conrad et al. 2017; Mills et al. 2017; Soukup et al. 2020; Zhang et al. 2020; Zoller et al. 2020; Zouaoui et al. 2013). However, most absorbed glyphosate is rapidly excreted as parent compound, and urine is generally considered to be a stronger biomarker of exposure given that the level of detection (LOD) for glyphosate in urine is much lower than the LOD for glyphosate in blood (see Table 5-4). Meaningful quantification of exposure would require analysis of blood and/or urine within hours following exposure, though a case study on glyphosate poisoning reported plasma glyphosate levels over the course of 2 to 3 days, rather than hours (Talbot et al. 1991).

3.3.2 Biomarkers of Effect

No information was located regarding biomarkers of effect specific to glyphosate toxicity.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Information on the toxicological effects of glyphosate interacting with other chemicals such as inert ingredients is limited. Inert ingredients include other substances that alter the physico-chemical properties to improve plant absorption or stability of the active ingredient(s) (Defarge et al. 2016). Inert ingredients include surfactants. Surfactants such as polyethoxylated tallow amine (POEA) in glyphosate-containing products might enhance the toxicity of glyphosate; results from one study indicate that the surfactant may be more acutely toxic than glyphosate or the combination of glyphosate and POEA (e.g., Adam et al. 1997). In an *in vitro* study using three human embryotic cell lines (kidney, liver, and placenta), glyphosate

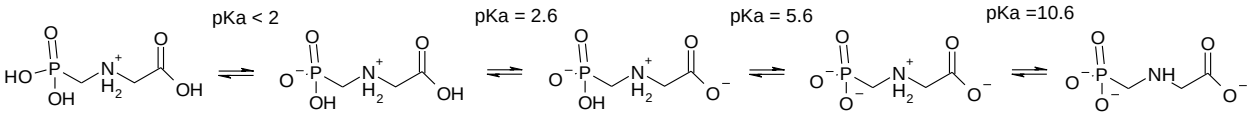
formulations and formulation additives were found to be more toxic than glyphosate technical alone. Based on measured cytotoxicity evaluated via mitochondrial respiration, membrane disruption, and caspases 3/7 activity, the glyphosate formulations were more toxic than glyphosate alone, and the adjuvants POE-15 and Genamin were more toxic than either the glyphosate formulations or glyphosate alone (Mesnage et al. 2013).

Increased toxicity of glyphosate formulations compared to glyphosate technical was also observed in another *in vitro* study. Defarge et al. (2016) observed *in vitro* that co-formulants including polyethoxylated tallow amine (POEA), alkyl polyglucoside (APG), polyoxyethylenealkyl ether phosphate (POE-APE), quaternary ammonium compound (QAC) and glyphosate formulations (inert and glyphosate combined) to exert toxic effects far greater than glyphosate alone. Cytotoxicity was determined by measuring mitochondrial respiration and endocrine disrupting activity was measured by aromatase activity inhibition. Although, Defarge et al. did not find that glyphosate inhibited mitochondrial respiration, disturbed cell membranes, or disrupted endocrine activity, co-formulants APG and POAE were up to 18 times and 200 times more cytotoxic than glyphosate, respectively, and co-formulants and glyphosate-based herbicide formulations were cytotoxic at concentration 18-2000 times and 8-141 times lower, than the recommended agricultural dilution of 1%, respectively. In short, co-formulants POEA, APG, POE-APE, QAC and glyphosate formulation including R classic were found to be more toxic than the active ingredient glyphosate.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Glyphosate is an organic acid composed of a phosphonomethyl and glycine component. The chemical name for glyphosate is *N*-(phosphonomethyl) glycine. Glyphosate is a zwitterion with four distinct dissociation constants (pKa values are depicted below) and exists as different ionic species depending on the pH of its surroundings. Glyphosate is an amphoteric chemical and may react as an acid or a base under certain conditions.



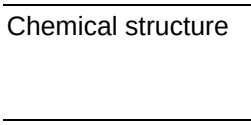
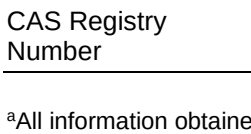
Glyphosate isopropylamine (Chemical Abstracts Registry Number [CASRN] 38641-94-0) is one of the salt forms of glyphosate used in commercial herbicides employing glyphosate as an active ingredient. This substance is registered as a pesticide by the EPA (1993) and is used to control broadleaf weeds and grasses; in food and nonfood settings, flower gardens, lawns, turf, residential areas, and forests; and along roadsides. Use of glyphosate as a pesticide outside of an agricultural context would be considered non-agricultural. Some labels may list the active ingredient in a formulation of glyphosate and the acid equivalents (AE), which is the theoretical yield of the parent acid from the formulated ester or salt. For example, the AE of glyphosate isopropylamine salts is 74%.

Detailed information on the chemical identity of glyphosate and glyphosate isopropylamine is provided in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Detailed information on the physical and chemical properties of glyphosate and glyphosate isopropylammonium is provided in Table 4-2.

Table 4-1. Chemical Identity of Glyphosate and Glyphosate Isopropylamine[a]

Characteristic	Information	
Chemical name	Glyphosate	Glyphosate isopropylamine
Synonym(s)	Glyphosphate; N-(phosphonomethyl) glycine; phosphonomethyliminoacetic acid; glyphosate acid	Glycine, N-(phosphonomethyl)-, compound with 2-propanamine (1:1); glyphosate-isopropylammonium; glyphosate mono(isopropylamine) salt; glyphosate-mono(isopropylammonium); N-(phosphonomethyl)glycine, isopropylamine salt
Partial list of registered trade name(s)	Pondmaster; Roundup® Max; Glifoglex; Glycel; Muster; Rondo; Sonic; Spasor; Sting; Tumbleweed; MON-0573; CP 67573	Roundup®; Rondo; Rodeo; Glifonox; Glycel; MON-0139; CP 70139; Shackle[b]
Chemical formula	$C_3H_8NO_5P$	$C_3H_8NO_5P.C_3H_9N$
Chemical structure		
CAS Registry Number	1071-83-6	38641-94-0

[a]All information obtained from McBean (2011), O'Neil et al. (2013), and/or ChemIDplus (2017) unless noted otherwise.
[b]EPA 1993.

CAS = Chemical Abstracts Service

Table 4-2. Physical and Chemical Properties of Glyphosate and its Isopropylamine Salt[a]

Property	Glyphosate	Glyphosate isopropylamine salt
Molecular weight	169.1	228.2
Color	White	White
Physical state	Solid; crystals	Powder
Melting point	230°C (decomposes)	Two stages: 143–164 and 189–223°C
Boiling point	No data	Decomposes without boiling
Density at 20°C	1.705	1.482
Odor	Odorless	Odorless
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water at 25°C	12,000 mg/L 10,500 mg/L (pH 1.9, 20°C)	1,050,000 mg/L (pH 4.3, 25°C)
Organic solvent(s)	Insoluble in most organic solvents: acetone, ethanol, and xylene	Dichloromethane 184 mg/L at 20°C; methanol 15,880 mg/L at 20°C
Dissociation constants:	pKa_1 0.8; pKa_2 3; pKa_3 6; pKa_4 11; pKa_1[b] <2; pKa_2[b] 2.6; pKa_3[b] 5.6; pKa_4[b] 10.6	pKa_1 2.18 at 20°C (monophosphate); pKa_2 5.77 at 20°C (carboxylic acid)
Partition coefficients:		
Log K_{ow}	<-3.4	-5.4
Log K_{oc}	3.4–3.7 (K_{oc}=2,600–4,900)[c] -2.8–3.1 (K_{oc}=0.00169–2,080 L/kg)[d]	3.3 (K_{oc} = 2,080 L/kg)[d]
Vapor pressure at 25°C	$9.8x10^{-8}$ mmHg	$1.58x10^{-8}$ mmHg
Henry's law constant	$2.1x10^{-12}$ atm-m^3/mol at 25°C[d]	$3.3x10^{-15}$ atm-m^3/mol at 25°C[e]
Autoignition temperature	No data	No data
Flashpoint	Not flammable	No data
Flammability limits	No data	No data
Explosive limits	No data	No data

[a]All information obtained from either McBean (2011) or O'Neil et al. (2013).
[b]Sprankle et al. 1975.
[c]Glass 1987.
[d]Predicted values from EPA CompTox Chemicals Dashboard
[d]EPI Suite 2012.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Glyphosate has not been identified in any of the 1,832 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2015). However, the number of sites evaluated for glyphosate is not known.

- Occupational and residential exposure is a result of glyphosate's use in agricultural, industrial, and residential settings. The highest potential for dermal, inhalation, and ocular exposure is expected for pesticide applicators, farm workers, and home gardeners who use herbicides containing glyphosate.

- The general population is exposed to glyphosate via ingestion of crops, plants, and foods with residues of this chemical. Residential exposure may occur via inhalation, dermal contact, and/or ocular contact during mixing or application of consumer products containing glyphosate or by coming into contact with crops, soils, or water to which glyphosate-containing products have been applied.

- Occupational exposure to glyphosate may occur via inhalation, dermal contact, and/or ocular contact during manufacture, transport, mixing, loading, application, and disposal processes. Accidental oral exposure may occur via unintentional ingestion. Dermal contact appears to be the major route of exposure to glyphosate for individuals involved in its application.

- Glyphosate mainly enters the environment as a direct result of its herbicidal use. Fate of this chemical in the environment includes degradation, transport, and partitioning processes, which are governed by its physicochemical properties and by abiotic or biotic degradation under certain environmental conditions. Glyphosate is a nonvolatile, highly polar, non-residual herbicide that has low potential for environmental persistence and is unlikely to bioaccumulate.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

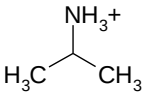
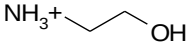
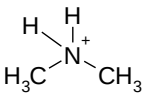
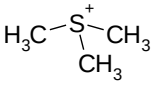
No information is available in the Toxics Release Inventory (TRI) database on facilities that manufacture or process glyphosate because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005b).

Production of glyphosate is achieved through heating phosphorous acid and *a*-amino acetic acid followed by the addition of formaldehyde (Muller and Applebyki 2010). Glyphosate may also be produced by heating glycine and chloromethylphosphonic acid in aqueous sodium hydroxide (IPCS 1994).

Glyphosate is produced commercially in the United States as a technical-grade substance with a purity ≥80%, but usually over 90% (IPCS 1994, McBean 2011).

Glyphosate is typically manufactured for commercial use as a salt available in soluble liquid and soluble granule formulations. Salt forms of glyphosate include the isopropylamine salt, sodium salt, and monoammonium salt. Table 5-1 summarizes some of the common glyphosate salts that may be used as active ingredients in herbicides. Due to the various salt forms, the active ingredient listed on products is sometimes expressed in terms of acid equivalent.

Table 5-1. Glyphosate Salts

Name	CAS Registry Number	EPA PC Code	Cation	U.S. registration[a]
Glyphosate isopropylamine salt	38641-94-0	103601		Yes
Glyphosate mono ammonium	40465-66-5	103604	NH_4^+	Yes
Glyphosate ethanolamine salt	40465-76-7	103605		Yes
Glyphosate triammonium salt	114370-14-8	103607	NH_4^+	Yes
Glyphosate diammonium salt	69254-40-6	103607	NH_4^+	Yes
Glyphosate dimethylammonium salt	34494-04-7	103608		Yes
Glyphosate potassium salts	70901-12-1; 70901-20-1; 39600-42-5	103613	K^+	Yes
Glyphosate monosodium salt	34494-03-6	103603	Na^+	No
Glyphosate sesquisodium salt	70393-85-0	103603	Na^+	No
Glyphosate trimesium	81591-81-3	128501		No

[a]Pan 2014

CAS = Chemical Abstracts Service; EPA = U.S. Environmental Protection Agency; PC = pesticide chemical

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). Polyoxyethylene amine (POEA) (CASRN 24911-53-5) is a surfactant used in the

commercial product Roundup® (PAN 2009). Surfactants are used in herbicide formulations to increase penetration of glyphosate into plants. Sulfuric acid (CASRN 7664-93-9), phosphoric acid (CASRN 7664-38-2), propylene glycol (CASRN 57-55-6), and sodium benzoate (CASRN 532-32-1) are examples of additives used in some formulations (IPCS 1994; PAN 2009). Products may contain other active ingredients such as simazine (CASRN 122-34-9) and 2-methyl-4-chlorophenoxyacetic acid (CASRN 94-74-6). The herbicide 2,4-dichlorophenoxyacetic acid (CAS 94-75-7) may also be present at concentrations ranging from 11.1 to 20.6% (IPCS 1994). Commercial products containing glyphosate have been reported with concentrations ranging from 0.96 to 94 w/w%. The common herbicide, Roundup®, has product formulations containing glyphosate concentrations ranging from 0.96% to 71% (w/w) (NPIRS 2017; PAN 2016b). These products may be diluted depending upon the labeled use as per manufacturers specifications.

The introduction of glyphosate-resistant crops such as soybeans in 1996, canola and cotton in 1997, and maize in 1998, along with the distribution of their genetically engineered seeds, had major impacts on the production and demand for glyphosate.

According to the National Pesticide Information Retrieval System (NPIRS), as of May 2017, there were 43 companies manufacturing EPA federally registered products under the active pesticide code 417300 (glyphosate) (since many chemical names are too long to be handled easily, EPA assigns a 6-digit chemical code number for every active chemical ingredient), which are available for use in the United States; see Table 5-2 (NPIRS 2017). In addition, there were 72 companies in the United States that were manufacturing chemicals under the active pesticide code 103601 (glyphosate isopropylamine salt) (NPIRS 2017).

Table 5-2. Companies Manufacturing Products Under Pesticide Code 417300 (Glyphosate)

Company	Address	City, State, Zip Code
Syngenta Crop Protection, LLC	410 Swing Road	Greensboro, North Carolina 27419
The Scotts Company	D/B/A The Ortho Group, 14111 Scottslawn Road	Marysville, Ohio 43041
FMC Corporation, Agricultural Products Group	1735 Market Street	Philadelphia, Pennsylvania 19103
Monsanto Company	Chesterfield Village Research Center, 700 Chesterfield Parkway North	Chesterfield, Missouri 63017
Winfield Solutions, LLC	P.O. Box 64589	St. Paul, Minnesota 55164

Table 5-2. Companies Manufacturing Products Under Pesticide Code 417300 (Glyphosate)

Company	Address	City, State, Zip Code
ABC Compounding Co., Inc.	P.O. Box 16247	Atlanta, Georgia 30321
Cheminova A/S	P.O. Box 9	DK-7620 Lemvig
Helena Chemical, Co.	225 Schilling Boulevard, Suite 300	Collierville, Tennessee 38017
Chemsico, A Division of United Industries Corporation	P.O. Box 142642	St. Louis, Missouri 63114
Adama Agan Ltd	P.O. Box 262	Ashdod, 77102, Israel
Drexel Chemical Company	P.O. Box 13327	Memphis, Tennessee 38113
Loveland Products, Inc.	P.O. Box 1286	Greeley, Colorado 80632
Nufarm Limited	103–105 Pipe Road	Laverton North, Victoria 3026 Australia
Albaugh, LLC	P.O. Box 2127	Valdosta, Georgia 31604
Atanor S.A.	Foreign Trade Department, Albarellos 4914	B1605 AFR, Munro, Providence de Buenos Aires
BASF Sparks, LLC	P.O. Box 13528	Research Triangle Park, North Carolina 27709
Control Solutions, Inc.	5903 Genoa-Red Bluff Road	Pasadena, Texas 77507
Tenkoz, Inc.	1725 Windward Concourse	Alpharetta, Georgia 30005
Dow AgroSciences, LLC	9330 Zionsville Rd 308/2e	Indianapolis, Indiana 46268
Makhteshim Agan of North America, Inc.	d/b/a Adama, 3120 Highwoods Boulevard, Suite 100	Raleigh, North Carolina 27604
United Phosphorus, Inc.	630 Freedom Business Center, Suite 402	King of Prussia, Pennsylvania 19406
Monsanto Company	Lawn & Garden Products, 600 13th Street, NW, Suite 660	Washington, DC 20005
Helm Agro US, Inc.	401 E. Jackson Street, Suite 1400	Tampa, Florida 33602
Mey Corporation	121 South Estes Drive, Suite 101	Chapel Hill, North Carolina 27514
Sharda Cropchem, Limited	Domnic Holm, 29th Road	Bandra (West), Mumbai 400050
Rotam Agrochemical Company, Ltd.	26/F, E-Trade Plaza, 24 Lee Chung Street	Chaiwan, Hong Kong
Sharda USA LLC	P.O. Box 640	Hockessin, Delaware 19707
Ragan and Massey, Inc.	101 Ponchatoula Parkway	Ponchatoula Louisiana 70454
Tide International, USA, Inc.	21 Hubble	Irvine, California 92618
Agsaver II, LLC	P.O. Box 111	McGehee, Arkansas 71654
Repar-Glypho, LLC	8070 Georgia Avenue, Suite 209	Silver Spring, Maryland 20910
Farmway, Inc.	P.O. Box 640	Hockessin, Delaware 19707
Consus Chemicals, LLC	22 Pine Tree Drive	Wayne, New Jersey 07470
Axss Technical Holdings, LLC	111 Martin Road	Fulton, Mississippi 38843
Cinmax International, LLC	3050 Suite 113	Bloomington, Minnesota 55425

Table 5-2. Companies Manufacturing Products Under Pesticide Code 417300 (Glyphosate)

Company	Address	City, State, Zip Code
Agromarketing Co., Inc.	133 Mavety Street	Toronto, Ontario, Canada M6P
Glysorttech, LLC	281 Hampshire Drive	Plansboro, New Jersey 08536
Liberty Crop Protection, LLC	4850 Hahns Peak Drive, Suite 200	Loveland, Colorado 80538
Gly-Peak, LLC	224 South Bell Avenue	Ames, Iowa 60010
Tundra Agroindustrial, Ltd.	P.O. Box 10	Lemars, Iowa 51031
Argustoli H.C., LLC	10191 Park Run Drive, Suite 110	Las Vegas, Nevada 89145
Genmerica NA LLC	P.O. Box 1603	Cheyenne, Wyoming
Gruhn Mill Crop Solutions, LLC	701 Fifth Avenue, Suite 6100	Seattle, Washington 98104

Source: NPIRS 2017

5.2.2 Import/Export

No information was found concerning U.S. imports and exports of glyphosate.

5.2.3 Use

Glyphosate is a phosphonoglycine herbicide, first registered for use by the EPA in 1974. In June 1986, glyphosate was issued a Registration Standard (EPA 1986c) requiring additional data, which included phytotoxicity, environmental fate, toxicology, product chemistry, and residue chemistry studies; reregistration of single active ingredient formulations, plus one additional active ingredient formulation, were finalized in 1993 (EPA 1993). Glyphosate is registered for pre- and post-emergent applications for weed control in the production of various fruit, vegetable, and field crops. Glyphosate may be applied to fields prior to planting in order to remove unwanted weeds and vegetation or in preparation for harvesting in glyphosate resistant crops. Recommended application rates, methods of application and timing, temperature considerations, etc. may be found on individual product labels. Glyphosate is in the process of registration review by EPA; docket ID: EPA-HQ-OPP-2009-0361-0066 (EPA 2017c).EPA published an interim registration review decision in January 2020; docket ID: EPA-HQ-OPP-2009-0361 (EPA 2020), which will be finalized after an EPA Endocrine Disruptor Screening Program FFDCA

determination, evaluation of glyphosate under the Endangered Species Act, and the resolution of a petition by the Environmental Working Group.

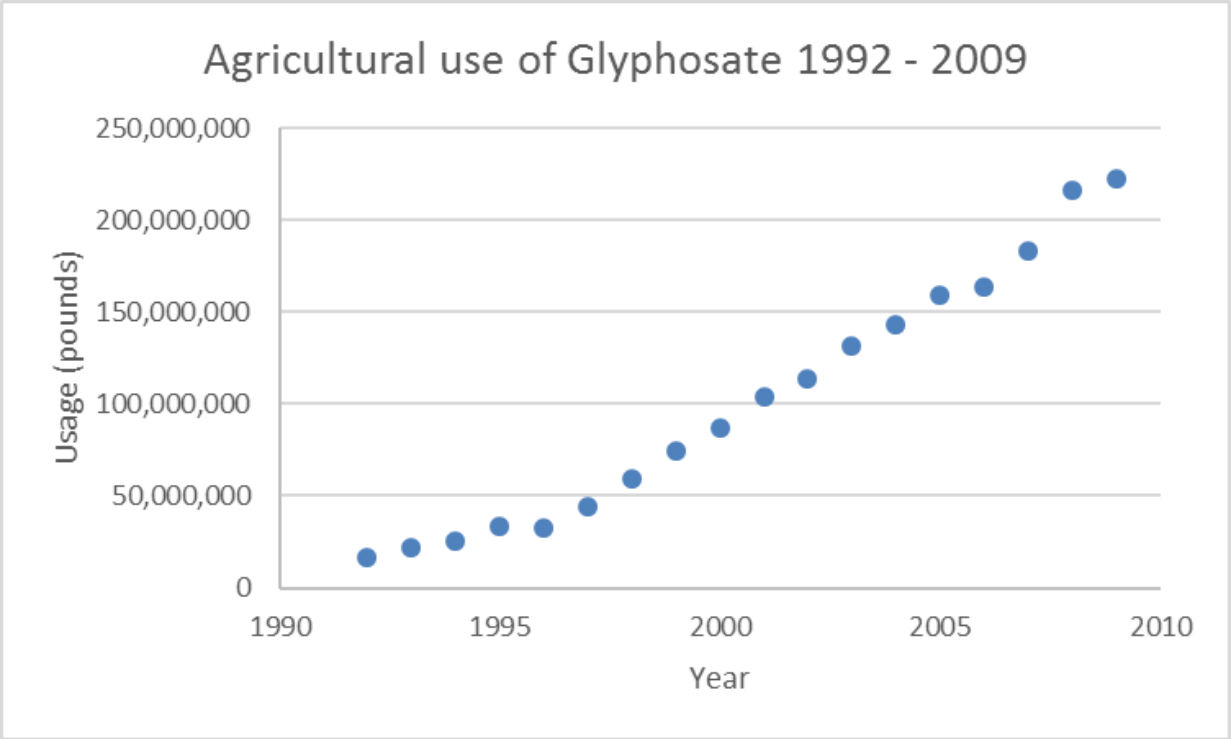
Glyphosate is used as a non-selective contact herbicide. Formulations are applied directly to control native and invasive weeds and vegetation around food crops and non-food field crops, and in non-crop areas such as roadsides, golf courses, right-of-way locations, and aquatic areas. Glyphosate is used in agriculture, forestry, industrial, lawn and garden, and aquatic (e.g., Rodeo®, Clearcast®) environments for weed control. In aquatic usage, the formulation typically contains no surfactant or a surfactant that is nontoxic to aquatic organisms and applications must be made as per the product instructions to avoid rapid vegetative decay, which can lead to anaerobic environments and potential fish kills (Dow 2017). Glyphosate is applied to control broad-leaved weeds and woody brush, as well as annual and perennial grasses (Muller and Applebyke 2010; Plimmer et al. 2004). The sodium salt (CASRN 34494-03-6) can be used as a plant growth regulator for peanuts and sugarcane (EPA 1993). Glyphosate is a foliar-applied herbicide. Before the introduction of genetically modified glyphosate-resistant crops, application generally occurred before crops were planted (Duke and Powles 2008). After successful production and approval of glyphosate-resistant crops, such as soybean, cotton, maize, and canola, application generally occurs after planting and before harvest; the timing depends on the specific application (Duke and Powles 2008; Muller and Applebyke 2010). The introduction of these glyphosate-resistant crops increased the use of herbicidal products containing this chemical because it is possible to use it post-emergence without actually harming the crop. Greater than 90% of the soybeans produced in the United States are glyphosate tolerant, and most cotton (72%) and about half of the corn (52%) planted in 2007 were glyphosate tolerant (Coupe et al. 2012). It has been estimated that genetically engineered glyphosate-tolerant crops now account for about 56 % of its global usage (Benbrook 2016). Application techniques include aerial treatments, typically used for large-scale purposes, and wiping equipment or spraying equipment attached to vehicles, generally used for small-scale applications (FAO 1997; IPCS 1994). Newer application practices, such as the addition of glyphosate to crops to simplify the harvesting process (referred to as “green burndown”), may have implications for usage rates of the herbicide (Zhang et al. 2019a).

According to data from the Pesticide Action Network (PAN) Pesticide Database, there are 102 products containing glyphosate (CASRN 1071-83-6) as the active ingredient, 94 of which have active registrations in the United States. There are 848 products containing glyphosate isopropylamine salt (CASRN 38641-

94-0) as the active ingredient, of which 739 have active registrations in the United States (PAN 2016a, 2016b).

Increasing trends in annual agricultural use data for the United States are reflected from the use statistics available from the U.S. Geological Survey (USGS) National Water-Quality Assessment (NAWQA) Program. Estimated yearly usage increased from approximately 20 to 60 million pounds from 1992 to 1998, from approximately 70 to 130 million pounds from 1999 to 2003, from approximately 140 to 250 million pounds from 2004 to 2011, and steady use of approximately 285–290 million pounds from 2012 through 2014 (USGS 2017). Figure 5-1 illustrates the agricultural use of glyphosate from 1992 to 2009 in the United States (USGS 2013).

Figure 5-1. Agricultural Application Trends of Glyphosate in the United States According to U.S. Geological Survey (USGS) Data



Source: USGS 2017

Benbrook (2016) compiled data from the National Agricultural Statistical Service (NASS) to estimate the amount of glyphosate applied for weed control in the production of major agricultural crops and non-agricultural (residential uses) in the United States from 1990–2014. The trends are summarized in Table 5-3.

Table 5-3. Glyphosate AI (Pounds) Usage Trends from 1990 to 2014

Crop	1990 Active ingredient (pounds)	2014 Active ingredient (pounds)	% Increase
Soybean	2,663,000	122,473,987	4,499.10%
Corn	880,066	68,949,452	7,734.58%
Cotton	192,429	17,421,787	8,953.62%
Wheat (winter)	331,758	12,353,488	3,623.64%
Alfalfa	381,525	8,853,600	2,220.58%
Sorghum	236,305	4,178,573	1,668.30%
Sugar beets	36,130	2,763,075	7,547.59%
Canola	0	219,392	NA
Wheat (spring)	75,308	1,201,807	1,495.86%
Barley	13,1568	1,064,160	708.83%
Other cops	1,897,522	4,526,043	138.52%
Total	7,683,070	249,906,307	3,152.69%
		Non-Agricultural Use	
	5,300,000	26,519,000	400.36%

Source: Benbrook 2016

The EPA recently granted the registration of a new herbicide named Enlist Duo™ containing 2,4-D choline salt and glyphosate for use on genetically modified corn and soybean crops designed to be resistant to 2,4-D and glyphosate (EPA 2014).

5.2.4 Disposal

Wastes resulting from products containing glyphosate should be disposed of at an approved waste disposal facility or in landfills approved for pesticide disposal. Disposal practices should be in accordance with federal, state, and local procedures. Non-refillable containers should never be reused. Empty containers should be rinsed thoroughly and offered for recycling, if available, or disposed of in accordance with container labels. Rinse-water can be emptied into formulation equipment and applied as residual pesticide in the appropriate manner. Do not contaminate fresh waters when disposing of equipment wash waters or container rinse waters. Containers that have not been completely rinsed may be considered hazardous and should be disposed of with regard to federal, state, and local regulations. Any unused product may be recycled by applying the product in an approved use setting or returning it to the manufacturer or supplier for safe disposal (Agrisolutions 2010; EPA 1993, 2011).

5.3 RELEASES TO THE ENVIRONMENT

TRI data should be used with caution because only certain types of facilities are required to report (EPA 2005b). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005b).

No information is available in the TRI database on facilities that manufacture or process glyphosate because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005b).

The use of glyphosate as an herbicide for crops and non-crop applications is the major source of glyphosate that intentionally enters the environment. Some glyphosate may be released from the manufacture, transport, and disposal of glyphosate or glyphosate-containing products. The majority of herbicidal formulations with glyphosate are directly applied to weeds to remove unwanted vegetation in residential and agricultural settings. Depending on its application, glyphosate may enter aquatic environments through direct application to control aquatic weeds (Dow 2017) or as a result of overspray in areas near aquatic environments. Aerial applications of glyphosate may result in unintended transport, depending on application technique and meteorological conditions, such as wind drift (EPA 1993; IPCS 1994; PAN 2009; Yates et al. 1978).

5.3.1 Air

There is no information on releases of glyphosate to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005b).

Glyphosate released to the air from aerial and ground equipment has the potential for downwind transport. Yates et al. (1978) assessed the loss due to drift after application. The lowest drift losses resulted when ground sprayers operating at low pressure were employed. The highest drift losses occurred when jet nozzles were employed during aerial application performed by helicopter.

The Air Quality System (AQS) database is EPA's repository of criteria air pollutants and hazardous air pollutants (HAPs), containing monitoring data from >2,600 monitoring sites across the United States. Glyphosate has not been included in the AQS ambient air monitoring data as of 2016 (EPA 2017a).

5.3.2 Water

There is no information on releases of glyphosate to water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005b).

Glyphosate may enter surface water systems either directly as a result of its aquatic use or indirectly due to overspray near surface water. Aquatic applications of glyphosate are used to control invasive aquatic species such as water chestnut (*Trapa natans*) or other labeled weeds (EPA 2010); however, no quantitative data are available regarding how much glyphosate is applied to aquatic waterways in the United States. Glyphosate may also enter surface waters indirectly due to transport of residues in run-off or erosion events. The amount of glyphosate transported to nearby water bodies from runoff and erosion is dependent upon several factors, including the frequency, timing, and application rate of glyphosate to nearby areas, meteorological conditions (e.g., rainfall events and duration), and the characteristics of the soils in the treated areas. Hydrological factors such as input to the waterbody from overland flow as compared to subsurface infiltration also effect potential pesticide loadings. Coupe et al. (2012) studied the glyphosate levels at three locations located in the United States (South Fork River Basin, Iowa; Sugar Creek River Basin, Indiana; and Bogue Phalia Basin, Mississippi). The basins are located in agricultural areas dominated by soybean, corn, rice, and cotton (Mississippi only) production, but have differing climates and soil characteristics. Water samples collected from 2007 to 2008 at three sites located in the Bogue Phalia basin all had detectable levels of glyphosate and its degradation product, aminomethylphosphonic acid (AMPA). Glyphosate concentrations at the sites ranged from 0.03 to 73 µg/L. Levels showed a distinctive seasonal pattern with lowest levels occurring in winter, followed by a steady increase into late fall, which coincided with seasonal application timings of glyphosate. Moreover, both glyphosate and AMPA loads into the basin were greater in 2008 as compared to 2007, which corresponded to a higher rainfall rate for that year. Approximately 59–72% of the water samples

collected from the South Fork River basin had detectable levels of glyphosate ranging from <0.02 to 5.7 µg/L. Higher glyphosate loadings as a percentage of usage into the Bogue Phalia Basin as compared to the South Fork River Basin is a result of a higher overland flow in the basin (as compared to subsurface water infiltration) and the fact that the majority of soils in the Bogue Phalia Basin are characterized as heavy clay soils classified as hydrologic soil groups C and D, which have higher runoff potential than the predominant soil types in the South Fork River Basin.

Glyphosate levels in the Sugar Creek River Basin, Indiana were limited to measurements taken during two heavy rainfall storm events in which 2.6 and 5.7 cm of rain were recorded. Glyphosate levels ranged from 0.16 to 430 µg/L, with the highest level recorded during the heavier rainfall event.

Battaglin et al. (2005) discussed the occurrence of glyphosate in 51 streams in the Midwestern United States from pre-emergence, post-emergence, and harvest runoff samples. Maximum levels in runoff water ranged from 1.00 µg/L (pre-emergence runoff) to 8.7 µg/L in harvest season runoff samples. Glyphosate levels in surface water are summarized in Section 5.5.2.

Aparicio et al. (2013) measured the environmental fate of glyphosate and AMPA in surface water of agriculture basins in Argentina. Forty-two streams were sampled in April, August and September of 2012. Between the collection months, glyphosate was measured in 4% to 35% of samples with levels ranging between trace to 7.6 µg l^{-1}. AMPA was detected in up to 33% of samples collected and concentration levels were measured between non-detect to 2.3 µg l^{-1}. There was a decrease in the number of samples detecting glyphosate or AMPA overtime, and this may be due to the dilution effect caused by rainfall, which was measured as 65.7 mm (April) and 253.5 mm (August) (Aparcio et al. 2013).

5.3.3 Soil

There is no information on releases of glyphosate to soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005b).

Glyphosate applied directly to vegetation may migrate to the soil from foliar washoff or translocation from the plants to the root zone. As discussed in Section 5.2.3, glyphosate agricultural uses in the United States increased from about 20 million pounds in 1992 to about 300 million pounds by 2014 (USGS 2017). Battaglin et al. (2014) estimated that nonagricultural uses of glyphosate were about 9,300 metric

tons (20.5 million pounds) in the United States in 2007 and Benbrook (2016) estimated that about 26.5 million pounds were used for nonagricultural purposes in 2014.

A 2008 survey of pesticide application in Ontario, Canada, conducted by the Ministry of Agriculture, Food, and Rural Affairs reported that glyphosate use increased from an estimated 1,170,762 kg active ingredient in 2003 up to an estimated 2,062,648 kg active ingredient in 2008 (OMAFRA 2008). A total of 527,952 kg of glyphosate were used on field crops, 6,700 kg were used on fruit, 6,110 kg were used on vegetables, and 6,635 kg of glyphosate were used on nursery crops, sod, and ginseng; greenhouse crops were not included. Specific 2008 glyphosate applications for weed control by crop use amounted to 527,952 kg in production of field corn, 1,253,773 kg for soybean production, 11,087 kg for canola, 155,428 kg for wheat, 9,206 kg for oats, 6,588 kg for barley, 6,167 kg for mixed grains, 3,185 kg for rye, 18,054 kg for white beans, 18,661 kg for dry beans, 27,011 kg for hay, 2,717 kg for pasture, 1,386 kg for sugar beets, and 1,991 kg for other field crops (OMAFRA 2008).

A 2013/2014 survey of pesticide application in Ontario, Canada, conducted by the Ministry of Agriculture, Food, and Rural Affairs reported pesticide use for glyphosate (OMAFRA 2015). An estimated total of 2,909,184 kg of glyphosate were used on all surveyed field crops in 2013/2014; 13,194 kg were used for fruit and 9,869 kg were used for vegetables. Specific crop use in 2013 for the amount of the active ingredient glyphosate applied as an herbicide equaled 1,151,051 kg for field corn, 1,544,954 kg for soybeans, 65,230 kg for wheat, 34,573 kg for oats and mixed grains, 11,542 kg for white beans, 27,980 kg for hay and pasture, and 24,144 kg for other field crops (OMAFRA 2015).

5.4 ENVIRONMENTAL FATE

The environmental fate of glyphosate, which includes the transport, partitioning, and transformation of this substance, is controlled by various physicochemical properties, degradation, and other loss processes. Glyphosate is a non-volatile, highly polar, non-residual herbicide that has low potential for environmental persistence and is unlikely to bioaccumulate; the chemical is either degraded or inactivated by adsorption to soil (Smith and Oehme 1992). Microbial degradation in soils and water is an important fate process; reported half-lives range from 2 to 215 days in soils and from 1.5 to 130 days in waters (Battaglin et al. 2014; IPCS 1994; PAN 2009; Rueppel et al. 1977). The wide range of half-lives is a result of environmental conditions such as soil characteristics, pH, and endogenous microbial populations, which are factors that influence the rate of degradation. Glyphosate is not expected to be susceptible to

hydrolysis; photodegradation has not been confirmed as an important fate process in any environmental media (Smith and Oehme 1992).

5.4.1 Transport and Partitioning

Glyphosate is not expected to change ionic form at pH levels of 5–8 and is expected to exist in its anionic form under most environmental conditions.

Air. Glyphosate has a low vapor pressure and is expected to exist in the particulate phase in the ambient atmosphere. There is potential for spray drift after application of herbicides, the extent of which is dependent on the mode of application. Aerial applications may result in considerable transport depending on climate conditions (Silva et al. 2018; IPCS 1994; Yates et al. 1978). Drift analysis has shown that 10–37% of applied herbicide can drift to non-target plants. Seedling and plant fatalities were found 20–100 m downwind after application, and residues have been detected at 400 and 800 m downwind following ground and aerial applications, respectively (PAN 2009). Wind erosion is one pathway in which glyphosate and its primary metabolite, AMPA, are transported into the atmosphere; Silva et al. (2018) estimated wind only can contribute between 1941 to 30,000 mg/ ha^{-1} $year^{-1}$ in offsite transport in soils with low to medium and high glyphosate content, respectively (Silva et al. 2018). Furthermore, Bento et al. (2017), reported that glyphosate and AMPA content were highest in the smallest particle sample size (8 µm) tested across three soil types (clay, organic matter, and silt). Glyphosate concentration ranged between 5.5 to 15 µg/g and AMPA content ranged between 0.07 to 0.7 µg/g when particle sizes (8 µm to 715 µm) were analyzed. Because particles <20 µm can be transported in long-term suspension, it's possible that combined with wind speeds, glyphosate particles have the potential to travel long distances and be transported into non-agricultural areas, particularly in conditions where topsoil is sufficiently dry (Bento et al. 2017).

Particulate-phase glyphosate can be removed from the atmosphere by wet or dry deposition. Wet deposition of glyphosate and its major degradation product, AMPA, from the atmosphere ranged from 3.9 to 16 µg/m^2 and from 1.7 to 5.2 µg/m^2, respectively, as reported in a study conducted in Pace, Mississippi, and Blairsburg, Iowa in 2007 and 2008 (Chang et al. 2011). In a study conducted in 2001, the total annual deposition for glyphosate was reported as 49,000 ng/m^2 and the maximum concentration detected was 6,200 ng/L. Glyphosate was detected in about 10% of the collected samples. The total annual deposition for AMPA was reported as 12,757 ng/m^2 and the maximum concentration detected was 1,200 ng/L. The majority of glyphosate detections occurred during the spraying season. Deposition rates

and concentrations of glyphosate were higher at the urban sites; this was attributed to its non-agricultural uses. The concentration of glyphosate and several other herbicides/pesticides were monitored in rainwater in Belgium from 1997 to 2001, and glyphosate was found to have an average annual concentration of 78 ng/L. The concentration increased dramatically during spraying season, reaching a maximum of 6,200 ng/L (Quaghebeur et al. 2004).

Water. Depending on its application, glyphosate may enter aquatic environments through direct application, or as a result of overspray in areas near aquatic environments .Water erosion is another route in which glyphosate and AMPA are transported into surface water bodies; Silva et al. (2018) estimated water erosion can contribute between 9753 to 47,557 mg/ ha^{-1} $year^{-1}$ in soils with low to medium and high glyphosate content, respectively (Silva et al. 2018). There is evidence of limited run-off and leaching with sandy soils and heavy rainfall (Borggaard and Gimsing 2008). Partitioning into aqueous environments is attenuated by adsorption to soils and sediments.

Sediment and Soil. Glyphosate will have strong adsorption to most soils due to its ionic nature and is expected to bind to positively charged metal surfaces present in clay and soils. Adsorption occurs through hydrogen bonding ion exchange or complexes of the phosphonate anion as well as the ammonium cation with minerals present in soils (Miles and Moye 1988). In an unpublished report by Monsanto in 1978, <0.1–6.6% of applied activity was recovered in the solution that washed off of the soil columns under leaching conditions simulating a heavy rainfall (IPCS 1994). The potential for run-off and leaching ability of glyphosate was examined by Rueppel et al. (1977) in three soils. Using inclined soil beds and artificial rainfall scenarios, a maximum runoff off $<2x10^{-4}$ kg/ha was reported. Using thin layer chromatography and beta camera analysis, 97–100% adsorption to all three soils indicated that there is minimal possibility for leaching into groundwater. Although glyphosate is expected to adsorb strongly to soil particles and clay minerals, desorption may occur under certain conditions. It has been demonstrated that sorption decreases with increasing soil pH, increasing concentrations of inorganic soil phosphate, and decreasing mineral concentrations (Glass 1987; Gerritse et al. 1996; Piccolo et al. 1994; Plimmer et al. 2004; Smith and Oehme 1992; Sprankle 1975). However, because of the strong sorption to most soils, mobility and the potential for migration into groundwater are low. It is known that glyphosate and AMPA strongly adsorb and accumulate in the top of soils (Silva et al. 2018). The major degradation product, AMPA (CASRN 1066-51-9), also binds to soils and may be more mobile than glyphosate (Duke and Powles 2008; IPCS 1994). Leaching of glyphosate may be possible under certain environmental conditions. In a study examining the environmental fate and leaching risk of aged glyphosate and its metabolite, AMPA, large amounts of glyphosate and AMPA were extracted from soil after treating it with

phosphate solution (to simulate rainwater in the presence of fertilizer) compared to pure water (to stimulate rainwater in non-fertilized soil). The presence of phosphate based fertilizer in soil appears to enhance the probability that glyphosate and its metabolite residue will leach from the soil matrix (Simonsen et al. 2008). While glyphosate and AMPA have been reported to reach shallow groundwater and then transfer to surface water (Grandcoin et al. 2017), the chemical is not expected to leach into groundwater as it is mostly concentrated in the topsoil layers; Glyphosate and AMPA are infrequently detected in deep groundwater systems, and when found, concentrations are generally at low levels (Silva et al. 2018).

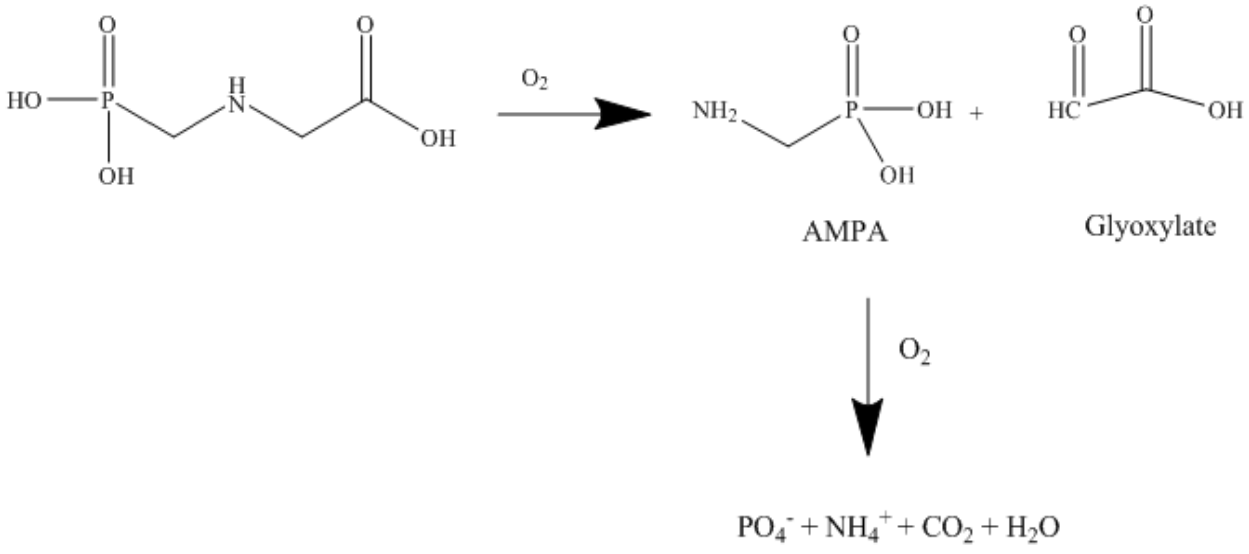
Other Media. Glyphosate is not generally taken up from the soil by a plant's root system since it typically forms bound residues with organic matter in most soils. Absorption of glyphosate via the roots has been discussed in a review by Saunders and Pezeshki (2015); however, many of the studies cited were conducted under hydroponic conditions, which are not likely to be typical of field environments. However, some uptake has been demonstrated to occur under field conditions with low organic-containing soils and in laboratory growing conditions. The EPA Registration Eligibility Decision (RED) document for glyphosate showed that lettuce, carrots, and barley contained glyphosate and AMPA residues after a sandy loam containing 0.3–0.5% organic matter was treated with 3.71 pounds of glyphosate per acre, but accumulation decreased as the length of rotation increased. For example, glyphosate residues were 0.097 ppm in lettuce planted 30 days post-treatment, but only 0.037 ppm in lettuce planted 119 days post-treatment (EPA 1993). After surface application of glyphosate, it may move from the point of application, typically the leaves, to other parts of the plant. In a plant uptake study where glyphosate was aged for 6.5 months in soil before either rape or barley seeds were planted, radioactivity demonstrated translocation of glyphosate into the parts of the plant above the soil after a growth period of 41 days. The measured uptake for rape and barely were equivalent to 14.0 and 11.5 ng/glyphosate/g plant fresh weight, respectively (Simonsen et al. 2008). Glyphosate can be absorbed into the plant or vegetable through its outer wall or skin and can move throughout the stem and leaves of the entire plant. Metabolism of glyphosate within the plant occurs slowly (Doublet et al. 2009; Smith and Oehme 1992; WHO 2005). Glyphosate is mobile inside the plant and may be transported within the phloem system into other tissues before the plant is killed (Duke and Powles 2008; Pankey 2000; Plimmer et al. 2004). Boerboom and Wyse (1988) investigated absorption and translocation of glyphosate using Canada thistle seeds with various concentrations of a formulation of glyphosate (356 g/L) and the surfactant POEA (178 g/L). Translocation from the treated leaf to the root was clearly observed. Translocation generally decreased as the concentration of glyphosate increased. Application of

the smaller droplets resulted in greater translocation to the roots compared to application of larger droplets.

5.4.2 Transformation and Degradation

Glyphosate is readily and completely degraded in the environment mainly by microbial processes. Microorganisms that degrade glyphosate into its metabolite include *Pseudomonas sp*., *Arthrobacter atrocyaneus* and *Flavobacterium sp*. (Singh and Singh 2016). Modes of degradation involving glyphosate oxidoreductase (GOX) and C-Plyase enzymatic pathways have been suggested. AMPA has been identified as the major metabolite in both soils and water. Sarcosine is an additional degradation product produced by the C-Plyase enzymatic pathway (Singh and Singh 2016). However, sarcosine has mostly been found in pure culture experiments, likely due to its fast degradation compared to AMPA (Borggaard and Gimsing 2008). Glyoxylic acid (CASRN 298-12-4) is an additional degradation product by the GOX enzymatic pathway. Both pathways result in complete mineralization to inorganic phosphate, carbon dioxide, ammonium, and water (Balthazor and Hallas 1986; Kishore and Jacob 1987; Shinabarger and Braymer 1986). AMPA is more persistent than glyphosate and has reported soil half-lives ranging from 32 to 240 days depending on edaphic and environmental conditions such as temperature and soil moisture (Simonsen et al. 2008; Battaglin 2014; Silva et al. 2018). At colder and drier conditions, degradation of AMPA is slower (Silva et al. 2018). Aquatic half-lives are similar to glyphosate (Battaglin 2014). Figure 5-2 illustrates the degradation of glyphosate under aerobic conditions.

Figure 5-2. Degradation of Glyphosate Under Aerobic Conditions



Source: Adapted from Schuette 1998

The high water solubility, low log K_{ow}, and ionic nature of glyphosate suggest that this compound would not be expected to bioaccumulate in aquatic organisms (IPCS 1994; WHO 2005). Jackson et al. (2009) measured whole-body bioconcentration factor (BCF) values for glyphosate in bluegill fish (*Lepomis macrochirus*) using EPA guideline method OPPTS 850.1730 for an exposure period of 28 days. A BCF value of 0.52 (log BCF -0.284) was reported, suggesting that bioconcentration was low. Accumulated residues of glyphosate in fish, crustaceans, and mollusks exposed to water containing glyphosate declined approximately 50–90% over 14–28 days after removal from the glyphosate water into glyphosate-free water (WHO 2005). Bioaccumulation of glyphosate in blackworms (*Lumbriculus variegatus*), following soil application of glyphosate and a commercial formulation, was investigated (Contardo-Jara et al. 2009). BCF values after 4 days of exposure to concentrations of 0.05–5 mg/L of both 98% pure glyphosate and the formulation Roundup Ultra® were measured at 20°C (Contardo-Jara et al. 2009). BCF values based on the fresh weight of the worms ranged from 1.2 to 5.9; the BCF values for pure glyphosate at 0.05, 0.5, and 5.0 mg/L were approximately 2.9, 1.1, and 2.8, respectively and BCF values for Roundup Ultra® at 0.05, 0.5, and 5.0 mg/L were approximately 5.9, 3.8, and 2.7, respectively. The greater uptake of glyphosate from the Roundup Ultra® sample was attributed to the surfactant in the formulation, POEA.

The mechanism of action for glyphosate's herbicidal properties involves the inhibition of enzymes in the shikimate pathway. Specifically, the enzyme enolpyruvylshikimate-3-phosphate synthase is inhibited, creating a deficiency of enolpyruvylshikimate-3-phosphate and an abundance of shikimate. It has been suggested that the actual death of the plant is due to the disruption of plant processes regulated by the shikimate pathway essential to plant health and growth such as the primary biosynthesis of aromatic amino acids like phenylalanine, tryptophan, and tyrosine, as well as lignin and chlorophyll, and secondary processes such as flavonoid synthesis. These primary processes are exclusive to plants and some microorganisms and do not occur in any animals; therefore, the inhibition of enzyme production induced by glyphosate only affects species in the plant kingdom. It has also been suggested that the increased carbon flow to the shikimate pathway decreases carbon available for other essential photosynthetic processes (Muller and Applebyke 2010; Pankey 2000; Plimmer et al. 2004; Servaites et al. 1987).

In one version of transgenic plants modified to be glyphosate tolerant, glyphosate is converted to N-acetylglyphosate (CASRN 129660-96-4), a chemical that lacks herbicidal properties (Pioneer 2006). This chemical may be further metabolized to N-acetyl (aminomethyl)phosphonic acid (N-acetyl-AMPA) (PAN 2009). However, the more common method of conferring glyphosate-resistance to plants is promoting the

expression of enolpyruvulshikimate-3-phosphate synthase variants that are resistant to glyphosate-inhibition (Pioneer 2006).

Air. Glyphosate has low vapor pressure and is considered stable in ambient air. Experimental and monitoring studies have confirmed wind-driven transportation of both glyphosate and AMPA including in areas that never had glyphosate application (Silva et al. 2018; Aparicio et al. 2018).

Water. Glyphosate is polar, has high water solubility and is expected to exist as an anion at neutral pH (IPCS 1994; O'Neil et al. 2013; Singh and Singh 2016). Based on experimental adsorption coefficients ranging from 8 to 377 dm^3/kg for various soil and clay substrates, glyphosate is expected to adsorb to suspended solids and sediments in water. Precipitation from water has been suggested due to water-insoluble metal complexes with iron(III), copper(II), calcium, and magnesium that have been found; coordination occurs through the amine nitrogen, the carboxylic oxygen, and the phosphate oxygen (Subramaniam and Hoggard 1988). Photodegradation in water is not expected to be an important fate process for glyphosate under environmentally relevant conditions. Experimental half-lives of <28 days upon exposure to natural light have been reported (IPCS 1994; Rueppel et al. 1977). No detectable photodegradation was observed in a study using sterile water and exposure to ultraviolet (UV) light or natural sunlight (Smith and Oehme 1992). Lund-Hoie and Friestad (1986) exposed RoundUp® to UV light at 254 nm at 20°C in the laboratory and exposed 1% RoundUp® solutions in deionized water, polluted water, and water with suspended sediments to natural sunlight (measured λ=295–385 nm) outside at temperatures ranging from 20 to -5°C. Results indicated that photodegradation occurred faster in pure water as opposed to polluted water or water with sediments in which adsorption accounted for the majority of dissipated glyphosate. A photolytic half-life of 3–4 weeks was observed for glyphosate, at an initial concentration of 2,000 ppm in the deionized water exposed to UV light. A photolytic half-life of 5 weeks at 100 ppm was observed for glyphosate in deionized water, exposed to natural sunlight. The rate of hydrolysis is considered very slow. In a study at 35°C, glyphosate did not undergo hydrolysis in buffered solutions with a pH of 5, 7, or 9. Laboratory studies have reported 50% degradation in ≤14 days in water and sediment under aerobic conditions and 14–22 days under anaerobic conditions for glyphosate (IPCS 1994). In an aqueous hydrolysis study at 25°C in buffered solutions of pH 5, 7, and 9, glyphosate was considered hydrolytically stable, with extrapolated half-lives beyond 3 years (EPA Undated).

Rapid dissipation of glyphosate in small forest ponds was observed as a result of sediment sorption and microbial degradation (Goldsborough and Beck 1989). Dissipation in three ponds, pH 5.0–7.7, resulted

in half-lives of 1.5–3.5 days. After 38 days, glyphosate was not detected in any of the samples. AMPA concentrations were consistently low throughout the study.

Microbial degradation of glyphosate in water sediments has been investigated. AMPA has been identified as the major metabolite in water. Rueppel at al. (1977) performed non-sterile and sterile soil/water shake flask experiments to examine the degradation of glyphosate under aerobic and anaerobic conditions. The ^{14}C-labeled glyphosate samples used were between 94.8 and 98.1% pure. Ray silt loam, Norfolk sandy loam, and Drummer silty clay loam soil samples were used. In the sterile soil test, 1.0% degradation was achieved after 7 days; the report suggests that abiotic chemical degradation is not a likely fate process for glyphosate. In non-sterile aerobic and anaerobic tests using Ray silt loam and 14C-labeled glyphosate, 46.8–55.3 and 33.5–51.4% TCO_2 (theoretical CO_2 evolution), respectively, was achieved after 28 days. In the non-sterile aerobic tests using fresh and bin-stored Drummer loams, just over 40% and just under 20% TCO_2, respectively, was achieved after 28 days. In the fresh Drummer loam and Ray loam samples, no lag phases were observed, and the bulk of the degradation occurred by day 7, after which time, the rate of degradation declined. The slowing of degradation was attributed to adsorption to soil. In Ray silt loam and Drummer silty clay loam, degradation of glyphosate reached 90% after 14 and 80 days, respectively, and half-lives were reported as 3 and 25–27 days, respectively. The results were similar at different concentrations of glyphosate. In the non-sterile aerobic test in Norfolk sandy loam, carbon-labeled glyphosate achieved <10% mineralization after 28 days, measured by applied ^{14}C as CO_2 evolution, and 43% dissipation occurred after 112 days. A half-life of 130 days was reported for Norfolk soil. The principle degradation product identified, AMPA, was confirmed in soil samples by nuclear magnetic resonance (NMR) imaging, mass spectral analysis, ion-exchange chromatography, and thin-layer chromatography. Minor degradation products identified included N-methylaminomethylphosphonic acid, glycine, N,N-dimethylaminomethylphosphonic acid, and hydroxymethylphosphonic acid, all of which were typically present at <1% (Rueppel et al. 1977). The metabolite, AMPA, achieved 16.1 and 34.8% degradation after 63 days in Drummer and Ray loams, respectively, measured by applied ^{14}C as CO_2 evolution.

Abiotic degradation was examined by Ascolani Yael et al. (2014) in aqueous solution in the presence of copper salts; results indicated that glyphosate interactions with metal ions in soils may catalyze degradation to AMPA. Further investigation was proposed.

Sediment and Soil. Glyphosate is readily degraded in the terrestrial environment by a variety of microorganisms. Bacteria, actinomycetes, fungi, and other soil microbes have the ability to degrade

glyphosate. AMPA has been identified as the major metabolite in soil. Glyphosate may also be degraded in soil to sarcosine and inorganic phosphate. Photodegradation is not expected to be an important fate process in soil.

After application of Roundup® at about 2.0 kg/ha (acid equivalent of isopropylamine salt of glyphosate) to Carnation Creek watershed (10 km^2 study area), 50% of the glyphosate residues in soil dissipated after 45–60 days and 82–94% dissipated after 360 days (Feng et al. 1990a).

It has been demonstrated that inorganic phosphate present in soils may inhibit some microbial degradation of glyphosate (Kishore and Jacob 1987). Strains capable of using glyphosate as a sole carbon, nitrogen, or phosphorus source, thereby degrading glyphosate, include *Flavobacterium* sp. (Balthazor and Hallas 1986), which is known to degrade glyphosate in the presence of phosphate, *Pseudomonas* sp. PG2982 (Kishore and Jacob 1987; Shinabarger and Braymer 1986), *Arthrobacter atrocyaneus* (Pipke and Amrhein 1988), and *Rhizobium* spp. (Liu et al. 1991). Biodegradation may involve co-metabolism with other energy sources as well (Sprankle et al. 1975). Degradation products include AMPA and glyoxylic acid, which are subsequently degraded to inorganic phosphate, carbon dioxide, and ammonium. In addition, some bacterial degradation results in the production of sarcosine and inorganic phosphate (Borggaard and Gimsing 2008; Kishore and Jacob 1987; Liu et al 1991; Pipke and Amrhein 1988; Shinabarger and Braymer 1986).

Microbial degradation of bound and unbound glyphosate in several soils resulted in 17.4–45% ultimate degradation after 28 days; the highest degradation rate was observed in Conover sandy clay loam soil (Sprankle et al. 1975). The majority of the degradation was attributed to co-metabolic processes of soil microbes, with possible chemical degradation occurring.

In a biodegradation experiment with activated sludge, the bacterial strain, *Flavobacterium* sp., was identified as the microorganism metabolizing glyphosate to AMPA. This degradation was followed by complete mineralization of AMPA, using the enzyme phosphonatase, to carbon dioxide (CO_2), phosphate (PO_4^{3-}), ammonium (NH^{4+}), and water (H_2O) (Balthazor and Hallas 1986).

A variety of microorganisms are capable of degrading glyphosate. In one degradation pathway, the initial step involves cleavage of the carbon-phosphate bond to produce sarcosine and inorganic phosphate. This is followed by conversion of sarcosine to glycine and formaldehyde. *Pseudomonas* sp. PG2982 uses the enzyme, C-P lyase, to cleave the carbon-phosphate bond in glyphosate, producing sarcosine. This is

followed by the cleavage of sarcosine into glycine and formaldehyde (Kishore and Jacob 1987; Shinabarger and Braymer 1986). Glycine and formaldehyde are metabolized in other biosynthesis processes, such as the oxidation of formaldehyde to carbon dioxide. Multiple strains in the bacterial family *Rhizobiaceae* have the ability to metabolize glyphosate. Liu et al. (1991) found that rhizobia bacterial cells took up close to 85% of available glyphosate within 30 minutes, after which time, the percentage began to decrease. Thin layer chromatography confirmed the presence of sarcosine and glycine as degradation products.

Doublet et al. (2009) studied the degradation of plant absorbed glyphosate in soils. Plants containing residues of glyphosate can enter the soils during crop cycling or harvesting. Degradation of glyphosate was different depending on the plant tissue in which it was absorbed. Mineralization rate constants (k (day^{-1})) ranged from 0.031 to 0.097 in the apex of oilseed rape and in the lamina of maize, respectively. It was noted that absorption of glyphosate in plants delayed degradation in soil.

Glyphosate is expected to adsorb strongly to soil particles and clay minerals; however, the amount of glyphosate sorbed decreases with increasing soil pH. Adsorption and desorption of glyphosate were examined using HPLC (Gerritse et al. 1996; Glass 1987; Piccolo et al. 1994; Sprankle et al. 1975). Adsorption to agricultural soils and clay minerals and the effects of pH and cation saturation were examined by Glass (1987). The K_{oc} values were 4,900 for clay loam with pH 7.5 and organic content (OC) of 1.56%; 3,400 for silt loam with pH 5.8 and OC of 1.64%; and 2,600 for sandy loam with pH 5.6 and OC of 1.24%. The adsorption and desorption of glyphosate and the effects of soil characteristics in four various soil types were assessed (Piccolo et al. 1994). Some characteristics for the four soils follow: Sample A, pH 8.0 and 0.00 OC % (64.1% silt); sample B, pH 5.8 and 3.73 OC% (46.3% sand); sample C, pH 4.6 and 9.23 OC % (81.5% sand); and sample D, pH 8.3 and 0.45 OC % (82.4% silt). The greatest adsorption occurred in the soil with the highest concentrations of iron (4.74%) and aluminum (1.57) oxides (sample B); the greatest desorption occurred in the soil with lowest concentration of iron (0.18%) and aluminum (0.16%) oxides (sample A). The percent desorptions of glyphosate from the four soils were 81% in sample A, 15% in sample B, 72% in sample C, and 35% in sample D. A ligand exchange mechanism is hypothesized for the adsorption of glyphosate involving either the phosphonic component or the carboxylic component of this substance and adsorption to iron and aluminum sites (Benetoli et al. 2010; Piccolo et al. 1994). The adsorption and desorption of both glyphosate and its metabolite, AMPA, were examined by Gerritse et al. (1996) using five soil types. K_{oc} values calculated for soil organic carbon ranged from 8.5 to $5x10^6$ after 1 day and from 45 to $>5x10^6$ after 1 week. The strongest adsorption occurred in the soil with the highest iron and aluminum content. The weakest adsorption

occurred in the soil with the highest organic content. These results indicate that glyphosate has a notable affinity towards some soils, particularly with lower pH values and greater mineral content, and desorption occurs under certain environmental conditions especially as pH values increase and mineral concentrations decrease. The EPA CompTox Chemicals Dashboard provided a predicted K_{oc} range of 0.00169–2,080 L/kg, which again indicates a range of mobility in soil likely determined by affinity towards these soil properties.

During a monitoring study with mixtures of Roundup® plus an additional herbicide, soil adsorption and desorption studies were performed on soils from Baton Rouge, Bridge City, and Hammond Louisiana (LaDOTD 1995). The Hammond soil with a pH <8 adsorbed >90% of the applied glyphosate. Adsorption values (Kf) were 8.7, 0.1, and 0.34 for Baton Rouge, Bridge City, and Hammond soils, respectively. Desorption values (Kd) were 355, 0.04, and 0.005 µg/g for Baton Rouge, Bridge City, and Hammond soils, respectively.

Greater than 90% of the glyphosate residues detected in forest soil samples (pH 4.20–5.28), where herbicides containing glyphosate had been sprayed, were found in the upper layers (depth of 0–15 cm) of the soils in both seasonally flooded and well-drained soils, indicating minimal leaching of glyphosate (Feng et al. 1990b).

Glyphosate dissipates from soil under certain environmental conditions. Half-life values between 2 and 215 days have been reported (Battaglin et al. 2014). In field experiments, dissipation from the soil due to run-off has been demonstrated (IPCS 1994). Landry et al. (2005) examined the leaching potential and mineralization of glyphosate in vineyard soils by monitoring outdoor soil columns from May 2001 to May 2002. Bare and grass-covered soils with pH values ranging from 8.0 to 8.4 were studied. Sand, silt, and clay contents were 23.8–34.4, 36.5–39.6, and 29.1–36.9%, respectively, of the bare soils and 26.2–35.6, 34.2–41.3, and 29.6–32.5%, respectively, of grass-covered soils. An aqueous solution of herbicide containing 340 mg/L glyphosate was applied to both soil column surfaces. Effluents from the bare and grass-covered soils were collected weekly and after heavy precipitation to evaluate leaching of glyphosate and AMPA. Glyphosate was detected in 37% of the bare soil leachates and 27% of the grass-covered soil leachates. The highest concentrations measured from the bare soil leachate and grass-covered leachate were 17 and 2.7 µg/L, respectively. AMPA was detected in 90% (maximum concentration 9.4 µg/L) of the bare soil leachates and 41% (maximum concentration 3.5 µg/L) of the grass-covered soil leachates. Mineralization analysis was performed at 20°C for 42 days in both soils. In the grass-covered soil and bare soil, ^{14}C-labeled glyphosate achieved 46.5 and 43.5% CO_2 evolution after 42 days, respectively.

Rapid degradation was observed with no lag phase; the highest rate of degradation occurred within the first 2 days. It was suggested that the initial rapid degradation was based on the degradation of free glyphosate and slowing rates of degradation were attributed to the degradation of adsorbed glyphosate.

Other Media. After application of herbicides, 30–97% of the applied glyphosate may be taken up by the plant by absorption from the treated leaves. Glyphosate-based formulations containing surfactants (and adjuvants) have a higher rate of absorption compared to glyphosate water solutions (Doublet et al. 2009). Surfactants in herbicide formulations aid in the adsorption and absorption of the active ingredient. Glyphosate is absorbed by plant foliage and transported or moved through the plant via phloem vessels; translocation patterns depend on the specific species of plant. Glyphosate enters these vessels slowly, but once inside, it becomes 'trapped' because of the pH within the vessels, which causes ionization (Gomes et al. 2014; IPCS 1994). Glyphosate may be degraded or metabolized in plants, AMPA is a notable degradation product (Duke 2011). An examination of the metabolism of glyphosate in soybean and canola suggest that some plants use a GOX enzyme for the conversion of glyphosate to AMPA. Degradation of glyphosate in glyphosate-resistant crops may give a better picture of the metabolic processes without interferences found in conventional crops. In transgenic plants modified to be glyphosate tolerant, glyphosate is converted to N-acetylglyphosate, which lacks herbicidal properties (Pioneer 2006). This chemical may be further metabolized to N-acetyl-AMPA (PAN 2009). Glyphosate and AMPA accumulate less in glyphosate-resistant crops than in conventional crops. Lower glyphosate and AMPA levels in glyphosate-resistant canola compared to conventional crops suggested that metabolism is more rapid in glyphosate-resistant canola (Duke 2011).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to glyphosate depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of glyphosate in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on glyphosate levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-4 shows the lowest limits of detection (LODs) that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-5.

Table 5-4. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.01 ng/m^3	Chang et al. 2011
Drinking water	5.99 µg/L (ppb)	EPA 1990
Surface water and groundwater	Glyphosate and AMPA 0.02–0.10 µg/L 0.005 µg/L	Lee et al. 2002; USGS 2002 Ibanez et al. 2005
Soil and sediment	Organic soil =0.05 µg/g Mineral soil=0.02 µg/g Foliage=0.10 µg/g Sediment=0.03 µg/g Soil=0.005 µg/g	Thompson et al. 1989 Ibanez et al. 2005
Whole blood	15 ng/mL	Aris and LeBlanc 2011
Urine	0.09 ng/mL 0.1 ng/mL	Biagini et al. 2004 Jensen et al. 2016
Milk (human and bovine)	10 µg/L (ppb)	Jensen et al. 2016
Crops and commodities	0.01 mg/kg	Alferness 1993

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

AMPA = aminomethylphosphonic acid

Table 5-5. Summary of Environmental Levels of Glyphosate

Media	Low	High	For more information
Outdoor air (ng/m^3)	<0.01 (glyphosate) <0.01 (AMPA)	9.1 (glyphosate) 0.97 (AMPA)	Table 5-6
Surface water (ppb)	0.02	427	Table 5-8
Ground water (ppb)	0.01	4.7	Table 5-9
Drinking water (ppb)	Not detected		Table 5-9
Food (ppb)	0.078	5.47	Section 5.5.4, Other Media
Sediment	Not detected		Table 5-10

AMPA = aminomethylphosphonic acid

A study by the USGS evaluated 3,732 environmental samples across 38 states and the District of Columbia from several studies examining glyphosate in the environment; the samples were collected between 2001 and 2010 from 1,341 different sites, including groundwater; lakes, ponds, and wetlands; soil water; streams; large rivers; precipitation; ditches and drains; soil and sediment; and waste water treatment plant outfall (Battaglin et al. 2014). Glyphosate was detected in 39.4% of all the samples, with a median value of <0.02 µg/L and a maximum value of 476 µg/L. Its degradation product, AMPA, was detected in 55% of all the samples, with a median value of 0.04 µg/L and a maximum value of 397 µg/L.

Groundwater (n=1,171) had the smallest percentage of detections, with 5.8% for glyphosate and 14.3% for AMPA. Glyphosate was detected in 53% of the 1,508 stream samples and AMPA was detected in 72%. Glyphosate was detected in 34% and AMPA was detected in 30% of the 104 small body water samples such as lakes and ponds. Out of 11 wastewater treatment plant (WWTP) samples, glyphosate and AMPA were detected in 9.1 and 82%, respectively. Out of 85 precipitation samples, glyphosate was detected in 71% and AMPA was detected in 72%. Glyphosate was detected in 71% of the 374 ditch and drain samples, with a median value of 0.02 µg/L and a maximum value of 427 µg/L. Glyphosate was only detected without its degradation product, AMPA, in 2.3% of all of the samples; AMPA was detected without glyphosate in 17.9% of the samples. In 42.7% of all of the samples, neither analyte was detected. Several sites with multiple samples during the years 2001–2005 and 2006–2010 indicated that the detection frequency and median concentration of both glyphosate and AMPA had increased in the environment (Battaglin et al. 2014). The highest level of glyphosate was detected in soils and sediments. Out of 45 samples, glyphosate was detected in 91%, with a median value of 9.6 µg/kg and a maximum value of 476 µg/kg. AMPA was detected in 93.3% of 45 samples, with a median value of 18 µg/kg and a maximum value of 341 µg/kg.

5.5.1 Air

Ambient air monitoring data for glyphosate are compiled in Table 5-6.

Table 5-6. Outdoor Air Monitoring Data for Glyphosate

Location	Date	Median concentration (range) in ng/m^3	Notes	Reference
Agricultural ambient air; Mississippi	2007	Glyphosate: 0.48 (<0.01–9.1) AMPA: 0.06 (<0.01–0.49)	Glyphosate and AMPA detected in 19/22 air samples	Chang et al. 2011
	2008	Glyphosate: 0.24 (<0.01–1.5) AMPA: 0.02 (<0.01–0.09)	Glyphosate and AMPA detected in 27/27 and 19/27 air samples, respectively	
Agricultural ambient air; Iowa	2007	Glyphosate: 0.08 (<0.01–5.4) AMPA: 0.02 (<0.01–0.97)	Glyphosate and AMPA detected in 11/18 and 10/18 air samples	Chang et al. 2011
	2008	Glyphosate: 0.22 (<0.01–7.7) AMPA: 0.04 (<0.01–0.38)	Glyphosate and AMPA detected in 13/18 and 11/18 air samples	
Agricultural breathing zones; Baton Rouge, Bridge City,	June 19, 1990–October 9, 1990	<0.1–138.6 µg/m	Breathing zone air (110 samples); sampled in areas where mixtures of commercial herbicides were applied using spray equipment with operating capabilities of 0.37 L/minute	LaDOTD 1995

Table 5-6. Outdoor Air Monitoring Data for Glyphosate

Location	Date	Median concentration (range) in ng/m^3	Notes	Reference
Hammond, Louisiana;				

AMPA = aminomethylphosphonic acid

5.5.2 Water

A comprehensive study conducted by the USGS from 2001 to 2006 examined glyphosate and its degradation product, AMPA, in 2,135 groundwater and surface water samples, 14 rainfall samples, and 193 soil samples in major river basins in the United States (USGS 2007). Results indicated that AMPA was detected more frequently and at similar concentrations than parent glyphosate in many samples. The results are summarized in Table 5-7.

Table 5-7. Glyphosate and its Degradation Products in Water Samples in Major U.S. River Basins

	Glyphosate			AMPA		
N	Detections	Maximum (µg/L)	Minimum (µg/L)	Detections	Maximum (µg/L)	Minimum (µg/L)
Groundwater						
873	68	4.7	0.02	133	2.6	0.02
Surface water						
1,262	489	427	0.02	725	41	0.02
Rainfall						
14	12	1.1	0.3	12	0.47	0.02

Source: USGS 2007

Additional water monitoring data for glyphosate are compiled in Tables Table 5-8 and Table 5-9.

5.5.3 Sediment and Soil

Sediment and soil monitoring data for glyphosate are compiled in Table 5-10.

5.5.4 Other Media

In 2006, 20 prepared food samples were examined for glyphosate residues using electrospray ionization–liquid chromatography tandem mass spectrometry with limit of quantitation of 0.01 mg/kg and an LOD of 0.005 mg/kg (McQueen et al. 2012). Composite food samples assessed had a mean concentration of 0.08 mg/kg.

Four weeks post application of glyphosate at 4.5 kg/ha to separate pots planted with conventional corn, cotton, soybeans, and wheat, concentrations of glyphosate were 0.21, 0.26, 0.20, and 0.20 mg/kg, respectively. Six weeks after application, concentrations in corn, cotton, soybeans, and wheat were 0.14, 0.21, 0.29, and 0.18 mg/kg, respectively, and 8 weeks after application, concentrations in corn, cotton, soybeans, and wheat were 0.079, 0.42, 0.076, and 0.35 mg/kg, respectively (FAO 2005). Four-week concentrations of glyphosate in control crops of corn, cotton, soybeans, and wheat were 0.068, 0.04, 0.029, and 0.008 mg/kg, respectively. Six-week concentrations in control crops of corn, cotton, soybeans, and wheat were 0.089, 0.020, 0.11, and 0.015 mg/kg, respectively, and 8-week concentrations in control crops of corn, cotton, soybeans, and wheat were 0.022, 0.27, 0.045, and 0.061 mg/kg, respectively (FAO 2005).

Table 5-8. Surface Water Monitoring Data for Glyphosate

Location	Date	Concentration (range) in µg/L	Notes	Reference
Surface water United States	2016	Mean: 0.30 ; Median 0.10; (0.02–5.1)	EPA STORET data: Routine monitoring samples from USGS Science Centers in Arkansas, California, Colorado, Connecticut, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Michigan Center, Maryland, Massachusetts, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, North Dakota, Oregon, South Carolina, Texas, Utah, Washington, and Wyoming	WQP 2017
Surface water United States	2015	Mean: 0.27; Median 0.08; (0.02–24.20)	EPA STORET data: Routine monitoring samples from Minnesota Department of Agriculture–Pesticide and USGS Science Centers in Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Massachusetts, Michigan Center, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Dakota, North Washington, Ohio, Oklahoma, Oregon, South Carolina, South Dakota, Texas, Utah, Washington, and Wyoming	WQP 2017
Surface water United States	2014	Mean: 0.38; Median 0.10; (0.02–8.10)	EPA STORET data: Routine monitoring samples from Minnesota Department of Agriculture–Pesticide and USGS Science Centers in Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, Texas, Utah, Virginia, Washington, and Wyoming	WQP 2017
Surface water United States	March to October 2013	Mean: 0.85; Median 0.34; (0.02–27.80)	EPA STORET data: Routine monitoring samples from Minnesota Department of Agriculture and USGS Science Centers in Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Minnesota, Missouri, Nebraska, New York, North Carolina, Ohio, South Dakota, Wisconsin, and Wyoming	WQP 2017

Table 5-8. Surface Water Monitoring Data for Glyphosate

Location	Date	Concentration (range) in µg/L	Notes	Reference
Rivers, small streams, agricultural ditches, and low-flow wetlands Southern Ontario	May and mid-December 2004; April and November 2005	5–41	2004: 203 surface water samples collected from 26 sites 2005: 299 samples taken from 58 sites ~50% of sites detected glyphosate multiple times AMPA detected at trace levels (20–66 µg/L in 5.4% of samples)	Struger et al. 2008
Streams Minnesota, Wisconsin, Nebraska, Iowa, Illinois, Indiana, Ohio, Kansas, and Missouri	2002	Minimum: 0.10–0.46 detected in Iowa, Missouri, and Wisconsin Maximum: 0.54–8.7 detected in Illinois, Indiana, Kansas, Minnesota, Nebraska, and Wisconsin	51 locations (155 total samples); samples collected post-application of pre-emergence herbicides, post-application of post-emergence herbicides, and during the harvest season. Glyphosate detected at levels above the method reporting limit of 0.10 µg/L in 35% of pre-emergence samples, 40% of post-emergence samples, and 31% of harvest season samples. AMPA detected at levels >0.10 µg/L in 53% of pre-emergence samples, 83% of post-emergence samples, and 73% of harvest season samples.	Battaglin et al. 2005
Drainage basins for surface-water or rainwater sampling sites from multiple USGS studies in Florida, Georgia, Illinois, Iowa, Kansas, Mississippi, Nebraska, South Dakota, Vermont, and Washington	2001 through 2006	0.02–427 in surface water 0.3–1.1 in rainwater	Glyphosate and AMPA measured in 1,262 surface water samples and 14 rainwater samples. Glyphosate detected in 489 surface water samples and in 12 rainwater samples. AMPA detected in 725 surface water samples and 12 rainwater samples.	USGS 2007

Table 5-8. Surface Water Monitoring Data for Glyphosate

Location	Date	Concentration (range) in µg/L	Notes	Reference
Rainwater Mississippi	2007	Glyphosate: Median: 0.2 (<0.1–1.9) AMPA: Median: 0.1 (<0. 1–0.3)	Glyphosate and AMPA detected in 8/11 and 8/11 samples, respectively	Chang et al. 2011
	2008	Glyphosate: Median: 0.15 (<0.1–1.6) AMPA: Median: <0.1 (<0. 1–0.48)	Glyphosate and AMPA detected in 13/11 and 14/19 samples, respectively	
Rainwater Iowa	2007	Glyphosate: Median: 0.2 (<0.1–2.5) AMPA: Median: <0.1 (<0. 1–0.2)	Glyphosate and AMPA detected in 10/14 and 5/14 samples, respectively	Chang et al. 2011
	2008	Glyphosate: Median: 0.1 (<0.1–1.8) AMPA: Median: <0.1 (<0. 1–0.24)	Glyphosate and AMPA detected in 15/24 and 12/24 samples, respectively	
Rainwater Indiana	2004	Glyphosate: Median: 0.14 (<0.1–1.1) AMPA: Median: <0.1 (<0.1–47)	Glyphosate and AMPA detected in 11/12 and 11/12 samples, respectively	Chang et al. 2011
Rainwater Flanders, Belgium	2001	Maximum during spraying season: Glyphosate: 6,200 ng/L AMPA: 1,200 ng/L Average annual concentrations: Glyphosate: 78 ng/L AMPA: 20 ng/L	Glyphosate detected in 10% of samples; AMPA detected in 13% of samples	Quaghebeur et al. 2004
Streams of Southeast Buenos Aires, Argentina	2012	Glyphosate: 0.5 µg/L – 7.6 µg/L AMPA: non-detect to 2.3 µg/L	Glyphosate detected in 35%, 10% and 4% samples collected in April, August and September, respectively. AMPA detected in 33% and 7%, of samples in April and August, respectively. AMPA was not detected in samples collected in September.	Aparicio et al. 2013
Gualeguay or Gualeguaychu River, Argentina	2012	Glyphosate: 0.73 µg/L AMPA: 0.53 µg/L	Glyphosate detected in 3/11 samples; AMPA detected in 6/11 samples.	Primost et al. 2017

AMPA = aminomethylphosphonic acid; EPA = U.S. Environmental Protection Agency; MDL = method detection limit; STORET = STOrage and RETrieval; USGS = U.S. Geological Survey

Table 5-9. Groundwater Monitoring Data for Glyphosate

Location	Date	Concentration (µg/L)	Notes	Reference
Drainage basins for surface-water or rainwater sampling sites from multiple USGS studies in Florida, Georgia, Illinois, Iowa, Kansas, Mississippi, Nebraska, South Dakota, Vermont, and Washington	2001 through 2006	0.02–4.7	Glyphosate and AMPA measured in 873 groundwater samples. Glyphosate detected in 68 groundwater samples, and AMPA detected in 133 groundwater samples.	USGS 2007
Groundwater Wyoming	September 9, 2010	1.6	EPA STORET data: Routine monitoring sample from USGS Wyoming Water Science Center	WQP 2017
Groundwater Florida	March 2, 2010	0.14	EPA STORET data: Routine monitoring sample from USGS Florida Water Science Center	WQP 2017
Groundwater Louisiana	April, October, and November 2011	0.03–2.2	EPA STORET data: Routine monitoring sample from USGS Louisiana Water Science Center; depths 43.5–82 feet	WQP 2017
Groundwater Alabama Texas	February and April, 2012	0.01–0.06	EPA STORET data: Routine monitoring sample from USGS Alabama Water Science Center; USGS Texas Water Science Center	WQP 2017
Groundwater Kansas	June and August 2014, June 2015, July 2016	0.02–0.24	EPA STORET data: Routine monitoring sample from USGS Kansas Water Science Center	WQP 2017

Table 5-9. Groundwater Monitoring Data for Glyphosate

Location	Date	Concentration (µg/L)	Notes	Reference
Groundwater 23 U.S. states	2001–2010	Median: <0.02 Maximum: 2.03	Detected in 68 out of 1,171 samples	Battaglin et al. 2014
Groundwater Washington, DC	2008	0.02	Detected in 1 out of 13 well; not detected in 14 wells sampled in 2005	USGS 2010
Well water Minnesota	October and November 2014, 2015	Not detected	EPA STORET data: Routine monitoring sample from Minnesota Department of Agriculture Pesticide Monitoring Program; activity depth reported at 0 m	WQP 2017
Aquifer, Mesopotamia Pampas, Argentina	January and March 2012	Not detected	Ground water collected from pump 40 to 60 meter deep aquifer	Primost et al. 2017

EPA = U.S. Environmental Protection Agency; STORET = STOrage and RETrieval; USGS = U.S. Geological Survey

Table 5-10. Sediment and Soil Monitoring Data for Glyphosate

Location	Date	Concentration (µg/g)	Notes	Reference
Sediment Big Valley Rancheria, California	July 6, 2010	Not detected	EPA STORET data: Routine monitoring samples from Big Valley Band of Pomo Indians of the Big Valley Rancheria, California: two samples; depth: 0.152 m; MDL: 0.017 mg/kg	WQP 2017
Soil and sediment Indiana, Mississippi	2001–2010	Median: 0.0096; maximum: 0.476	Detected in >90% of 45 samples	Battaglin et al. 2014
Estuary Willapa Bay, Washington	July 1997–1999	1997 mudflat samples: 2.58–16.3 1998 mudflat samples: 3.11–9.94 1999 mudflat samples: 0.311–1.21 1997 meadow samples: 0.090–0.265 1998 meadow samples: 0.163–2.30 1999 meadow samples 0.472–1.32 (dry weight)	Aqueous herbicide formulated with Rodeo (5% solution v/v) and LI-700 (2% solution) applied in mudflat and cordgrass plots of land in 1997 and 1998	Kilbride and Paveglio 2001
Major river basins in the United States	2011–2006	193 samples collected; 119 glyphosate detections (0.001–0.476); 154 detections AMPA, (0.001–0.956)	Samples collected as part of USGS study	USGS 2007
Streams Southeast Buenos Aires, Argentina	September 2012	Glyphosate minimum: 5.7 µg/kg; maximum: 221.2 µg/kg AMPA minimum: 5.1 µg/kg; maximum: 235 µg/kg	Glyphosate was detected in 66% of samples from 44 streams in Southeast Buenos Aires AMPA was found in 89% of samples from 44 streams in Southeast Buenos Aires	Aparicio et al. 2013
Soils of Southeast Buenos Aires, Argentina	September 2012	Glyphosate: 35 to 1502 µg/kg AMPA: 299 to 2256 µg/kg	Sixteen farms were selected for soil sampling in the southeast of the Province of Buenos Aires where glyphosate had been used	Aparicio et al. 2013
Los Frentones (Chaco), Argentina	November 2004 to November 2010	Glyphosate: 2.4 µg/kg AMPA: 6.3 µg/kg	Soil analysis conducted in semiarid regions of Argentina; no history of herbicide application, but in the surrounding area, there were patches with 2 and 3 years of annual crops (mainly soybean)	Aparicio et al. 2018
Santa Rosa (La Pampa), Argentina	November 2004 to	Glyphosate: 9.5 µg/kg AMPA: 66.2 µg/kg	Soil analysis conducted in semiarid regions of Argentina in soils with 4 years of annual crops	Aparicio et al. 2018

	November 2010		(oats, rye, and sorghum) under conventional tillage with little use of pesticides.	
Villa Mercedes (San Luis), Argentina	November 2004 to November 2010	Glyphosate: 131. 5 µg/kg AMPA: 703.5 µg/kg	Soil analysis conducted in semiarid regions of Argentina in soil with 5 years of agricultural activity, mainly annual crops under no tillage and a high use of pesticides.	Aparicio et al. 2018
Mesopotamia Pampas, Argentina	January and March 2012	Glyphosate: 2,299 µg/kg (average) AMPA: 4,204 µg/kg (average)	Samples were collected from 17 agricultural farms. Glyphosate detected in 5/6 samples detected. AMPA detected in 6/6 samples.	Primost et al. 2017

AMPA = aminomethylphosphonic acid; EPA = U.S. Environmental Protection Agency; MDL = method detection limit; STORET = STOrage and RETrieval; USGS = U.S Geological Survey

A Joint FAO/WHO Meeting on Pesticide Residues summarized glyphosate concentrations found in edible foods following applications of glyphosate formulations representative of several authorized use patterns. Glyphosate concentrations ranged from undetectable, ≤0.05 mg/kg, in several foods like bananas and selected meats to 3.7 mg/kg in a variety of grains and grain-based products (FAO 2005; FAO and WHO 2016). Genetically modified, and conventional food samples were studied. Herbicidal application techniques used on the food samples examined included pre-harvest application, directed ground spray, pre-emergence, and recirculating spray application methods. Application rates ranged from 0.36 to 7.7 kg/ha. The highest concentration found in banana pulp was 0.16 mg/kg. All kiwifruit assessed in the study had undetectable residues. Olives had residues ranging from undetectable to 12 mg/kg. Dry beans had residues ranging from undetectable to 10 mg/kg. Dry peas had residues ranging from undetectable to 8.9 mg/kg. Lentils had residues ranging from undetectable to 17 mg/kg. Glyphosate-tolerant sugar beet root had residues ranging from undetectable to 8.6 mg/kg. Conventional maize had residues ranging from undetectable to 3 mg/kg. Glyphosate-tolerant maize had residues ranging from undetectable to 0.83 mg/kg. Oats had residues ranging from undetectable to 19 mg/kg. Rye grain had residues ranging from 0.1 to 4.6 mg/kg. Wheat grain had residues ranging from 0.09 to 6.4 mg/kg. Sugarcane had residues ranging from undetectable to 15 mg/kg. Coffee and tea had levels ranging from undetectable to 9.6 mg/kg. Glyphosate residues in Kona Hawaiian coffee beans prior to roasting were 0.58 mg/kg, and the roasted beans had residues of 0.06 mg/kg.

Glyphosate was not included in compounds tested for by the Food and Drug Administration's (FDA) Pesticide Residue Monitoring Program (PRMP), nor in the United States Department of Agriculture's Pesticide Data Program (PDP) (FDA 2015; NPIC 2015).

A review by WHO reported that glyphosate was not detected in cereal grains at harvest when application of the herbicide occurred before planting (WHO 2005). Glyphosate was detected in cereals at mean residue levels of 0.2–4.8 mg/kg when application of the herbicide was prior to harvesting. In one assessment, levels of glyphosate were found to decrease upon industrial processing grains to flour from 1.6 to 0.16 mg/kg (WHO 2005). In wheat treated with either Glyfos or Roundup® herbicides, levels of glyphosate were also found to decrease upon processing grains to flour from 0.28–1.0 mg/kg in the grains to <0.05 mg/kg in the flour (FAO 2005). Glyphosate residues in oats stored at room temperature compared to frozen storage were similar, 3.5 and 3.1 mg/kg, respectively (FAO 2005). After exposure to glyphosate at 10 mg/L for 14 days, fish concentrations ranged from 0.2 to 0.7 mg/kg and decreased upon exposure to glyphosate-free water (WHO 2005).

A review by Williams et al. (2000) reported U.S. glyphosate residue data for wheat treated with maximum rates of Roundup®. Wheat crop residues consisted of a mean glyphosate concentration of 0.69 µg/g (mg/kg), with a maximum concentration of 2.95 µg/g (mg/kg). Glyphosate-tolerant soybeans treated with maximum rates of Roundup® showed a mean glyphosate concentration of 2.36 µg/g (mg/kg) and a maximum concentration of 5.47 µg/g (mg/kg).

Glyphosate was detected in carrot samples at average concentrations of 0.078±0.002 mg/kg and in spinach at 0.104±0.005 mg/kg (Zhao et al. 2011).

Glyphosate residues were examined on alder and salmonberry foliage and leaf litter sprayed with glyphosate at 2.0–2.1 kg/ha (Feng et al. 1990b). Foliar residues on alder and salmonberry were 261 and 448 ppm (dry weight), respectively, after the initial application of the herbicide. Leaf litter of alder and salmonberry collected 15 days post-application had glyphosate residues of 12.5 and 19.2 ppm (mg/kg), respectively. After 8–9 days, 50% dissipation was reported for the glyphosate residue. AMPA residues in the leaf litter decreased, and at 29 days after application of the herbicide, concentrations of AMPA were not detected.

5.6 GENERAL POPULATION EXPOSURE

The main routes of exposure to glyphosate for the general public result from the ingestion of foods with residues of glyphosate and foods made from these crops, as well as dermal, ocular, or inhalation exposure from application of herbicides containing glyphosate (EPA 2009c). Glyphosate has been detected in dust samples from homes near glyphosate application sites or from people who brought it indoors on their bodies and/or clothing from glyphosate-treated areas (Curwin et al. 2005). Additionally, pesticide application equipment, such as backpack sprayers, may leak, causing workers to be dermally exposed to glyphosate formulations (NIOSH 2017). Upon dermal exposure, absorption through the skin is expected to be low based on dermal absorption studies, where an estimated 0.8–2.2% percutaneous absorption of glyphosate occurred in a study using ^{14}C-radiolabeled glyphosate in Roundup® (Wester et al. 1991). Evidence has shown that proper hygiene removes glyphosate from skin and will deter absorption through the skin (Wester et al. 1991). Limited monitoring data indicate that oral exposure may occur from drinking contaminated well water supplied from groundwater contaminated with glyphosate; concentrations reported in groundwater are relatively low, and this chemical has low leaching potential from soil to groundwater. Exposure may also occur via ingestion of food with herbicidal residues containing glyphosate as a result of its application. The FDA has not performed a total diet study on

glyphosate. Glyphosate has not been included in the FDAs Pesticide Residue Monitoring Program Reports for the fiscal years 2009 through 2015 (FDA 2013a, 2013b, 2014, 2015, 2016, 2017); however, the FDA in 2016 and 2017 began preliminary testing of samples of soybeans, corn, milk, and eggs for glyphosate residues (FDA 2018). Preliminary results showed no pesticide residue violations for glyphosate in all four commodities tested (soybeans, corn, milk, and eggs). The Joint FAO/WHO Meeting on Pesticide Residues listed International Estimated Daily Intake (IEDI) of glyphosate from 17 GEMS/Food (Global Environment Monitoring System-Food Contamination Monitoring and Assessment Programme) cluster diets to range from 140.5 to 443.0 µg/person (FAO and WHO 2016). Glyphosate is a non-volatile compound, and drift of herbicidal sprays may occur with aerial and ground equipment (Yates et al. 1978); therefore, some exposure via inhalation and direct contact with skin and eyes may occur after members of the general population apply glyphosate during residential use. Although the effects of glyphosate exposure of populations living in areas where glyphosate-containing products have been aerially-applied to eradicate coca crops have been evaluated (Paz-y-Miño et al. 2007, 2011; Solomon et al. 2009), such reports did not include monitoring of exposure levels.

Occupational exposure may occur in both forestry, landscaping, and agricultural settings from the direct use of herbicides containing glyphosate. The most probable routes for occupational exposure are via inhalation and dermal contact with this chemical at workplaces where glyphosate or products containing this chemical are produced or used. Oral exposure may occur from accidental ingestion. During the years 1990–1993, exposure to glyphosate of field workers applying mixtures of Roundup® plus an additional herbicide in areas of Louisiana was assessed (LaDOTD 1995). Mixtures of Roundup® (active ingredient glyphosate) plus Garlon-3A (active ingredient triclopyr) and Roundup® (active ingredient glyphosate) plus 2,4-D (active ingredient 2,4-dichlorophenoxyacetic acid) were applied by 13 workers using spray equipment with operating capabilities of 0.37 L/minute. Glyphosate was detected in the workers' urine using HPLC with a detection limit of 100 ppb. Total excreted urinary amounts of glyphosate ranging from non-detectable to 175 µg/day were reported for both working and non-working days. Urine concentrations were higher than concentrations found in the collected air samples of the breathing zone. It was noted that inhalation exposure was very low compared with threshold limits; the maximum air concentration was 17.9 $\mu g/m^3$. Dermal contact and improper hygiene leading to ingestion of the herbicides were noted as the probable routes of exposure.

One-hundred adults older than 50 years who resided in Southern California, as part of the Rancho Bernardo study, were sampled for glyphosate and its metabolite AMPA in 1993-1996 and again in 2014-2016 (Mills et al. 2017). The study did not indicate that any of these adults were involved in application

of pesticides containing glyphosate. In 1993-1996, only 12 participants had glyphosate above the level of detection (LOD=0.03 µg/L) in urine and mean levels were 0.024 for all participants, and 5 participants had detected levels of AMPA (LOD=0.04 µg/L) with the mean levels of 0.008 µg/L for all participants. By 2014-2016 sampling, 70/100 participants had detectable levels of glyphosate and 71/100 of AMPA. Means levels in all 100 participants were 0.314 µg/L and 0.285 µg/L for glyphosate and AMPA, respectively (Mills et al. 2017).

Farmers, with an average age of 45 years licensed as pesticide applicators in South Carolina and Minnesota, who applied herbicides containing glyphosate had average urinary glyphosate levels of 3 µg/L on the day of application (Acquavella et al. 2004). Lack of wearing rubber gloves was associated with higher concentrations in farmers' urine. Spouses, with an average age of 42.2 years residing with the farmers but having minimal or no involvement in the preparation or application of the herbicide, had relatively low and consistent urine concentrations of glyphosate, while children (ages 4–18 years) had an increase followed by a decrease in urine concentrations correlated with application (see Table 5-11). For the entire assessment period, 88–95% of all samples of children's urine were below the detection limit (1 µg/L [ppb] for a 100-mL urine sample). Farmers applying the pesticide had the highest concentrations. The highest concentration of glyphosate found in a child was from a teenage male (29 µg/L [ppb]) who had assisted with mixing and application of the herbicide. An estimated dermal and inhalation exposure value of about 8,000 µg/hour was reported as the highest value from a study of workers employing spray applicators; when corrected for incomplete absorption, this corresponds to an approximate exposure of 50 µg/kg body weight/day (8-hour working day for a 70-kg adult) (IPCS 1994).

Table 5-11. Available Glyphosate Human Monitoring Data

Medium		Concentrations/ minimum, maximum	Average	Notes	Reference
Tissue (brain, blood, liver, kidney)	Postmortem, approximately 12–13 hours after ingestion	Glyphosate (ppm): kidney 3,650; liver 600; blood; 550; brain; 100		After one individual ingested 200–250 mL Roundup® with 72–91 g/mL glyphosate	Menkes et al. 1991
Urine	Pre-application	<1–15 µg/L (ppb)	Not reported	Farmers applying pesticide; average age: 45 years	Acquavella et al. 2004
	Day of pesticide application	<1–233 µg/L (ppb)	Geometric mean: 3.2 µg/L (ppb)		
	1-Day post-pesticide application	<1–126 µg/L (ppb)	Geometric Mean: 1.7 µg/L (ppb)		

Table 5-11. Available Glyphosate Human Monitoring Data

Medium	Concentrations/ minimum, maximum	Average	Notes	Reference
2-Day post-pesticide application	<1–81 µg/L (ppb)	Geometric mean: 1.1 µg/L (ppb)		
3-Day post-pesticide application	<1–68 µg/L (ppb)	Geometric mean: 1.0 µg/L (ppb)		
Pre-application	<1–3 µg/L (ppb)	Not reported	Spouses not involved with application; average age: 42 years	
Day of pesticide application	<1–2 µg/L (ppb)	Not reported		
1–3-Day post-pesticide application	<1–1 µg/L (ppb)	Not reported		
Pre-application	<1–17 µg/L (ppb)	Not reported	Children not involved with application; average age: 11.5 years	
Day of pesticide application	<1–29 µg/L (ppb)	Not reported		
1-Day post-pesticide application	<1–24 µg/L (ppb)	Not reported		
2-Day post-pesticide application	<1–12 µg/L (ppb)	Not reported		
3-Day post-pesticide application	<1–6 µg/L (ppb)	Not reported		
Daily during 1-week working period	<0.1 ng/µL		Forest workers using pressurized herbicide sprayers; 8% Roundup® (active ingredient 360 g/L isopropylamine salt)	Jauhiainen et al. 1991
3 Weeks after 1-week working period	<0.1 ng/µL			
General population exposure	Not reported	0.024 µg/L (ppb)	Adults >50 years of age not involved in application in 1993-1996	Mills et al. 2017
General population exposure	Not reported	0.314 µg/L (ppb)	Adults involved in application in 2014-2016; average age: 77.7 years	
Following mild to fatal ingestions of 20–500 mL pesticide	Glyphosate: 228 mg/L mild/moderate case; 22,300 mg/L fatal case; AMPA: 0.54 mg/L mild/moderate case; 91.5 mg/L fatal case		13 individuals ages 25–69 years	Zouaoui et al. 2013
Two occasions (1 month apart) during spring and	0.13–5.4 µg/L	1.4 µg/L	Farm fathers	Curwin et al. 2007b
	0.20–18 µg/L	1.9 µg/L	Non-farm fathers	
	0.062–5.0 µg/L	1.2 µg/L	Farm mothers	
	0.10–11 µg/L	1.5 µg/L	Nonfarm mothers	

Table 5-11. Available Glyphosate Human Monitoring Data

Medium		Concentrations/ minimum, maximum	Average	Notes	Reference
	summer of 2001 (LOD 0.9 µg/L)	0.10–9.4 µg/L	2.7 µg/L	Farm children	
		0.022–18 µg/L	2 µg/L	Non-farm children	
Blood	Following mild to fatal ingestions of 20–500 mL pesticide	Glyphosate: 3.7 mg/L mild/moderate case; 6,640 mg/L fatal case; AMPA: 0.13 mg/L mild/moderate case; 15.4 mg/L fatal case			Zouaoui et al. 2013

AMPA = aminomethylphosphonic acid; LOD = limit of detection

Acquavella et al. (1999) evaluated 1,513 reported cases to the American Association of Poison Control Centers during the years 1993–1997 of ocular or dermal/ocular exposure to Roundup® herbicides with glyphosate concentrations ranging from <2 to >20%. Of all exposure cases, 62% involved male subjects, >80% were in a residential setting, and about 15% were in occupational settings. During the time period, California and Texas had the greatest number of reported cases. Dilute Roundup® formulations accounted for about 82% of the exposures; 5% were with concentrated Roundup®.
Acquavella et al. (2005) analyzed biomonitoring data of farmers before, during and after pesticide application and para-occupational exposure to their spouses and children over a course of five days (1 day before, 1 day during and 3 days post-exposure). Glyphosate was measured in urine at a peak of 3 ppb (LOD 1 ppb) on the day of application and then decreased rapidly. Among the spouse and children of farmers, glyphosate urinary levels remained relatively stable with only appreciable changes in concentration after exposure to pesticide application.

Brouwer et al. (2016) pooled exposure data from three agriculture cohorts from USA, France and Norway, specifically, the Agricultural Health Study (AHS), Agriculture and Cancer Study (AGRICAN) and the Cancer in the Norwegian Agricultural Population (CNAP), respectively. Among 316,270 participants who were pesticide applicators or farmers (active or retired), 99% reported ever using any pesticide of which 44% reported to have ever been exposed to glyphosate, ranging between 1 to 21 years of exposure. Specifically, 129,327 men (54%) and 41,276 (14%) females were exposed to glyphosate across the three cohorts.

Aris and LeBlanc (2011) examined blood concentrations of glyphosate in a group of 30 pregnant and 39 non-pregnant females residing in Sherbrooke, Canada. The study noted that none of the subjects

worked or lived with an individual who worked with pesticides. Neither glyphosate nor AMPA were detected in the maternal or fetal cord serum of pregnant subjects. Additionally, AMPA was not detected in non-pregnant subjects. Glyphosate was detected in 5% of the non-pregnant subjects at a range of not detectable to 93.6 ng/mL, with a mean of 73.6 ng/mL (LOD=15 ng/mL).

The Fourth National Report on Human Exposures to Environmental Chemicals, published and updated by the Centers for Disease Control and Prevention reporting biomonitoring data from the National Health and Nutrition Examination Survey (NHANES), does not include data for glyphosate or its metabolite, AMPA (CDC 2019).

As with the adult general population, exposure of children to glyphosate may occur through ingestion of foods with residues of glyphosate and foods made from these crops, as well as inhalation, dermal contact, and/or ocular contact when in the proximity of areas where glyphosate containing herbicides have been recently applied. Glyphosate has been detected in dust samples from homes near glyphosate application sites or from people who brought it indoors on their bodies and/or clothing from glyphosate-treated areas (Curwin et al. 2005). Limited monitoring data indicate that oral exposure may occur from drinking contaminated well water supplied from groundwater contaminated with glyphosate; concentrations reported in groundwater are relatively low, and this chemical has low leaching potential from soil to groundwater. It is unclear if breastmilk is a route of exposure for glyphosate as there are only two studies which have evaluated this route (Bus 2015 and McGuire et al., 2016). According to Bus (2015) glyphosate is not likely to bioaccumulate in breast milk and McGuire et al., 2016 did not detect it in breast milk from lactating mothers with detectable glyphosate in their urine (McGuire et al. 2016).

During the spring and summer of 2001, urinary pesticide concentrations were investigated in families residing in non-farm and farm households located in Iowa (Curwin et al. 2007a, 2007b). Urinary glyphosate levels were fairly similar between farm and non-farm households. In addition, glyphosate concentrations were fairly similar when comparing individuals living on farms where the pesticide was used with those living on farms where the pesticide was not used. Glyphosate was detected at urinary levels equal to or greater than the LOD (0.9 µg/L) in 66% of the 23 non-farm fathers, 75% of the 24 farm fathers, 65% of the 24 non-farm mothers, 67% of the farm mothers, 88% of the non-farm children, and 81% of the farm children (Curwin et al. 2007b). Estimated glyphosate intakes among 40 children (17 homes) living on farms where glyphosate was applied ranged from 0.001 to 0.33 µg/kg/day, with 16% of the samples below the LOD (Curwin et al. 2007a). Estimated glyphosate intakes among 25 children

(8 homes) living on farms where glyphosate was not applied ranged from 0.003 to 0.64 µg/kg/day, with 20% of the samples below the LOD.

McQueen et al. (2012) estimated the mean glyphosate dietary exposure of 43 pregnant women at 0.001 mg/kg body weight/day and these exposures were well below applicable health guidelines. Since only a small percentage of glyphosate crosses the placenta, fetal exposure resulting from maternal exposure to glyphosate was minimal.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Farm workers, farming families, landscaping workers, and people of all ages living and or working in agricultural sectors will incur higher exposure to glyphosate, as agriculture is the largest industry for herbicide use. Field workers who apply herbicides containing glyphosate will likely incur higher exposures to this chemical. Levels of glyphosate in field workers' urine has been shown to increase during spraying season; however, glyphosate levels did not appear to carry over from previous seasons (LaDOTD 1995).

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of glyphosate is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of glyphosate.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

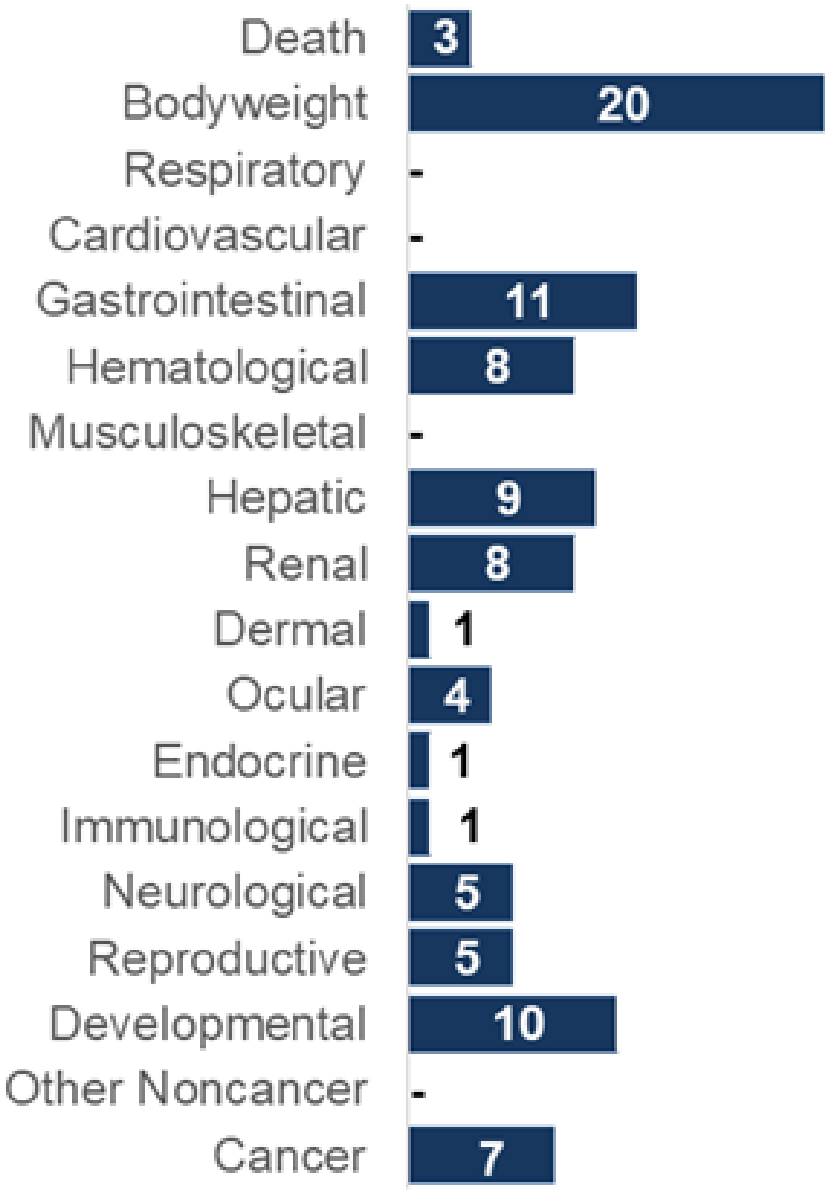
6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and/or dermal exposure of humans and animals to glyphosate that are discussed in Chapter 2 are summarized in Figure 6-1 for glyphosate technical and Figure 6-2 for glyphosate formulations. As described in Chapter 2, data on inhalation and dermal exposure to glyphosate technical were limited. Therefore, Figure 6-1 only summarizes oral exposure studies. The purpose of these figures is to illustrate the information concerning the health effects of glyphosate. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

The health effects of glyphosate have been evaluated in epidemiology and animal studies. Epidemiological studies are predominantly case-control and cohort epidemiology studies that examined possible associations between glyphosate exposure and selected health outcomes (noncancer and cancer endpoints), or case reports following accidental or intentional ingestion of glyphosate-containing products. These studies do not include data regarding the extent of the exposure or relative contribution of inhalation, oral and/or dermal exposure. Most health effects data come from animal studies that employed oral exposure and examined potential body weight, gastrointestinal, hematological, hepatic, and/or developmental effects.

Figure 6-1. Summary of Existing Health Effects Studies of Animals Orally Exposed to Glyphosate Technical (Listed by Endpoint)*

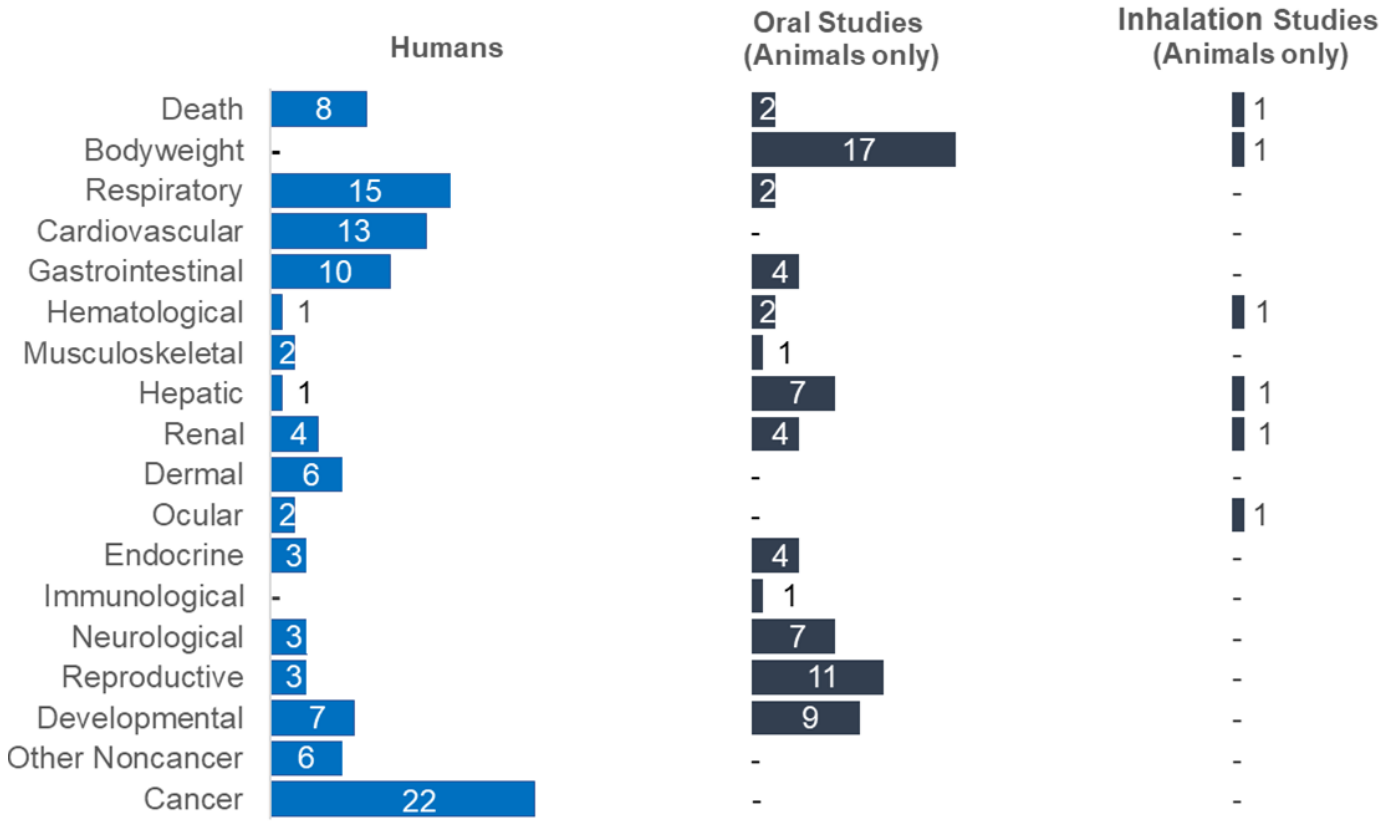
Potential body weight and gastrointestinal effects of glyphosate technical were the most studied endpoints



*Includes studies discussed in Chapter 2; the numbers of studies include those finding no effect.

Figure 6-2. Summary of Existing Health Effects Studies on Glyphosate Formulations (Listed by Endpoint)*

Potential cancer, respiratory, and developmental effects were the most studied in humans; potential body weight and developmental effects were the most studied in animals



*Includes studies discussed in Chapter 2; the numbers of studies include those finding no effect. Human exposures likely included multiple exposure routes.

6.2 Identification of Data Needs

Missing information in Figure 6-1 and Figure 6-2 should not be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information about glyphosate technical missing from the scientific literature. Therefore, uncertainties with regard to glyphosate-based formulations (GBFs) would not be considered a data gap for the purposes of this Profile. However, exposure to GBFs is widespread, and studies investigating the toxicity and components of the individual GBFs are important. EPA's 2016 Glyphosate Issue Paper states, "additional research could also be performed to determine whether formulation components, such as surfactants, influence the toxicity of glyphosate formulations," and describes plans to investigate the potential toxicity of GBF components (EPA 2016c).

Oral studies in animals indicate that glyphosate technical toxicity is associated with oral doses levels many times higher than levels allowed as residues in food products. The general population is most likely to be exposed to glyphosate residues in food sources. Humans should continue to be monitored for possible associations between glyphosate intake from food sources and adverse health outcomes. Individuals can also be exposed to glyphosate via inhalation, dermal contact, and/or ocular contact during application of the herbicide or by being in the vicinity where it is applied. However, available dermal studies indicate that only 3–4% of dermally-applied glyphosate enters the blood, though local dermal toxicity is possible (see Section 2.11). Data regarding the extent of absorption and potential health effects following inhalation exposure are lacking. Therefore, human and animal studies should be designed to evaluate airborne exposure levels and possible health effects from inhalation exposure. Additional animal studies should be designed to assess the toxic effects of exposure to a variety of glyphosate formulations and individual components suspected to be toxic. Such studies could also be designed to evaluate possible interactions among individual components that might enhance toxicity.

Acute-, Intermediate-, and Chronic-Duration MRLs. No inhalation MRLs were derived for glyphosate due to the lack of quantitative exposure-response data for humans or animals.

As stated previously, most information is available from animal studies submitted to EPA's Office of Pesticides Programs using glyphosate technical (typically >90% purity) to fulfill requirements for the registration of a particular glyphosate formulation for use in the United States. 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 as well as to other substances that may be added by the end user. 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.

Acute- and chronic-duration oral MRLs were derived for glyphosate based on gastrointestinal effects in animal studies. The chronic-duration oral MRL was adopted as the intermediate-duration oral MRL.

Health Effects

Respiratory. Limited information was located regarding the effects of inhalation exposure in laboratory animals. A single 4-week repeated-exposure rat study found no effects at the highest exposure concentration tested (36 mg Roundup®/m^3). Studies should be designed to evaluate respiratory effects in animals exposed to glyphosate by inhalation.

Developmental. Developmental toxicity studies in animals that employed oral exposure to glyphosate technical found no evidence of treatment-related effects at levels below the threshold of maternal toxicity. One study reported testicular lesions in weanling rats administered a glyphosate formulation orally at doses as little as 5 mg/kg/day. Additional studies should be designed to substantiate or refute this finding and to determine whether glyphosate or other ingredients in glyphosate formulations are involved in developmental effects on male reproductive organs.

Epidemiology and Human Dosimetry Studies. Limited information was located regarding respiratory effects associated with human exposure to glyphosate-based formulations. Additional studies

should be designed to monitor exposure levels and health effects associated with individuals involved in the application of glyphosate-based products. There is limited evidence for glyphosate-related developmental effects in humans. Additional studies should be designed to evaluate possible associations between exposure to glyphosate and developmental endpoints in humans. Numerous agencies have evaluated glyphosate for possible associations between exposure and risk of various cancers. The majority of the human studies used self-reported ever/never glyphosate use as the biomarker of exposure. The results of these studies should be interpreted cautiously given the lack of quantitative or semi-quantitative glyphosate exposure information and the likely exposure to other pesticides. Most studies found no association between exposure to glyphosate-based products and risk of cancer. However, a possible association between exposure to glyphosate and risk of non-Hodgkin's lymphoma could not be ruled out, based on conflicting results.

Biomarkers of Exposure and Effect. The most reliable biomarker of exposure to glyphosate is its detection in blood and urine. However, the limit of detection (LOD) for glyphosate in blood is higher than the LOD for glyphosate in urine (see Table 5-4), meaning using urine as a biomarker of exposure may be more informative, especially in cases where human glyphosate levels are expected to be low. Recent biomarker studies seem to show a preference for urine as a biomarker (Soukup et al. 2020, Zoller et al. 2020, Zhang et al. 2020).

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of glyphosate following oral and dermal exposure have been adequately described. Additional studies should be designed to evaluate the toxicokinetics of inhaled glyphosate.

Comparative Toxicokinetics. Significant species differences in the toxicokinetics of glyphosate are not likely.

Children's Susceptibility. Age-related differences in susceptibility to glyphosate have not been elucidated. Due to relatively large oral doses required to elicit adverse effects in glyphosate-exposed animals, it may be difficult to evaluate age-related differences in susceptibility. As additional epidemiological data become available, age-related issues regarding susceptibility to glyphosate toxicity should be evaluated.

Physical and Chemical Properties. The physical chemical properties of glyphosate are summarized in Chapter 4. No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. No information is available in the TRI database on facilities that manufacture or process glyphosate because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005b). There is no information on releases of glyphosate from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005b). Data on current manufacturing, processing, import/export values would be useful information. Data on current uses and disposal practices are outlined in Sections 5.2.3 and 5.2.4. Further studies on these practices do not appear to be essential.

Environmental Fate. Transport, partitioning, and bioconcentration data are available for glyphosate summarized in Section 5.4. In glyphosate-tolerant plants, glyphosate is converted to N-acetylglyphosate; therefore, studies evaluating the possibility of additional crop and plant metabolites, along with the characteristic fates, may be beneficial (Pioneer 2006). Additional studies should be designed to further assess potential for glyphosate to persist in foods, water, and soil.

Bioavailability from Environmental Media. Glyphosate degrades quickly in the environment and adsorbs to soils and sediment and possesses low bioconcentration in aquatic organisms, suggesting that bioavailability from environmental media is low. A study regarding the bioavailability of glyphosate in soil indicated that degradation rates decreased in lower soil horizons as microbial populations of glyphosate degrading organisms decreased, but bioremediation practices that incorporate anthropic bacteria can be useful to remediate highly polluted glyphosate-containing soils and maintain low bioavailability (Shushkova et al. 2010). Additional studies on glyphosates bioavailability from different types of soil would be helpful to expand our understanding of potential human exposures to glyphosate bound residues.

Food Chain Bioaccumulation. Studies are available that indicate that glyphosate has very low potential to bioconcentrate in aquatic organisms and is not expected to bioaccumulate in the food chain. No data needs are identified.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of glyphosate in environmental media surrounding areas where it is applied are available (Chang et al. 2011; USGS 2007; WQP 2017). The USGS NAWQA frequently reports on levels of glyphosate and other substances

in both surface water and groundwater. No data needs are identified; however, monitoring studies in air, water, soil, and other environmental media should continue as this is an herbicide used globally.

Exposure Levels in Humans. Studies are needed to investigate human intake of glyphosate via food and water, such as total diet studies. Up until 2016–2017, the FDA did not test for glyphosate residues in food sources because its multi-residue testing protocols did not include glyphosate. The FDA has now developed a method to specifically test for glyphosate residues in foods and results are expected to be provided through the FDA Pesticide Residue Monitoring Program (FDA 2018). Biomonitoring information of glyphosate for the general population would be useful in conducting future risk assessments.

Exposures of Children. Monitoring of children's exposure to glyphosate would be useful, in combination with children's health and susceptibility information, to assess the potential risk for deleterious effects.

Analytical Methods. Standardized methods that yield low detection limits for glyphosate and aminomethylphosphonic acid (AMPA) in biological samples (e.g., urine analysis, blood analysis) may provide more sensitivity and a more complete exposure analysis.

6.3 Ongoing Studies

Glyphosate is a potential candidate for addition to the California Environmental Contaminant Biomonitoring Program (CDPH 2013). Ongoing research identified in the National Institutes of Health (NIH) RePORTER (2017) database is summarized in Table 6-1. In addition, NTP (2017) is performing research to investigate potential genetic and mechanistic toxicity of glyphosate and glyphosate formulations. NTP will also evaluate published literature for information regarding glyphosate on non-cancer outcomes. Researchers at the Cesare Maltoni Cancer Research Centre at the Ramazzini Institute in Italy are conducting research into potential genetic, reproductive, and developmental effects in rats administered glyphosate at levels equivalent to those allowed in humans.

Table 6-1. Ongoing Studies on Glyphosate

Investigator	Affiliation	Research description	Sponsor
De Roos, AJ	Drexel University	Occupational pesticide use and risk of lymphoid cancers	National Cancer Institute
Keating, AF	Iowa State University	Investigating modes of action of glyphosate-induced ovotoxicity	National Institute of Environmental Health Sciences
Curl, CL	Boise State University	Measurement of agricultural and dietary glyphosate exposure among pregnant women	National Institute of Environmental Health Sciences
Ford, B	University of California Berkeley	Understanding complex toxicological mechanisms of glyphosate and mechanism-sharing environmental chemical mixtures	National Institute of Environmental Health Sciences
Newman, LS	University of Colorado Denver	Etiologic and mechanistic factors underlying chronic kidney disease in Guatemalan sugarcane workers	National Institute of Environmental Health Sciences
Petropoulos, Z	Boston University Medical Campus	Occupational heat exposure and gene-environment interactions in Mesoamerican nephropathy	National Institute of Environmental Health Sciences
Scammell, M	Boston University Medical Campus	Longitudinal study of risk factors for Mesoamerican nephropathy among agricultural workers in El Salvador, central America	National Institute of Environmental Health Sciences
Von Ehrenstein, O	University of California Los Angeles	Pesticide exposure and birth outcomes	National Institute of Environmental Health Sciences
Mitchell, KS	VA Boston Health Care System	Eating disorders in veterans: risk, resilience, and service use	Not specified

Source: RePORTER 2020

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding glyphosate in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for glyphosate.

Table 7-1. Regulations and Guidelines Applicable to Glyphosate

Agency	Description	Information	Reference
	Air		
EPA	RfC	Not evaluated	IRIS 1989
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2012d
	1-Day (10-kg child)	20 mg/L	
	10-Day (10-kg child)	20 mg/L	
	DWEL	70 mg/L	
	National primary drinking water regulations		EPA 2009b
	Maximum Contaminant Level	0.7 mg/L	
	Maximum Contaminant Level Goal	0.7 mg/L	
	RfD	1.0 mg/kg/day[a]	EPA 2017d
WHO	Drinking water quality guidelines	Not established[b]	WHO 2017
FDA	EAFUS	No data[c]	FDA 2013c
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	Not likely to be carcinogenic to humans	EPA 2017c, 2017d, 2020
IARC	Carcinogenicity classification	Group 2A[d]	IARC 2017
	Occupational		
ACGIH	TLV	No data	ACGIH 2016
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2016b
	PEL (8-hour TWA) for shipyards and construction	No data	OSHA 2016c
	PEL (8-hour TWA) for construction	No data	OSHA 2016a

Table 7-1. Regulations and Guidelines Applicable to Glyphosate

Agency	Description	Information	Reference
NIOSH	REL (up to 10-hour TWA)	No data	NIOSH 2016
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016b
DOE	PACs-air	No data	DOE 2018

[a]EPA's Office of Pesticides Program (OPP) published an interim registration review decision on glyphosate in January 2020, which finalized the Glyphosate Draft Human Health Risk Assessment in Support of Registration Review. The human health risk assessment derived an RfD of 1.0 mg/kg/day based on the same study that ATSDR used for derivation of the acute-duration MRL.
[b]Glyphosate and aminomethylphosphonic acid occur in drinking water at concentrations well below those of health concern, so a guideline value was not deemed necessary.
[c]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[d]Group 2A: Probably carcinogenic to humans.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; CFR = Code of Federal Regulations; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = reference dose TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

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, the general population may be exposed via food or water sources containing glyphosate residues from glyphosate-based formulations registered for use in agricultural and residential environments. Therefore, health effects data associated with oral exposure to glyphosate technical are considered relevant to potential derivation of oral MRLs for glyphosate.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Glyphosate technical
CAS Numbers: 1071-83-6
Date: August 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: No acute-duration inhalation exposure-response studies were identified for glyphosate.

Agency Contact (Chemical Manager): Hana R. Pohl, M.D., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Glyphosate technical
CAS Numbers: 1071-83-6
Date: August 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL.

Rationale for Not Deriving an MRL: No intermediate-duration inhalation exposure-response studies were identified for glyphosate.

Agency Contact (Chemical Manager): Hana R. Pohl, M.D., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Glyphosate technical
CAS Numbers: 1071-83-6
Date: August 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: No chronic-duration inhalation exposure-response studies were identified for glyphosate.

Agency Contact (Chemical Manager): Hana R. Pohl, M.D., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Glyphosate technical
CAS Numbers: 1071-83-6
Date: August 2020
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 1 mg/kg/day
Critical Effect: Gastrointestinal effects
Reference: EPA 2017b
Point of Departure: NOAEL of 100 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 7
Species: Rabbit

MRL Summary: An acute-duration oral MRL of 1 mg/kg/day was derived for glyphosate based on gastrointestinal effects (diarrhea, few feces) observed in pregnant female New Zealand white rabbits administered glyphosate acid (96.5% purity) by daily gavage (in deionized water) during GDs 8–20 (EPA 2017b). The MRL is based on a NOAEL of 100 mg/kg/day and a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

Selection of the Critical Effect: Several acute-duration oral studies were available regarding the toxicity of glyphosate technical following acute-duration oral exposure (see Table A-1). The lowest LOAELs were 175 mg/kg/day for gastrointestinal effects (diarrhea, few feces) in maternal rabbits and 300 mg/kg/day for developmental effects (depressed fetal weight) following gavage treatment with glyphosate technical during GDs 8–20 at 175 mg/kg/day. Based on available data, gastrointestinal disturbance is considered to represent the most sensitive effect of glyphosate toxicity following oral exposure in laboratory animals.

Table A-1. NOAELs and LOAELs Identified in Acute-Duration Oral Studies of Glyphosate Technical

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Body weight	28.5% depressed maternal body weight gain in rats	1,000	3,500	EPA 1992e
	No effect in pregnant rats	1,000		EPA 2017b
	No effect in pregnant rabbits	300		EPA 2017b
Gastrointestinal	Diarrhea in 2/8 rats gavaged once		2,000	Adam et al. 1997
	Diarrhea in rats gavaged once	1,000	2,000	EPA 2013c
	Diarrhea, soft stools in pregnant rats gavaged on GDs 6–19	1,000	3,500	EPA 1992e
	Diarrhea, few feces in pregnant rabbits gavaged on GDs 8–20	100	175	EPA 2017b

Table A-1. NOAELs and LOAELs Identified in Acute-Duration Oral Studies of Glyphosate Technical

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Developmental	Decreased fetal weight; delayed ossification	1,000	3,500	EPA 1992e
	No effect in fetuses from pregnant rats gavaged on GDs 7–16	1,000		EPA 2017b
	Depressed weight in fetuses from pregnant rabbits gavaged on GDs 8–20	175	300	EPA 2017b
Other	Hypothermia in rats gavaged once	1,000	2,000	EPA 2013c

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: Among available acute-duration oral toxicity studies for glyphosate, the developmental toxicity study in rabbits (EPA 2017b) identified the lowest LOAEL (gastrointestinal effects in pregnant rabbits gavaged with glyphosate acid); the corresponding NOAEL was 100 mg/kg/day. Therefore, this study was selected as the principal study for deriving an acute-duration oral MRL for glyphosate.

Summary of the Principal Study:

EPA. 2017b. Memorandum. December 13, 2017. Glyphosate: Preparation of data evaluation records for developmental rat and rabbit toxicity studies. MRID No.: 43320615, 43320616. Washington, DC: U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention.

Groups of sperm-positive female New Zealand white rabbits (20/group) were administered glyphosate acid (95.6% active ingredient) by daily gavage (in deionized water vehicle; dosing volume 2 mL/kg body weight) on GDs 8–20 at target concentrations of 0, 100, 175, or 300 mg/kg/day (adjusted for purity of active ingredient). Dams were monitored for survival, clinical signs, body weight, and food intake. On GD 30, dams were sacrificed and subjected to gross external and internal examination, pregnancy status, weight of gravid uteri, number of corpora lutea, number and position of implantations, live fetuses, and early and late intrauterine deaths. Fetuses were evaluated for weight and sex. External, visceral, and skeletal examinations were performed; brains were subjected to macroscopic examination.

The 100 mg/kg/day dose level represented a NOAEL for maternal toxicity. At 175 and 300 mg/kg/day, maternal rabbits exhibited diarrhea and reduced production of feces. Mean body weight in the 300 mg/kg/day group of maternal rabbits ranged from 5.2 to 7.4% less than that of controls during GDs 16–26. The depressed maternal body weight was <10% in magnitude, and was therefore not considered to represent an adverse effect. Furthermore, there were no statistically significant differences between controls and glyphosate-treated groups regarding GD 30 mean maternal body weight. Gross pathologic examination of maternal rabbits revealed no treatment-related effects. There were no treatment-related effects on pregnancy rate, numbers of corpora lutea, total number of implantation sites, litter size, sex ratio, or pre- or post-implantation loss. The 300 mg/kg/day dose group exhibited 8.3% lower mean fetal weight ($p<0.05$). Gross and visceral examination of fetuses revealed no treatment-related effects. Increased incidences of fetuses with selected minor skeletal defects (e.g., delayed sternebral and vertebral ossification) were observed at the 300 mg/kg/day maternal dose level. However, incidences of these skeletal defects did not appear to be increased in glyphosate-treated groups when

evaluated on a per litter basis; therefore, they were not considered treatment-related developmental effects.

Selection of the Point of Departure: Incidence data for the gastrointestinal effects were not presented in the available data evaluation record (DER) for the study, thus precluding a benchmark dose (BMD) approach to deriving an MRL. Therefore, the NOAEL of 100 mg/kg/day was selected as the point of departure for deriving an acute-duration oral MRL for glyphosate.

Uncertainty Factor: The NOAEL of 100 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

Other Additional Studies or Pertinent Information: Glyphosate-induced gastrointestinal effects were observed in acute-duration oral studies of rats (Adam et al. 1997; EPA 1992e, 2013c), although rabbits appear to be much more sensitive than rats to glyphosate-induced gastrointestinal effects following oral dosing.

Agency Contacts (Chemical Managers): Hana R. Pohl, M.D., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Glyphosate technical
CAS Numbers: 1071-83-6
Date: August 2020
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: The chronic-duration oral MRL of 1 mg/kg/day is adopted as the intermediate-duration oral MRL.

Rationale for Not Deriving an MRL: Several intermediate-duration oral animal studies were available for glyphosate technical (see Table A-2).

Table A-2. NOAELs and LOAELs Identified in Intermediate-Duration Oral Studies of Glyphosate Technical

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Body weight	12–18% depressed paternal body weight gain in rats	M: 754 F: 802	M: 2,219 F: 3,134	EPA 1992a
	No effect in rats (highest dose)	M, F: 30		EPA 1992g
	No effect in rats (highest dose)	M: 1,234 F: 1,273		EPA 2013a
	18% lower mean body weight and body weight gain in male rats	M: 1,678 F: 3,393	M: 3,393	NTP 1992
	No effect in mice (highest dose)	F: 1,447.5		EPA 2013b
	10–11% lower mean final body weight in mice	M: 2,273 F: 5,846	M: 4,776 F: 11,977	NTP 1992
	No effect in maternal rabbits (highest dose)	F: 350		EPA 1992f
Gastrointestinal	Soft stool in rats	M: 754 F: 802	M: 2,219 F: 3,134	EPA 1992a
	Increased severity of basophilia and hypertrophy of acinar cells in parotid and submandibular salivary glands of rats	M: 205 F: 213	M: 410 F: 421	NTP 1992
	Increased severity of basophilia of acinar cells in parotid salivary gland of mice	M: 1,065 F: 1,411	M: 2,273 F: 2,707	NTP 1992
	Increased incidence of soft stool and/or diarrhea in pregnant rabbits	175	350	EPA 1992f
Hematological	No effect in rats (highest dose)	M, F: 3,393		NTP 1992

Table A-2. NOAELs and LOAELs Identified in Intermediate-Duration Oral Studies of Glyphosate Technical

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Hepatic	No effect in rats (highest dose)	M: 1,234 F: 1,273		EPA 2013a
	M: Increases in liver weight and serum ALT F: Increases in liver weight and serum AP, ALT, and bile acids	M: 811 F: 1,690	M: 1,678 F: 3,393	NTP 1992
	No effect in mice	M: 10,780 F: 11,977		NTP 1992
Renal	No effect in rats (highest dose)	M: 1,234 F: 1,273		EPA 2013a
Immunological	No effect in mice (highest dose)	F: 1,447.5		EPA 2013b
Neurological	No effect in rats (highest dose)	M: 1,546.5 F: 1,630.6		EPA 2013c
Reproductive	No effect in rats (highest dose)	M: 2,219 F: 3,234		EPA 1992a
	No effect in rats (highest dose)	M, F: 30		EPA 1992g
	No effect in rats (highest dose)	M: 1,234 F: 1,273		EPA 2013a
Developmental	14–20% depressed pup body weight during lactation (maternally toxic dose level)	802	3,134	EPA 1992a
	Delayed preputial separation	408	1,234	EPA 2013a
	No effect in rabbits (highest dose)	350		EPA 1992f

ALT = alanine aminotransferase; AP = alkaline phosphatase; F = female; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level

Increased incidence of kidney tubular dilation was reported for F3b male weanlings of a 3-generation study of glyphosate technical (98.7% purity) administered to male and female Sprague-Dawley rats in the diet at an estimated dose level of 30 mg/kg/day; the reported NOAEL was 10 mg/kg/day (EPA 1992g). However, there were no signs of treatment-related effects on kidneys of rat offspring in two subsequent 2-generation rat studies at dietary doses up to 1,234 or 1,273 mg/kg/day for parental males and females, respectively (EPA 2013a), or 2,633 or 3,134 mg/kg/day for parental males and females, respectively (EPA 1992a). Therefore, the finding of increased incidence of kidney tubular dilation in the 3-generation rat study (EPA 1992g) was considered a spurious result rather than a glyphosate-induced adverse developmental effect. In one 2-generation oral rat study, exposure via the diet at estimated parental dose levels of 1,234 or 1,273 mg/kg/day (parental males and females, respectively) resulted in delayed preputial separation in male pups (EPA 2013a). In the other 2-generation study, the highest dietary dose level (up to 2,633 and 3,134 mg/kg/day for parental males and females, respectively) resulted in up to 14–20% depressed pup body weight and/or body weight gain during the lactation period (EPA 1992a). There were no apparent treatment-related developmental effects in a study of rabbits treated by gavage at up to 350 mg/kg/day during GDs 6–27 (EPA 1992f).

Consideration was given to the increased anogenital distance (AGD) reported by Manservisi et al. (2019). This pilot study found that male F1 Sprague-Dawley rats exposed to 1.75 mg/kg/day glyphosate technical from gestation day 6 to post-natal day 120 showed increased anogenital distance at postnatal day 4. However, this result was determined to be insufficient for MRL derivation. The study used only one dose, which was substantially lower than the other lowest observed adverse effect levels (LOAELs) and the no observed adverse effect levels (NOAELs) identified in the body of literature. Furthermore, while decreases in AGD are sometimes considered an adverse effect related to endocrine disruption, increases in AGD are less commonly used because the toxicological significance of such increases is not well understood (Schwartz et al. 2019). Given that only one dose was tested, the observed effect was small (6%) and not observed in other studies, and because the relevance of such an effect to human health is not well-understood, it is not appropriate to use this study for MRL derivation.

As shown in Table A-2, gastrointestinal endpoints are the most sensitive to intermediate-duration oral exposure of laboratory animals to glyphosate technical. Pregnant rabbits gavaged with glyphosate technical daily at 350 mg/kg/day (LOAEL) during GDs 6–27 exhibited increased incidence of soft stool and/or diarrhea; the NOAEL was 175 mg/kg/day (EPA 1992f). Similar results were observed among other pregnant rabbits gavaged daily with glyphosate technical at 175 mg/kg/day (LOAEL) during GDs 8–20 (an acute-duration oral exposure scenario); the NOAEL was 100 mg/kg/day (EPA 2017b).

Increased severity of basophilia and hypertrophy of acinar cells in parotid and submandibular salivary glands were observed among male and female rats receiving glyphosate from the diet for 13 weeks at 410 and 421 mg/kg/day, respectively; NOAELs were 205 and 213 mg/kg/day, respectively (NTP 1992). Increased severity of basophilia of acinar cells in parotid salivary glands were observed in male and female mice similarly treated at estimated doses of 2,273 and 2,707 mg/kg/day, respectively; NOAELs were 507 and 753 mg/kg/day, respectively (NTP 1992). Thus, rats appear to be much more sensitive than mice to glyphosate treatment-related effects on salivary glands.

Among reliable animal study results, the LOAEL of 350 mg/kg/day for gastrointestinal effects (increased incidence of soft stool and/or diarrhea) in maternal rabbits gavaged daily during GDs 6–27 represents the most sensitive adverse effect from intermediate-duration oral exposure to glyphosate technical (EPA 1992f); the corresponding NOAEL is 175 mg/kg/day (see Table A-2). Incidence and severity data were not available for review. Application of a NOAEL/LOAEL approach using the NOAEL of 175 mg/kg/day as the point of departure and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) would result in an intermediate-duration oral MRL of 2 mg/kg/day (rounded up from 1.75 mg/kg/day). An intermediate-duration oral MRL was not derived for glyphosate because an intermediate-duration oral MRL of 2 mg/kg/day is higher than the acute- and chronic-duration oral MRL of 1 mg/kg/day. Glyphosate-induced microscopic changes in salivary glands of the rats treated orally for 13 weeks are not considered an adequate basis for MRL derivation due to uncertainty regarding the adversity of the effect. However, application of a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to the NOAEL of 205 mg/kg/day for salivary gland changes in male rats administered glyphosate in the diet for 13 weeks would result in an intermediate-duration oral MRL of 2 mg/kg/day. The chronic-duration oral MRL of 1 mg/kg/day for glyphosate is adopted as the intermediate-duration oral MRL because 1 mg/kg/day is considered protective of intermediate-duration oral exposure to glyphosate as well.

Agency Contact (Chemical Manager): Hana R. Pohl, M.D., Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Glyphosate technical
CAS Numbers: 1071-83-6
Date: August 2020
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 1 mg/kg/day
Critical Effect: Inflammation of gastric squamous mucosa
Reference: EPA 1991a, 1991b
Point of Departure: NOAEL of 113 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 19
Species: Rat

MRL Summary: A chronic-duration oral MRL of 1 mg/kg/day was derived for glyphosate based on gastrointestinal effects (inflammation of gastric squamous mucosa) observed in female rats administered glyphosate technical in the diet for up to 24 months at an estimated dose of 457 mg/kg/day; the NOAEL was 113 mg/kg/day (EPA 1991a, 1991b). The MRL is based on a NOAEL of 113 mg/kg/day and a total uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

Selection of the Critical Effect: Several chronic-duration oral animal studies were available for glyphosate technical (see Table A-3).

Table A-3. NOAELs and LOAELs Identified in Chronic-Duration Oral Studies of Glyphosate Technical

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Body weight	13% lower body weight in female rats at treatment week 81	M: 940 F: 457	F: 1,183	EPA 1991a, 1991b
	No effect in rats (highest dose)	M: 31.45 F: 34.02		EPA 1992d
	No effect in rats (highest dose)	M: 1,214 F: 1,498		EPA 2013a
	11–14% lower body weight and body weight gain in rats	300	1,000	EPA 2015c
	No effect in mice (highest dose)	M: 4,945 F: 6,069		EPA 2015a
	No effect in mice (highest dose)	1,000		EPA 2015c
	No effect in dogs (highest dose)	500		EPA 1986a, 1987

Table A-3. NOAELs and LOAELs Identified in Chronic-Duration Oral Studies of Glyphosate Technical

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Gastrointestinal	Inflammation of gastric squamous mucosa	M: 940 F: 113	F: 457	EPA 1991a, 1991b
	No effect in rats (highest dose)	M: 31.45 F: 34.02		EPA 1992d
	Increased severity of basophilia and hypertrophy of acinar cells in parotid and mandibular salivary gland in rats	100	300	EPA 2015c
	No effect in mice (highest dose)	M: 4,945 F: 6,069		EPA 2015a
Hematological	No effect in rats (highest dose)	M: 940 F: 1,183		EPA 1991a, 1991b
	No effect in rats (highest dose)	M: 31.45 F: 34.02		EPA 1992d
	No effect in rats (highest dose)	M: 1,214 F: 1,498		EPA 2015c
	No effect in rats (highest dose)	1,000		EPA 2015c
	No effect in mice (highest dose)	M: 4,945 F: 6,069		EPA 2015a
	No effect in dogs (highest dose)	500		EPA 1986a, 1987
Hepatic	No effect in rats (highest dose)	M: 940 F: 1,183		EPA 1991a, 1991b
	No effect in rats (highest dose)	M: 31.45 F: 34.02		EPA 1992d
	Increased serum AP, ALT, bilirubin in male rats; increased serum AP, ALT in female rats	M: 361 F: 437	M: 1,214 F: 1,498	EPA 2015c
	No effect in rats	1,000		EPA 2015c
	Centrilobular hepatocellular necrosis in male rats	M: 835 F: 6,069	M: 4,945	EPA 2015a
	No effect in mice (highest dose)	1,000		EPA 2015c
Renal	Increased specific gravity, decreased pH of urine in male rats	M: 362 F: 1,183	M: 940	EPA 1991a, 1991b
	No effect in rats (highest dose)	M: 31.45 F: 34.02		EPA 1992d
	M: Decreased pH of urine in rats M, F: Papillary necrosis in kidney in rats	M: 361 F:437	M: 1,214 F: 1,498	EPA 2015c
	Decreased pH of urine in male rats	M: 300 F: 1,000	M: 1,000	EPA 2015c
	Renal tubular epithelial basophilia in female mice	M: 4,945 F: 968	F: 6,069	EPA 2015a
	No effect in mice (highest dose)	1,000		EPA 2015c

Table A-3. NOAELs and LOAELs Identified in Chronic-Duration Oral Studies of Glyphosate Technical

Endpoint	Effect	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Reference
Ocular	Lens abnormalities in male rats	M: 362 F: 1,183	M: 940	EPA 1991a, 1991b
	No effect in rats	M: 1,214 F: 1,498		EPA 2015c
	No effect in rats	1,000		EPA 2015c
	No effect in dogs (highest dose)	500		EPA 1986a, 1987
Neurological	No effect in rats (highest dose)	M: 1,214 F: 1,498		EPA 2013c

ALT = alanine aminotransferase; AP = alkaline phosphatase; F = female; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level

As shown in Table A-3, gastrointestinal endpoints are the most sensitive to chronic-duration oral exposure of laboratory animals to glyphosate technical. Inflammation of gastric squamous mucosa was observed in female (but not male) rats administered glyphosate technical in the diet for up to 24 months at an estimated dose of 457 mg/kg/day; the NOAEL was 113 mg/kg/day (EPA 1991a, 1991b). Increased severity of cytoplasmic changes in salivary gland cells (basophilia and hypertrophy of acinar cells in parotid and submandibular salivary glands) was reported for rats receiving glyphosate from the diet for 2 years at doses ≥300 mg/kg/day (EPA 2015c). Although salivary gland cytoplasmic changes were noted in rats at doses <300 mg/kg/day as well, the changes were reported to be only of minimal or mild severity; therefore, they are not considered adverse effects. Furthermore, the toxicological significance of the glyphosate treatment-related effects on salivary glands is uncertain. One chronic-duration oral study of male and female mice found no evidence of glyphosate treatment-related gastrointestinal effects at doses as high as 4,945 and 6,069 mg/kg/day, respectively (EPA 1985a, 1985b, 1986b, 1989, 1991c, 1993, 2015a).

Summary of the Principal Study:

EPA. 1991a. June 03, 1991. Memorandum. 40 Page(s). William Dykstra. Toxicology Branch. Glyphosate; 2-Year combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats - List A Pesticide for Reregistration Pages 29-40 removed-registrant data. MRID 416438-01. Tox review 008390. U.S. Environmental Protection Agency. https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/103601/103601-263.pdf. April 10, 2016.

EPA. 1991b. December 13, 1991. Memorandum. 38 Page(s). William Dykstra. Toxicology Branch I. Glyphosate - EPA Registration No. 524-308 - 2-Year chronic feeding/oncogenicity study in rats with technical glyphosate. MRID 416438-01. Tox review 008897. U.S. Environmental Protection Agency. https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/103601/103601-268.pdf. April 10, 2016.

Groups of albino Sprague Dawley rats (60/sex/group) were administered technical glyphosate (96.5% purity) in the diet at target concentrations of 0, 2,000, 8,000, or 20,000 ppm (mean measured concentrations of 0, 1,900, 7,600, and 19,000 ppm, respectively) for up to 24 months. Rats were monitored for survival, clinical signs, food intake, and body weight. Ten rats/sex/dose were subjected to

comprehensive evaluations at 12-month interim sacrifice. Rats were subjected to ophthalmologic examinations prior to the initiation of treatment and twice prior to scheduled terminal sacrifice. Blood and urine samples were collected at 6, 12, 18, and 24 months for hematology, clinical chemistry, and urinalysis. Evaluations of all rats that died or survived until scheduled sacrifice included organ weight determinations (brain, liver, kidneys, testes, epididymides, prostate) and comprehensive gross and histopathologic examinations.

There were no indications of glyphosate-related clinical signs or effects on survival. Mean body weights of all glyphosate-treated male rats were not significantly different from that of controls. Mean body weights and of high-dose female rats were significantly lower than that of controls at weeks 7, 13, 81, and 104 (approximately 3–4% less than that of controls); by week 81, the magnitude of the mean body weight difference between high-dose females and their controls reached 13% (470.6 g versus 543.2 g for controls). There were no significant differences between controls and glyphosate-treated groups regarding food consumption. Based on mean body weight and food consumption data, estimated glyphosate doses to controls and low-, mid-, and high-dose groups were 0, 89, 362, and 940 mg/kg/day, respectively, for the males and 0, 113, 457, and 1,183 mg/kg/day, respectively, for the females.

Glyphosate treatment-related nonneoplastic effects included increased incidence of ocular effects (lens abnormalities), renal effects (increased specific gravity and decreased pH of urine) in high-dose (940 mg/kg/day) male rats, and significantly increased incidence of inflammation of gastric squamous mucosa in female rats at 457 and 1,183 mg/kg/day (incidences of 0/59, 3/60, 9/60 [p=0.0015], and 6/59 [p=0.014] among controls, low-, mid-, and high-dose groups, respectively; statistical significance determined using Fisher's exact test). The high-dose (1,183 mg/kg/day) group of female rats exhibited as much as 13% lower mean body weight at treatment week 81. Relative liver weight was significantly increased in high-dose male rats evaluated at 12 months and terminal sacrifice (13–14% greater than controls); however, histopathologic examinations of liver sections revealed no evidence of significant treatment-related nonneoplastic effects.

Selection of the Point of Departure: A chronic-duration oral MRL can be derived for glyphosate based on incidences of female rats exhibiting gastric lesions in the 2-year dietary study of rats (EPA 1991a, 1991b). Incidences of female rats with gastric lesions were 0/59, 3/60, 9/60, and 6/59 for controls, low-, mid-, and high-dose groups, respectively. All dichotomous models in the Benchmark Dose Modeling Software (BMDS; Version 2.6) were fit to the incidence data for female rats exhibiting inflammation of gastric squamous mucosa. A benchmark response (BMR) of 10% extra risk was applied. None of the models produced adequate fit to the dataset, likely due to 33% lower incidence for the gastric lesion in the high-dose group compared to the mid-dose group. Therefore, a NOAEL/LOAEL approach was employed to derive a chronic-duration oral MRL for glyphosate. The point of departure is the NOAEL of 113 mg/kg/day for gastrointestinal lesions in the female rats of the 2-year dietary study (EPA 1991a, 1991b).

Uncertainty Factor: The NOAEL of 113 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

Per ATSDR guidance, MRLs are expressed to one significant figure, making the MRL 1 mg/kg/day.

The glyphosate-induced cytoplasmic changes in salivary glands of the chronically-treated rats were not considered for MRL derivation because the toxicological significance of the changes is uncertain. However, consideration of the NOAEL of 113 mg/kg/day (EPA 2015c) as a point of departure, application of a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) would also result in a chronic-duration oral MRL of 1 mg/kg/day.

Other Additional Studies or Pertinent Information: Glyphosate-induced gastrointestinal effects were observed in acute-duration oral studies of rats and rabbits (Adam et al. 1997; EPA 1992e, 2013c, 2017b), intermediate-duration oral studies of rats, mice, and rabbits (EPA 1992a, 1992f; NTP 1992), and chronic-duration oral studies of rats (EPA 1991a, 1991b, 2015c).

Agency Contact (Chemical Manager): Hana R. Pohl, M.D., Ph.D.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR GLYPHOSATE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to glyphosate.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for glyphosate. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of glyphosate have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of glyphosate are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

	Other noncancer effects
	Cancer
Toxicokinetics	
	Absorption
	Distribution
	Metabolism
	Excretion
	PBPK models
Biomarkers	
	Biomarkers of exposure
	Biomarkers of effect
Interactions with other chemicals	
Potential for human exposure	
	Releases to the environment
	Air
	Water
	Soil
	Environmental fate
	Transport and partitioning
	Transformation and degradation
	Environmental monitoring
	Air
	Water
	Sediment and soil
	Other media
	Biomonitoring
	General populations
	Occupation populations

B.1.1 Literature Search

The following main databases were searched in February 2015 and September 2017:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, and Medical Subject Headings (MeSH) terms for glyphosate. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases

were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to glyphosate were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations. The reference sections of the gray literature were used as quality assurance (QA) to ensure that no studies were missed during the literature review process. The ToxProfiles rely on peer reviewed data such as published studies and reports from government agencies or international organizations. In certain cases (e.g. ATSDR's use of EPA's DERs), ATSDR will rely on peer reviewed studies and reports evaluating unpublished data or original studies that are not available to ATSDR.

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
PubMed 9/2017	("glyphosate"[nm] OR "1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw] OR "Roundup"[tw] OR "34494-03-6"[tw] OR "MON 0459"[tw] OR "40465-66-5"[tw] OR "MON 14420"[tw] OR "MON 8750"[tw] OR "Roundup Hi-Load"[tw] OR "Roundup PRODry"[tw] OR "70393-85-0"[tw] OR "MON 8000"[tw] OR "Monsanto 8000"[tw] OR "Polado"[tw] OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate"[tw] OR "39600-42-5"[tw] OR "Glyphosate potassium"[tw] OR "Glyphosate monopotassium salt"[tw] OR "Glyphosate potassium"[tw] OR "Glyphosate-potassium"[tw] OR "Monopotassium glyphosate"[tw] OR "Roundup Attack"[tw] OR "Roundup Energy"[tw] OR "Roundup Maxload"[tw] OR "Roundup Original Max"[tw] OR "Roundup Power Max"[tw] OR "Roundup Ultramax II"[tw] OR "Roundup Weathermax"[tw] OR "Touchdown Forte HiTech"[tw] OR "Transorb R"[tw] OR "Weathermax"[tw] OR "Zapp Qi"[tw] OR "70901-12-1"[tw] OR "Glyphosate-potassium"[tw] OR "Potassium glyphosate"[tw] OR "Potassium N-(phosphonomethyl)glycine"[tw] OR "Uragan Forte"[tw] OR "VisionMAX"[tw] OR "N-(phosphonomethyl)glycine potassium salt"[tw] OR "114370-14-8"[tw] OR "Glyphosate ammonium"[tw] OR "N-(phosphonomethyl)glycine ammonium salt"[tw] OR "69254-40-6"[tw] OR "Glyphosate-diammonium"[tw] OR "Diammonium N-(phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)glycine diammonium salt"[tw]) AND (cancer[sb] OR "neoplasms"[mh] OR "carcinogenicity tests"[mh] OR "carcinogens"[mh] OR "cell division/drug effects"[mh] OR "cell cycle/drug effects"[mh] OR "cell line, tumor/drug effects"[mh] OR "gene expression regulation, neoplastic"[mh] OR "neoplasm proteins/drug effects"[mh] OR "angiogenesis inducing agents"[mh] OR "myelodysplastic-myeloproliferative diseases"[mh] OR cancer*[tw] OR carcinog*[tw] OR carcinom*[tw] OR cocarcinog*[tw] OR lymphoma*[tw] OR neoplas*[tw] OR oncogen*[tw] OR precancer*[tw] OR tumor*[tw] OR tumour*[tw]) AND

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	(2014/02/01 : 3000[dp] OR 2015/02/01 : 3000[mhda] OR 2015/02/01 : 3000[crdat] OR 2015/02/01 : 3000[edat])
	("glyphosate, isopropyl amine salt"[nm] OR "N-(phosphonomethyl)glycine trimethylsulfonium salt"[nm] OR "38641-94-0"[tw] OR "Glyphosate-isopropylammonium"[tw] OR "Glyphosate isopropylamine salt"[tw] OR "Azural AT"[tw] OR "CP 70139"[tw] OR "Fosulen"[tw] OR "Glifosato estrella"[tw] OR "Glycel"[tw] OR "Glycine, N-(phosphonomethyl)-, cmpd with 2-propanamine (1:1)"[tw] OR "Glyfos AU"[tw] OR "Glyfos BIO"[tw] OR "Glyphosate isopropylamine salt"[tw] OR "Glyphosate mono(isopropylamine) salt"[tw] OR "Glyphosate-isopropylammonium"[tw] OR "Glyphosate-mono(isopropylammonium)"[tw] OR "Landmaster"[tw] OR "MON 139"[tw] OR "MON 39"[tw] OR "N-(Phosphonomethyl)glycine isopropylamine salt"[tw] OR "N-(Phosphonomethyl)glycine isopropylammonium salt"[tw] OR "N-(Phosphonomethyl)glycine monoisopropylamine salt"[tw] OR "Nitosorg"[tw] OR "Ron-do"[tw] OR "Utal"[tw] OR "Utal (herbicide)"[tw] OR "Vision (herbicide)"[tw] OR "2-Propanamine, compd, with N-(phosphonomethyl)glycine (1:1)"[tw] OR "Glycine, N-(phosphonomethyl)-, compd. with 2-propanamine (1:1)"[tw] OR "N-(Phosphonomethyl)glycine, compound with 2-propylamine (1:1)"[tw] OR "Isopropylamine glyphosate"[tw] OR "81591-81-3"[tw] OR "Glyphosate-trimesium"[tw] OR "Glyphosphate-trimesium"[tw] OR "Avans 330"[tw] OR "Glyphosate mono(trimethylsulfonium) salt"[tw] OR "Glyphosate trimethylsulfonium salt"[tw] OR "Glyphosate-trimesium"[tw] OR "Medallon"[tw] OR "Ouragan"[tw] OR "R 50224"[tw] OR "SC 0224"[tw] OR "Sulfosate"[tw] OR "Sulphosate"[tw] OR "Touchdown herbicide"[tw] OR "Trimethylsulfonium carboxymethylamino-methylphosphonate"[tw] OR "Trimethylsulfonium glyphosate"[tw] OR "Glycine, N-(phosphonomethyl)-, ion(1-), trimethylsulfonium"[tw] OR "Sulfosate"[tw]) AND (cancer[sb] OR "neoplasms"[mh] OR "carcinogenicity tests"[mh] OR "carcinogens"[mh] OR "cell division/drug effects"[mh] OR "cell cycle/drug effects"[mh] OR "cell line, tumor/drug effects"[mh] OR "gene expression regulation, neoplastic"[mh] OR "neoplasm proteins/drug effects"[mh] OR "angiogenesis inducing agents"[mh] OR "myelodysplastic-myeloproliferative diseases"[mh] OR cancer*[tw] OR carcinog*[tw] OR carcinom*[tw] OR cocarcinog*[tw] OR lymphoma*[tw] OR neoplas*[tw] OR oncogen*[tw] OR precancer*[tw] OR tumor*[tw] OR tumour*[tw]) AND (2014/02/01 : 3000[dp] OR 2015/02/01 : 3000[mhda] OR 2015/02/01 : 3000[crdat] OR 2015/02/01 : 3000[edat])
2/2015	("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb])
	("Roundup"[tw] AND (monsanto[tw] OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR "antifungal"[tw] OR "anti-fungal"[tw] OR "enzyme inhibitors"[Pharmacological Action] OR "enzyme inhibitors"[MeSH Terms] OR ("enzyme"[tw] AND inhibitor*[tw]) OR "enzyme inhibitors"[tw] OR "enzyme inhibitor"[tw] OR "herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[tw] OR "herbicide"[tw] OR "uncoupling agents"[Pharmacological Action] OR "uncoupling agents"[MeSH Terms] OR ("uncoupling"[tw] AND agent*[tw]) OR "uncoupling agent"[tw] OR "uncoupling agents"[tw] OR "pesticides"[mh] OR pesticide*[tw])) NOT (("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	"peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb])) ("34494-03-6"[tw] OR "MON 0459"[tw] OR "40465-66-5"[tw] OR "MON 14420"[tw] OR "MON 8750"[tw] OR "Roundup Hi-Load"[tw] OR "Roundup PRODry"[tw] OR "70393-85-0"[tw] OR "MON 8000"[tw] OR "Monsanto 8000"[tw] OR "Polado"[tw] OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr]) ("39600-42-5"[tw] OR "Glyphosate potassium"[tw] OR "Glyphosate monopotassium salt"[tw] OR "Glyphosate potassium"[tw] OR "Glyphosate-potassium"[tw] OR "Monopotassium glyphosate"[tw] OR "Roundup Attack"[tw] OR "Roundup Energy"[tw] OR "Roundup Maxload"[tw] OR "Roundup Original Max"[tw] OR "Roundup Power Max"[tw] OR "Roundup Ultramax II"[tw] OR "Roundup Weathermax"[tw] OR "Touchdown Forte HiTech"[tw] OR "Transorb R"[tw] OR "Weathermax"[tw] OR "Zapp Qi"[tw] OR "70901-12-1"[tw] OR "Glyphosate-potassium"[tw] OR "Potassium glyphosate"[tw] OR "Potassium N-(phosphonomethyl)glycine"[tw] OR "Uragan Forte"[tw] OR "VisionMAX"[tw] OR "N-(phosphonomethyl)glycine potassium salt"[tw] OR "114370-14-8"[tw] OR "Glyphosate ammonium"[tw] OR "N-(phosphonomethyl)glycine ammonium salt"[tw] OR "69254-40-6"[tw] OR "Glyphosate-diammonium"[tw] OR "Diammonium N-(phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)glycine diammonium salt"[tw]) NOT (("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	"Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb]) OR ("Roundup"[tw] AND (monsanto[tw] OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR "antifungal"[tw] OR "anti-fungal"[tw] OR "enzyme inhibitors"[Pharmacological Action] OR "enzyme inhibitors"[MeSH Terms] OR ("enzyme"[tw] AND inhibitor*[tw]) OR "enzyme inhibitors"[tw] OR "enzyme inhibitor"[tw] OR "herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[tw] OR "herbicide"[tw] OR "uncoupling agents"[Pharmacological Action] OR "uncoupling agents"[MeSH Terms] OR ("uncoupling"[tw] AND agent*[tw]) OR "uncoupling agent"[tw] OR "uncoupling agents"[tw] OR "pesticides"[mh] OR pesticide*[tw]))) (((("glyphosate, isopropyl amine salt"[nm]) OR ("N-(phosphonomethyl)glycine trimethylsulfonium salt"[nm])) NOT (("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb]) OR ("Roundup"[tw] AND (monsanto[tw] OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR "antifungal"[tw] OR "anti-fungal"[tw] OR "enzyme inhibitors"[Pharmacological Action] OR "enzyme inhibitors"[MeSH Terms] OR ("enzyme"[tw] AND inhibitor*[tw]) OR "enzyme inhibitors"[tw] OR "enzyme inhibitor"[tw] OR "herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[tw] OR "herbicide"[tw] OR "uncoupling agents"[Pharmacological Action] OR "uncoupling agents"[MeSH Terms] OR ("uncoupling"[tw] AND agent*[tw]) OR "uncoupling agent"[tw] OR "uncoupling agents"[tw] OR "pesticides"[mh] OR pesticide*[tw])))) OR (("38641-94-0"[tw] OR "Glyphosate-isopropylammonium"[tw] OR "Glyphosate isopropylamine salt"[tw] OR "Azural AT"[tw] OR "CP 70139"[tw] OR "Fosulen"[tw] OR "Glifosato estrella"[tw] OR "Glycel"[tw] OR "Glycine, N-(phosphonomethyl)-, cmpd with 2-propanamine (1:1)"[tw] OR "Glyfos AU"[tw] OR "Glyfos BIO"[tw] OR "Glyphosate isopropylamine salt"[tw] OR "Glyphosate mono(isopropylamine) salt"[tw] OR "Glyphosate-isopropylammonium"[tw] OR "Glyphosate-mono(isopropylammonium)"[tw] OR "Landmaster"[tw] OR "MON 139"[tw] OR "MON 39"[tw] OR "N-(Phosphonomethyl)glycine isopropylamine salt"[tw] OR "N-(Phosphonomethyl)glycine isopropylammonium salt"[tw] OR "N-(Phosphonomethyl)glycine monoisopropylamine salt"[tw] OR "Nitosorg"[tw] OR "Ron-do"[tw] OR "Utal"[tw] OR "Utal (herbicide)"[tw] OR "Vision (herbicide)"[tw] OR "2-Propanamine, compd, with N-

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	(phosphonomethyl)glycine (1:1)"[tw] OR "Glycine, N-(phosphonomethyl)-, compd. with 2-propanamine (1:1)"[tw] OR "N-(Phosphonomethyl)glycine, compound with 2-propylamine (1:1)"[tw] OR "Isopropylamine glyphosate"[tw] OR "81591-81-3"[tw] OR "Glyphosate-trimesium"[tw] OR "Glyphosphate-trimesium"[tw] OR "Avans 330"[tw] OR "Glyphosate mono(trimethylsulfonium) salt"[tw] OR "Glyphosate trimethylsulfonium salt"[tw] OR "Glyphosate-trimesium"[tw] OR "Medallon"[tw] OR "Ouragan"[tw] OR "R 50224"[tw] OR "SC 0224"[tw] OR "Sulfosate"[tw] OR "Sulphosate"[tw] OR "Touchdown herbicide"[tw] OR "Trimethylsulfonium carboxymethylamino-methylphosphonate"[tw] OR "Trimethylsulfonium glyphosate"[tw] OR "Glycine, N-(phosphonomethyl)-, ion(1-), trimethylsulfonium"[tw] OR "Sulfosate"[tw]) NOT (("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb]) OR ("Roundup"[tw] AND (monsanto[tw] OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR "antifungal"[tw] OR "anti-fungal"[tw] OR "enzyme

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	inhibitors"[Pharmacological Action] OR "enzyme inhibitors"[MeSH Terms] OR ("enzyme"[tw] AND inhibitor*[tw]) OR "enzyme inhibitors"[tw] OR "enzyme inhibitor"[tw] OR "herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[tw] OR "herbicide"[tw] OR "uncoupling agents"[Pharmacological Action] OR "uncoupling agents"[MeSH Terms] OR ("uncoupling"[tw] AND agent*[tw]) OR "uncoupling agent"[tw] OR "uncoupling agents"[tw] OR "pesticides"[mh] OR pesticide*[tw]))))
Toxline 9/2017	("lancer herbicide" OR "mon 2139" OR "mon 3539" OR "mon 6000" OR "phorsat" OR "phosphonomethyliminoacetic acid" OR "rebel garden" OR "roundup max" OR "safal" OR "scout herbicide") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	(" (carboxymethylamino) methylphosphonic acid" OR "carboxymethylaminomethanephosphinic acid" OR "c k yuyos fav" OR "cp 67573" OR "folusen" OR "forsat" OR "glialka" OR "glifosan 747" OR "glygran" OR "glyphodin a" OR "glyphomax" OR "ground bio" OR "herbatop" OR "hm 2028" OR "kickdown") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("glifoglex" OR "gliphosate" OR "gliz" OR "glyfos" OR "glyphosate" OR "glyphosphate" OR "n (phosphonomethyl) glycine" OR "n (phosphonomethyl) glycine" OR "n phosphomethylglycine" OR "n phosphonomethylglycine" OR "phosphonomethylglycine" OR "pondmaster" OR "silglif" OR "yerbimat") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	1071-83-6 [rn] AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org] (#7 NOT #4) AND NOT PubMed [org] AND NOT pubdart [org]
	"roundup" AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org]
	("mon 0459" OR "40465 66 5" OR "mon 14420" OR "mon 8750" OR "roundup hi load" OR "roundup prodry" OR "mon 8000" OR "monsanto 8000" OR "polado" OR "trisodium hydrogen bis (n (phosphonatomethyl) aminoacetate) ") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	(34494-03-6 [rn] OR 70393-85-0 [rn]) AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org]

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("glyphosate diammonium" OR "diammonium n (phosphonomethyl) glycine" OR "n (phosphonomethyl) glycine diammonium salt") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("roundup weathermax" OR "touchdown forte hitech" OR "transorb r" OR "weathermax" OR "zapp qi" OR "glyphosate potassium" OR "potassium glyphosate" OR "potassium n (phosphonomethyl) glycine" OR "uragan forte" OR "visionmax" OR "n (phosphonomethyl) glycine potassium salt" OR "glyphosate ammonium" OR "n (phosphonomethyl) glycine ammonium salt") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("glyphosate potassium" OR "glyphosate monopotassium salt" OR "glyphosate potassium" OR "glyphosate potassium" OR "monopotassium glyphosate" OR "roundup attack" OR "roundup energy" OR "roundup maxload" OR "roundup original max" OR "roundup power max" OR "roundup ultramax ii") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	(39600-42-5 [rn] OR 39600-55-0 [rn] OR 39600-56-1 [rn] OR 39600-58-3 [rn] OR 40465-59-6 [rn] OR 40465-64-3 [rn] OR 40465-67-6 [rn] OR 40465-70-1 [rn] OR 40465-90-5 [rn] OR 40465-91-6 [rn] OR 70901-12-1 [rn] OR 114370-14-8 [rn] OR 69254-40-6 [rn]) AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("sulphosate" OR "touchdown herbicide" OR "trimethylsulfonium carboxymethylamino methylphosphonate" OR "trimethylsulfonium glyphosate" OR "glycine n (phosphonomethyl) ion (1) trimethylsulfonium") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("isopropylamine glyphosate" OR "glyphosate trimesium" OR "glyphosphate trimesium" OR "avans 330" OR "glyphosate mono (trimethylsulfonium) salt" OR "glyphosate trimethylsulfonium salt" OR "glyphosate trimesium" OR "medallon" OR "ouragan" OR "r 50224" OR "sc 0224" OR "sulfosate") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	("n (phosphonomethyl) glycine monoisopropylamine salt" OR "nitosorg" OR "utal" OR "utal (herbicide) " OR "vision (herbicide) " OR "2 propanamine compd with n (phosphonomethyl) glycine (1 1) " OR "glycine n (phosphonomethyl) compd with 2 propanamine (1 1) " OR "n (phosphonomethyl) glycine compound with 2 propylamine (1 1) ") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("glyphosate mono (isopropylamine) salt" OR "glyphosate isopropylammonium" OR "glyphosate mono (isopropylammonium) " OR "landmaster" OR "mon 139" OR "mon 39" OR "n (phosphonomethyl) glycine isopropylamine salt" OR "n (phosphonomethyl) glycine isopropylammonium salt") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("glyphosate isopropylammonium" OR "glyphosate isopropylamine salt" OR "azural at" OR "cp 70139" OR "fosulen" OR "glifosato estrella" OR "glycel" OR "glycine n (phosphonomethyl) cmpd with 2 propanamine (1 1) " OR "glyfos au" OR "glyfos bio" OR "glyphosate isopropylamine salt") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	(38641-94-0 [rn] OR 81591-81-3 [rn]) AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
2/2015	"Glifoglex" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "Glyphosate" OR "Glyphosphate" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phosphonomethylglycine" OR "Pondmaster" OR "Silglif" OR "yerbimat"
	"(Carboxymethylamino)methylphosphonic acid" OR "Carboxymethylaminomethanephosphinic acid" OR "C-K Yuyos FAV" OR "CP 67573" OR "Folusen" OR "Forsat" OR "Glialka" OR "Glifosan 747" OR "GlyGran" OR "Glyphodin A" OR "Glyphomax" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown"
	"Lancer herbicide" OR "MON 2139" OR "MON 3539" OR "MON 6000" OR "Phorsat" OR "Phosphonomethyliminoacetic acid" OR "Rebel Garden" OR "Roundup Max" OR "Safal" OR "Scout herbicide"
	"roundup"
	34494-03-6[rn] OR 70393-85-0[rn]
	"MON 0459" OR "40465-66-5" OR "MON 14420" OR "MON 8750" OR "Roundup Hi-Load" OR "Roundup PRODry" OR "MON 8000" OR "Monsanto 8000" OR "Polado" OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate)"

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	39600-42-5[rn] OR 39600-55-0[rn] OR 39600-56-1[rn] OR 39600-58-3[rn] OR 40465-59-6[rn] OR 40465-64-3[rn] OR 40465-67-6[rn] OR 40465-70-1[rn] OR 40465-90-5[rn] OR 40465-91-6[rn] OR 70901-12-1[rn] OR 114370-14-8[rn] OR 69254-40-6[rn]
	"Glyphosate potassium" OR "Glyphosate monopotassium salt" OR "Glyphosate potassium" OR "Glyphosate-potassium" OR "Monopotassium glyphosate" OR "Roundup Attack" OR "Roundup Energy" OR "Roundup Maxload" OR "Roundup Original Max" OR "Roundup Power Max" OR "Roundup Ultramax II"
	"Roundup Weathermax" OR "Touchdown Forte HiTech" OR "Transorb R" OR "Weathermax" OR "Zapp Qi" OR "Glyphosate-potassium" OR "Potassium glyphosate" OR "Potassium N-(phosphonomethyl)glycine" OR "Uragan Forte" OR "VisionMAX" OR "N-(phosphonomethyl)glycine potassium salt" OR "Glyphosate ammonium" OR "N-(phosphonomethyl)glycine ammonium salt"
	"Glyphosate-diammonium" OR "Diammonium N-(phosphonomethyl)glycine" OR "N-(phosphonomethyl)glycine diammonium salt"
	38641-94-0[rn] OR 81591-81-3[rn]
	"Glyphosate-isopropylammonium" OR "Glyphosate isopropylamine salt" OR "Azural AT" OR "CP 70139" OR "Fosulen" OR "Glifosato estrella" OR "Glycel" OR "Glycine, N-(phosphonomethyl)-, cmpd with 2-propanamine (1:1)" OR "Glyfos AU" OR "Glyfos BIO" OR "Glyphosate isopropylamine salt"
	"Glyphosate mono(isopropylamine) salt" OR "Glyphosate-isopropylammonium" OR "Glyphosate-mono(isopropylammonium)" OR "Landmaster" OR "MON 139" OR "MON 39" OR "N-(Phosphonomethyl)glycine isopropylamine salt" OR "N-(Phosphonomethyl)glycine isopropylammonium salt"
	"N-(Phosphonomethyl)glycine monoisopropylamine salt" OR "Nitosorg" OR "Utal" OR "Utal (herbicide)" OR "Vision (herbicide)" OR "2-Propanamine, compd, with N-(phosphonomethyl)glycine (1:1)" OR "Glycine, N-(phosphonomethyl)-, compd. with 2-propanamine (1:1)" OR "N-(Phosphonomethyl)glycine, compound with 2-propylamine (1:1)"
	"Isopropylamine glyphosate" OR "Glyphosate-trimesium" OR "Glyphosphate-trimesium" OR "Avans 330" OR "Glyphosate mono(trimethylsulfonium) salt" OR "Glyphosate trimethylsulfonium salt" OR "Glyphosate-trimesium" OR "Medallon" OR "Ouragan" OR "R 50224" OR "SC 0224" OR "Sulfosate"
	"Sulphosate" OR "Touchdown herbicide" OR "Trimethylsulfonium carboxymethylamino-methylphosphonate" OR "Trimethylsulfonium glyphosate" OR "Glycine, N- N-phosphonemethyl)-, ion(1-), trimethylsulfonium"
Toxcenter 9/2017	L1 9995 SEA 1071-83-6 L2 92 SEA 34494-03-6 OR 40465-66-5 OR 70393-85-0 L3 80 SEA 39600-42-5 OR 39600-55-0 OR 39600-56-1 OR 39600-58-3 OR 40465-59-6 OR 40465-64-3 OR 40465-67-6 OR 40465-70-1 OR 40465-90-5 OR 40465-91-6 L4 101 SEA 70901-12-1 OR 114370-14-8 OR 69254-40-6 L5 2022 SEA 38641-94-0 OR 81591-81-3 L6 10037 SEA L1 OR L2 OR L3 OR L4 L7 6132 SEA L6 NOT (TSCATS/FS OR PATENT/DT) L8 2048 SEA L6 AND (PY>2013 OR ED>=20150201) L9 1260 SEA L7 AND (PY>2013 OR ED>=20150201) L10 751 SEA L5 NOT L6

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	L11 530 SEA L10 NOT (TSCATS/FS OR PATENT/DT) L12 63 SEA L11 AND (PY>2013 OR ED>=20150201) L13 56 SEA L9 AND (CANCER? OR CARCINOG? OR CARCINOM? OR COCARCINOG? OR LYMPHOMA? OR NEOPLAS? OR ONCOGEN? OR PRECANCER? OR TUMOR? OR TUMOUR?) L14 6 SEA L12 AND (CANCER? OR CARCINOG? OR CARCINOM? OR COCARCINOG? OR LYMPHOMA? OR NEOPLAS? OR ONCOGEN? OR PRECANCER? OR TUMOR? OR TUMOUR?) L15 16 SEA L13 AND MEDLINE/FS L16 40 SEA L13 NOT L15 L17 44 DUP REM L15 L16 (12 DUPLICATES REMOVED) ANSWERS '1-44' FROM FILE TOXCENTER L*** DEL 16 S L13 AND MEDLINE/FS L*** DEL 16 S L13 AND MEDLINE/FS L18 16 SEA L17 L*** DEL 40 S L13 NOT L15 L*** DEL 40 S L13 NOT L15 L19 28 SEA L17 L20 28 SEA (L18 OR L19) NOT MEDLINE/FS D SCAN L20 L21 401072 SEA 14 NOT MEDLINE/FS L22 6 SEA L14 NOT MEDLINE/FS L23 6 DUP REM L22 (0 DUPLICATES REMOVED) ANSWERS '1-6' FROM FILE TOXCENTER D SCAN L23 FILE 'MEDLINE' ENTERED AT 19:10:42 ON 14 SEP 2017 CHARGED TO COST=EH011.10.01 L24 QUE ACROCHORDON OR ACROCHORDONS OR ADENOMATOSIS OR ADENOMATOUS OR ADENOSIS OR AMYLOIDOSES OR AMYLOIDOSIS OR ANAPLASIA OR ANGIOENDOTHELIOMATOSIS OR ANGIOMATOSIS OR BUSCHKE-LOWENSTEIN OR CANCER OR CANCEROUS OR CANCERS OR CARCINOGEN L25 QUE CARCINOGENESIS OR CARCINOGENIC OR CARCINOGENICITY OR CARCINOGENS OR CARCINOID OR CARCINOMATOSIS OR CHERUBISM OR CIN OR CLL OR COCARCINOGENESIS OR DERMOID OR DYSMYELOPOIESIS OR ENCHONDROMATOSIS OR EPIDERMOID OR ERYTHROLEUKAEMIA OR ERYTHROLE UKAEMIAS L26 QUE ERYTHROLEUKEMIA OR ERYTHROLEUKEMIAS OR ERYTHROPLAKIA OR ERYTHROPLAKIAS OR ERYTHROPLASIA OR ESSENTIAL-THROMBOCYTHEMIA OR EXOSTOSIS OR FIBROADENOSIS OR FIBROID OR FIBROIDS OR

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	FIBROMATOSIS OR GLIOMATOSIS OR GLOMANGIOMATOSIS OR GRANULOMATOS
	IS
	L27 QUE GYNAECOMASTIA OR GYNECOMASTIA OR HEMANGIOMATOSIS OR
	HODGKIN OR HODGKINS OR LEIOMYOMATOSIS OR LEUKAEMIA OR LEUKAEMIA
	S OR LEUKEMIA OR LEUKEMIAS OR LEUKOPLAKIA OR LEUKOPLAKIAS OR
	LEUKOSTASIS OR LIPOBLASTOMATOSIS OR LIPOMATOSIS
	L28 QUE LYMPHANGIOLEIOMYOMATOSIS OR LYMPHANGIOMATOSIS OR LYMPHANGIO
	MYOMATOSIS OR LYMPHOPROLIFERATION OR LYMPHOPROLIFERATIONS OR
	LYMPHOPROLIFERATIVE OR LYMPHOSCINTIGRAPHIC OR LYMPHOSCINTIGRAPH
	Y OR MACROGLOBULINEMIA OR MACROGLOBULINEMIAS
	L29 QUE MALIGNANCIES OR MALIGNANCY OR MALIGNANT OR MASTOCYTOSIS OR
	MEIGS-SYNDROME OR MELANOMATOSIS OR MENINGIOMATOSIS OR METAPLASI
	A OR MICROMETASTASES OR MICROMETASTASIS OR MYCOSIS-FUNGOIDES
	OR MYELODYSPLASIA OR MYELODYSPLASIAS
	L30 QUE MYELODYSPLASTIC OR MYELOFIBROSIS OR MYELOMATOSIS OR
	MYELOPROLIFERATION OR MYELOPROLIFERATIONS OR MYELOPROLIFERATIVE
	OR MYELOSUPPRESSION OR MYOFIBROMATOSIS OR NEOPLASIA OR
	NEOPLASM OR NEOPLASMS OR NEOPLASTIC OR NEURILEMMOMATOSIS
	L31 QUE NEUROFIBROMATOSIS OR NEURONEVUS OR NONHODGKIN OR NONHODGKIN
	S OR NONSEMINOMATOUS OR NSCLC OR ONCOGENE-FUSION OR OPSOCLONUS-
	MYOCLONUS OR PAPILLOMATA OR PAPILLOMATOSIS OR PARANEOPLASTIC
	OR PEUTZ-JEGHERS OR POLYPOSIS OR PRECANCER
	L32 QUE PRECANCEROUS OR SARCOMATOSIS OR SCHWANNOMATOSIS OR
	SEMINOMATOUS OR SEZARY-SYNDROME OR STRUMA-OVARII OR TUMOR OR
	TUMORGENESIS OR TUMORGENIC OR TUMORIGENESIS OR TUMORIGENIC OR
	TUMOR-MARKER OR TUMOR-MARKERS OR TUMOROGENESIS
	L33 QUE TUMOROGENIC OR TUMORS OR TUMOUR OR TUMOURS OR WALDENSTROM
	OR WALDENSTROMS OR "5Q-SYNDROME" OR "WAGR SYNDROME" OR (ASCO
	NOT FUNGI) OR (SENTINEL-LYMPH-NODE NOT BIOPSY)
	L34 QUE L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	DIS COST FILE 'TOXCENTER' ENTERED AT 19:12:52 ON 14 SEP 2017 CHARGED TO COST=EH011.10.01 L47 1 SEA L9 AND ?IOMA DIS COST L48 26 SEA L9 AND (?AOMA OR ?BOMA OR ?COMA OR ?DOMA OR ?EOMA OR ?FOMA OR ?GOMA OR ?HOMA OR ?IOMA OR ?JOMA OR ?KOMA OR ?LOMA OR ?MOMA OR ?NOMA OR ?OOMA OR ?POMA OR ?QOMA OR ?ROMA OR ?SOMA OR ?TOMA OR ?UOMA OR ?VOMA OR ?WOMA) L49 0 SEA L9 AND (?XOMA OR ?YOMA OR ?ZOMA OR ?AOMAS OR ?BOMAS OR ?COMAS OR ?DOMAS OR ?EOMAS OR ?FOMAS OR ?GOMAS OR ?HOMAS OR ?IOMAS OR ?JOMAS OR ?KOMAS OR ?LOMAS OR ?MOMAS OR ?NOMAS OR ?OOMAS OR ?POMAS OR ?QOMAS OR ?ROMAS) L50 0 SEA L9 AND (?SOMAS OR ?TOMAS OR ?UOMAS OR ?VOMAS OR ?WOMAS OR ?XOMAS OR ?YOMAS OR ?ZOMAS) L51 48 SEA L9 AND L34 L52 68 SEA L48 OR L49 OR L50 OR L51 L53 16 SEA L52 NOT L13 L54 20 SEA L52 AND MEDLINE/FS L55 7 SEA L53 AND MEDLINE/FS L56 12 DUP REM L53 (4 DUPLICATES REMOVED) ANSWERS '1-12' FROM FILE TOXCENTER D SCAN L56 L57 6 SEA L12 AND L34 L58 2 SEA L12 AND (?AOMA OR ?BOMA OR ?COMA OR ?DOMA OR ?EOMA OR ?FOMA OR ?GOMA OR ?HOMA OR ?IOMA OR ?JOMA OR ?KOMA OR ?LOMA OR ?MOMA OR ?NOMA OR ?OOMA OR ?POMA OR ?QOMA OR ?ROMA OR ?SOMA OR ?TOMA OR ?UOMA OR ?VOMA OR ?WOMA) L59 0 SEA L12 AND (?XOMA OR ?YOMA OR ?ZOMA OR ?AOMAS OR ?BOMAS OR ?COMAS OR ?DOMAS OR ?EOMAS OR ?FOMAS OR ?GOMAS OR ?HOMAS OR ?IOMAS OR ?JOMAS OR ?KOMAS OR ?LOMAS OR ?MOMAS OR ?NOMAS OR ?OOMAS OR ?POMAS OR ?QOMAS OR ?ROMAS) L60 0 SEA L12 AND (?SOMAS OR ?TOMAS OR ?UOMAS OR ?VOMAS OR ?WOMAS OR ?XOMAS OR ?YOMAS OR ?ZOMAS) L61 8 SEA L57 OR L58 L62 8 SEA L61 NOT (L13 OR L52) L63 7 DUP REM L62 (1 DUPLICATE REMOVED)

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	ANSWERS '1-7' FROM FILE TOXCENTER D SCAN L63
2/2017	FILE 'TOXCENTER' ENTERED AT 19:21:56 ON 18 FEB 2015 CHARGED TO COST=EH011.05.01.01 L1 8342 SEA 1071-83-6 L2 63 SEA 34494-03-6 OR 40465-66-5 OR 70393-85-0 L3 8 SEA L2 NOT L1 L4 53 SEA 39600-42-5 OR 39600-55-0 OR 39600-56-1 OR 39600-58-3 OR 40465-59-6 OR 40465-64-3 OR 40465-67-6 OR 40465-70-1 OR 40465-90-5 OR 40465-91-6 L5 59 SEA 70901-12-1 OR 114370-14-8 OR 69254-40-6 L6 1828 SEA 38641-94-0 OR 81591-81-3 L7 8369 SEA L1 OR L2 OR L4 OR L5 L8 5041 SEA L7 NOT (PATENT/DT OR TSCATS/FS) ACT TOXQUERY/Q --------- L9 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L10 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L11 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L12 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L13 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L14 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L15 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L16 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L17 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L18 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L19 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L20 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L21 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L22 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L23 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L24 QUE (ENDOCRIN? AND DISRUPT?) L25 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L26 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	L27 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L28 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L29 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L30 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L31 QUE (NEPHROTOX? OR HEPATOTOX?) L32 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L33 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L34 QUE L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33 L35 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L36 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L37 QUE L34 OR L35 OR L36 L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L39 QUE L37 OR L38 --------- L40 2675 SEA L8 AND L37 L41 525 SEA L40 AND MEDLINE/FS L42 833 SEA L40 AND BIOSIS/FS L43 1263 SEA L40 AND CAPLUS/FS L44 0 SEA L40 AND IPA/FS L45 54 SEA L40 NOT (L41 OR L42 OR L43) L46 2064 DUP REM L41 L42 L43 L45 (611 DUPLICATES REMOVED) ANSWERS '1-2064' FROM FILE TOXCENTER L*** DEL 525 S L40 AND MEDLINE/FS L*** DEL 525 S L40 AND MEDLINE/FS L47 525 SEA L46 L*** DEL 833 S L40 AND BIOSIS/FS L*** DEL 833 S L40 AND BIOSIS/FS L48 644 SEA L46 L*** DEL 1263 S L40 AND CAPLUS/FS L*** DEL 1263 S L40 AND CAPLUS/FS L49 859 SEA L46 L*** DEL 54 S L40 NOT (L41 OR L42 OR L43) L*** DEL 54 S L40 NOT (L41 OR L42 OR L43) L50 36 SEA L46 L51 1539 SEA (L47 OR L48 OR L49 OR L50) NOT MEDLINE/FS L52 1532 SEA L51 AND L1

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	L53 7 SEA L51 NOT L52 D SCAN L53 L54 688 SEA L6 NOT L7 L55 485 SEA L54 NOT (PATENT/DT OR TSCATS/FS) L56 314 SEA L55 AND L37 L57 0 SEA L56 AND MEDLINE/FS L58 85 SEA L56 AND BIOSIS/FS L59 218 SEA L56 AND CAPLUS/FS L60 1 SEA L56 AND IPA/FS L61 274 DUP REM L56 (40 DUPLICATES REMOVED) ANSWERS '1-274' FROM FILE TOXCENTER D SCAN L52

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
9/2017; 2/2015	Compounds searched: 1071-83-6; 34494-03-6; 40465-66-5; 70393-85-0; 38641-94-0; 81591-81-3
NTP	
9/2017	glyphosate AND cancer; Limited to 2010-2017
2/2015	"1071-83-6" OR "Glifoglex" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "Glyphosate" OR "Glyphosphate" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phosphonomethylglycine" OR "Pondmaster" OR "Silglif" OR "yerbimat" "34494-03-6" OR "40465-66-5" OR "70393-85-0" OR "MON 0459" OR "MON 14420" OR "MON 8750" OR "Roundup Hi-Load" OR "Roundup PRODry" OR "MON 8000" OR "Monsanto 8000" OR "Polado" OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate)" "38641-94-0" OR "Glyphosate-isopropylammonium" OR "Glyphosate isopropylamine salt" OR "Azural AT" OR "Buggy" OR "CP 70139" OR "Fosulen" OR "Glifosato estrella" OR "Glycel" OR "Glyfos AU" OR "Glyfos BIO" OR "Glyphosate isopropylamine salt" OR "Glyphosate mono(isopropylamine) salt" OR "Glyphosate-isopropylammonium" OR "Glyphosate-mono(isopropylammonium)" OR "Landmaster" OR "MON 139" OR "MON 39" OR "N-(Phosphonomethyl)glycine isopropylamine salt" OR "N-(Phosphonomethyl)glycine isopropylammonium salt" OR "N-(Phosphonomethyl)glycine monoisopropylamine salt" OR "Nitosorg" OR "Ron-do" OR "Utal" OR "Vision (herbicide)" OR "Roundup" OR "Isopropylamine glyphosate" OR "81591-81-3" OR "Glyphosate-trimesium" OR "Glyphosphate-trimesium" OR "Avans 330" OR "Glyphosate mono(trimethylsulfonium) salt" OR "Glyphosate trimethylsulfonium salt" OR "Glyphosate-trimesium" OR "Medallon" OR "Ouragan" OR "R 50224" OR "SC 0224" OR "Sulfosate" OR "Sulphosate" OR "Touchdown" OR "Trimethylsulfonium carboxymethylamino-methylphosphonate" OR "Trimethylsulfonium glyphosate"
NPIRS 9/2017; 2/2015	PC Codes searched: 417300; 103603; 103613; 103604; 103607; 103601; 128501

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
NIH RePORTER	
4/2017	Text Search: "Carboxymethylamino)methylphosphonic acid" OR "2-Propanamine, compd, with N-(phosphonomethyl)glycine (1:1)" OR "Avans 330" OR "Azural AT" OR "C-K Yuyos FAV" OR "Carboxymethylaminomethanephosphinic acid" OR "CP 67573" OR "CP 70139" OR "Diammonium N-(phosphonomethyl)glycine" OR "Folusen" OR "Forsat" OR "Fosulen" OR "Glialka" OR "Glifoglex" OR "Glifosan 747" OR "Glifosato estrella" OR "gliphosate" OR "Gliz" OR "Glycel" OR "Glycine, N-(phosphonomethyl)-, cmpd with 2-propanamine (1:1)" OR "Glycine, N-(phosphonomethyl)-, compd. with 2-propanamine (1:1)" OR "Glycine, N-(phosphonomethyl)-, ion(1-), trimethylsulfonium" OR "Glyfos" OR "Glyfos AU" OR "Glyfos BIO" OR "GlyGran" OR "Glyphodin A" OR "Glyphomax" OR "Glyphosate" OR "Glyphosphate" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown" OR "Lancer herbicide" OR "Landmaster" OR "Medallon" OR "MON 0459" OR "MON 139" OR "MON 14420" OR "MON 2139" OR "MON 3539" OR "MON 39" OR "MON 6000" OR "MON 8000" OR "MON 8750" OR "Monsanto 8000" OR "N-(phosphonomethyl)-Glycine" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)glycine ammonium salt" OR "N-(phosphonomethyl)glycine diammonium salt" OR "N-(Phosphonomethyl)glycine isopropylamine salt" OR "N-(Phosphonomethyl)glycine isopropylammonium salt" OR "N-(Phosphonomethyl)glycine monoisopropylamine salt" OR "N-(phosphonomethyl)glycine potassium salt" OR "N-(Phosphonomethyl)glycine, compound with 2-propylamine (1:1)" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Nitosorg" OR "Ouragan" OR "Phorsat" OR "Phosphonomethylglycine" OR "Phosphonomethyliminoacetic acid" OR "Polado" OR "Pondmaster" OR "Potassium N-(phosphonomethyl)glycine" OR "R 50224" OR "Rebel Garden" OR "Ron-do" OR "Roundup" OR "Safal" OR "SC 0224" OR "Scout herbicide" OR "Silglif" OR "Sulfosate" OR "Sulphosate" OR "Touchdown Forte HiTech" OR "Touchdown herbicide" OR "Transorb R" OR "Trimethylsulfonium carboxymethylamino-methylphosphonate" OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate" OR "Uragan Forte" OR "Utal" OR "Vision herbicide" OR "VisionMAX" OR "Weathermax" OR "yerbimat" OR "Zapp Qi" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects, 2017, 2016, 2015, 2014, 2013, 2012
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2015 and 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 5,592
- Number of records identified from other strategies: 211
- Total number of records to undergo literature screening: 5,803

Following the publication of the draft profile and receipt of public comments, ATSDR conducted an updated literature review to capture any references published after the conclusion of the original literature review. The updated literature review searches occurred in September and October 2019 using the following sources:

- Toxline
- IPA
- Science Direct
- PubMed
- BIOSIS
- MEDLINE
- SciFinder

In each database, searches were limited to references published from 2017 (i.e., the year the literature searches for glyphosate were last conducted) to the present date. Table B-4 includes the search strings used in each of these searches.

Table B-4. Database Query Strings Post-Public Comment Searches

Database search date	Query String
Toxline 9/2019	("lancer herbicide" OR "mon 2139" OR "mon 3539" OR "mon 6000" OR "phorsat" OR "phosphonomethyliminoacetic acid" OR "rebel garden" OR "roundup max" OR "safal" OR "scout herbicide")
	(" (carboxymethylamino) methylphosphonic acid" OR "carboxymethylaminomethanephosphinic acid" OR "c k yuyos fav" OR "cp 67573" OR "folusen" OR "forsat" OR "glialka" OR "glifosan 747" OR "glygran" OR "glyphodin a" OR "glyphomax" OR "ground bio" OR "herbatop" OR "hm 2028" OR "kickdown")
	("glifoglex" OR "gliphosate" OR "gliz" OR "glyfos" OR "glyphosate" OR "glyphosphate" OR "n (phosphonomethyl) glycine" OR "n (phosphonomethyl) glycine" OR "n phosphomethylglycine" OR "n phosphonomethylglycine" OR "phosphonomethylglycine" OR "pondmaster" OR "silglif" OR "yerbimat")
	1071-83-6 [rn]
	"roundup"
	("mon 0459" OR "40465 66 5" OR "mon 14420" OR "mon 8750" OR "roundup hi load" OR "roundup prodry" OR "mon 8000" OR "monsanto 8000" OR "polado" OR "trisodium hydrogen bis (n (phosphonatomethyl) aminoacetate) ")
	(34494-03-6 [rn] OR 70393-85-0 [rn])
	("glyphosate diammonium" OR "diammonium n (phosphonomethyl) glycine" OR "n (phosphonomethyl) glycine diammonium salt")
	(roundup weathermax OR touchdown forte hitech OR transorb r OR weathermax OR zapp qi OR glyphosate potassium OR potassium glyphosate OR potassium n (phosphonomethyl) glycine OR uragan forte OR visionmax OR n (phosphonomethyl) glycine potassium salt OR glyphosate ammonium OR n (phosphonomethyl) glycine ammonium salt)
	("glyphosate potassium" OR "glyphosate monopotassium salt" OR "glyphosate potassium" OR "glyphosate potassium" OR "monopotassium glyphosate" OR "roundup attack" OR "roundup energy" OR "roundup maxload" OR "roundup original max" OR "roundup power max" OR "roundup ultramax ii")
	(39600-42-5 [rn] OR 39600-55-0 [rn] OR 39600-56-1 [rn] OR 39600-58-3 [rn] OR 40465-59-6 [rn] OR 40465-64-3 [rn] OR 40465-67-6 [rn] OR 40465-70-1 [rn] OR 40465-90-5 [rn] OR 40465-91-6 [rn] OR 70901-12-1 [rn] OR 114370-14-8 [rn] OR 69254-40-6 [rn])
IPA 9/2019	("1071-83-6" or "38641-94-0").rn. and ("Glyphosate" or "glyphosate isopropylamine" or "Glyphosphate" or "N-(phosphonomethyl)glycine " or "glycine, N-(phosphonomethyl)-, compound with 2-propanamine (1:1)" or "phosphonomethyliminoacetic acid" or "glyphosate acid" or "glyphosate-isopropylammonium" or "glyphosate mono(isopropylamine) salt" or "glyphosate-mono(isopropylammonium)" or "N-(phosphonomethyl)glycine, isopropylamine salt" or "Pondmaster" or "Roundup Max" or "Glifoglex" or "Glycel" or "Rondo" or "Spasor" or "Tumbleweed" or "MON-0573" or "CP 67573" or "Roundup" or "Glifonox" or "MON-0139" or "CP 70139").rw. and ("Glyphosate" or "glyphosate isopropylamine").sh.

Table B-4. Database Query Strings Post-Public Comment Searches	
Database search date	Query String
Science Direct 9/2019	Glyphosate OR Glyphosphate OR "N phosphonomethyl glycine" OR "phosphonomethyliminoacetic acid" OR "glyphosate acid"
	"Glyphosate isopropylamine" OR "Glycine, N-phosphonomethyl-, compound with 2-propanamine 1:1" OR "glyphosate-isopropylammonium" OR "glyphosate monoisopropylamine salt" OR "glyphosate-monoisopropylammonium" OR "N phosphonomethyl)glycine, isopropylamine salt"
	"Pondmaster" OR "Roundup Max" OR Glifoglex OR Glycel OR Rondo OR Spasor OR Tumbleweed OR "MON-0573" OR "CP 67573"
	Roundup OR Rondo OR Glifonox OR Glycel OR "MON-0139" OR "CP 70139"
	(Sonic AND Herbicide NOT Ultrasonic) OR (Rodeo and Herbicide)
PubMed 9/2019	("glyphosate"[nm] OR "1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw] OR "Roundup"[tw] OR "34494-03-6"[tw] OR "MON 0459"[tw] OR "40465-66-5"[tw] OR "MON 14420"[tw] OR "MON 8750"[tw] OR "Roundup Hi-Load"[tw] OR "Roundup PRODry"[tw] OR "70393-85-0"[tw] OR "MON 8000"[tw] OR "Monsanto 8000"[tw] OR "Polado"[tw] OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate"[tw] OR "39600-42-5"[tw] OR "Glyphosate potassium"[tw] OR "Glyphosate monopotassium salt"[tw] OR "Glyphosate potassium"[tw] OR "Glyphosate-potassium"[tw] OR "Monopotassium glyphosate"[tw] OR "Roundup Attack"[tw] OR "Roundup Energy"[tw] OR "Roundup Maxload"[tw] OR "Roundup Original Max"[tw] OR "Roundup Power Max"[tw] OR "Roundup Ultramax II"[tw] OR "Roundup Weathermax"[tw] OR "Touchdown Forte HiTech"[tw] OR "Transorb R"[tw] OR "Weathermax"[tw] OR "Zapp Qi"[tw] OR "70901-12-1"[tw] OR "Glyphosate-potassium"[tw] OR "Potassium glyphosate"[tw] OR "Potassium N-(phosphonomethyl)glycine"[tw] OR "Uragan Forte"[tw] OR "VisionMAX"[tw] OR "N-(phosphonomethyl)glycine potassium salt"[tw] OR "114370-14-8"[tw] OR "Glyphosate ammonium"[tw] OR "N-(phosphonomethyl)glycine ammonium salt"[tw] OR "69254-40-6"[tw] OR "Glyphosate-diammonium"[tw] OR "Diammonium N-(phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)glycine diammonium salt"[tw]) AND (cancer[sb] OR "neoplasms"[mh] OR "carcinogenicity tests"[mh] OR "carcinogens"[mh] OR "cell division/drug effects"[mh] OR "cell cycle/drug effects"[mh] OR "cell line, tumor/drug effects"[mh] OR "gene expression regulation, neoplastic"[mh] OR "neoplasm proteins/drug effects"[mh] OR "angiogenesis inducing agents"[mh] OR "myelodysplastic-myeloproliferative diseases"[mh] OR cancer*[tw] OR carcinog*[tw] OR carcinom*[tw] OR cocarcinog*[tw] OR lymphoma*[tw] OR neoplas*[tw] OR oncogen*[tw] OR precancer*[tw] OR tumor*[tw] OR tumour*[tw]) AND (2017/01/01 : 3000[dp])
	("glyphosate, isopropyl amine salt"[nm] OR "N-(phosphonomethyl)glycine trimethylsulfonium salt"[nm] OR "38641-94-0"[tw] OR "Glyphosate-isopropylammonium"[tw] OR "Glyphosate isopropylamine salt"[tw] OR "Azural AT"[tw] OR "CP 70139"[tw] OR "Fosulen"[tw] OR "Glifosato estrella"[tw] OR "Glycel"[tw] OR "Glycine, N-(phosphonomethyl)-, cmpd with 2-propanamine (1:1)"[tw] OR "Glyfos AU"[tw] OR "Glyfos BIO"[tw] OR "Glyphosate isopropylamine salt"[tw] OR "Glyphosate mono(isopropylamine) salt"[tw] OR "Glyphosate-isopropylammonium"[tw] OR "Glyphosate-mono(isopropylammonium)"[tw] OR "Landmaster"[tw] OR "MON 139"[tw] OR "MON 39"[tw] OR "N-(Phosphonomethyl)glycine

Table B-4. Database Query Strings Post-Public Comment Searches	
Database search date	Query String
	isopropylamine salt"[tw] OR "N-(Phosphonomethyl)glycine isopropylammonium salt"[tw] OR "N-(Phosphonomethyl)glycine monoisopropylamine salt"[tw] OR "Nitosorg"[tw] OR "Rondo"[tw] OR "Utal"[tw] OR "Utal (herbicide)"[tw] OR "Vision (herbicide)"[tw] OR "2-Propanamine, compd, with N-(phosphonomethyl)glycine (1:1)"[tw] OR "Glycine, N-(phosphonomethyl)-, compd. with 2-propanamine (1:1)"[tw] OR "N-(Phosphonomethyl)glycine, compound with 2-propylamine (1:1)"[tw] OR "Isopropylamine glyphosate"[tw] OR "81591-81-3"[tw] OR "Glyphosate-trimesium"[tw] OR "Glyphosphate-trimesium"[tw] OR "Avans 330"[tw] OR "Glyphosate mono(trimethylsulfonium) salt"[tw] OR "Glyphosate trimethylsulfonium salt"[tw] OR "Glyphosate-trimesium"[tw] OR "Medallon"[tw] OR "Ouragan"[tw] OR "R 50224"[tw] OR "SC 0224"[tw] OR "Sulfosate"[tw] OR "Sulphosate"[tw] OR "Touchdown herbicide"[tw] OR "Trimethylsulfonium carboxymethylamino-methylphosphonate"[tw] OR "Trimethylsulfonium glyphosate"[tw] OR "Glycine, N-(phosphonomethyl)-, ion(1-), trimethylsulfonium"[tw] OR "Sulfosate"[tw]) AND (cancer[sb] OR "neoplasms"[mh] OR "carcinogenicity tests"[mh] OR "carcinogens"[mh] OR "cell division/drug effects"[mh] OR "cell cycle/drug effects"[mh] OR "cell line, tumor/drug effects"[mh] OR "gene expression regulation, neoplastic"[mh] OR "neoplasm proteins/drug effects"[mh] OR "angiogenesis inducing agents"[mh] OR "myelodysplastic-myeloproliferative diseases"[mh] OR cancer*[tw] OR carcinog*[tw] OR carcinom*[tw] OR cocarcinog*[tw] OR lymphoma*[tw] OR neoplas*[tw] OR oncogen*[tw] OR precancer*[tw] OR tumor*[tw] OR tumour*[tw]) AND (2017/01/01 : 3000[dp])
	("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR

Table B-4. Database Query Strings Post-Public Comment Searches	
Database search date	Query String
	"N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb]) AND (2017/01/01 : 3000[dp])
	("Roundup"[tw] AND (monsanto[tw] OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR "antifungal"[tw] OR "anti-fungal"[tw] OR "enzyme inhibitors"[Pharmacological Action] OR "enzyme inhibitors"[MeSH Terms] OR ("enzyme"[tw] AND inhibitor*[tw]) OR "enzyme inhibitors"[tw] OR "enzyme inhibitor"[tw] OR "herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[tw] OR "herbicide"[tw] OR "uncoupling agents"[Pharmacological Action] OR "uncoupling agents"[MeSH Terms] OR ("uncoupling"[tw] AND agent*[tw]) OR "uncoupling agent"[tw] OR "uncoupling agents"[tw] OR "pesticides"[mh] OR pesticide*[tw])) NOT (("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb])) AND (2017/01/01 : 3000[dp])

Table B-4. Database Query Strings Post-Public Comment Searches	
Database search date	Query String
	("34494-03-6"[tw] OR "MON 0459"[tw] OR "40465-66-5"[tw] OR "MON 14420"[tw] OR "MON 8750"[tw] OR "Roundup Hi-Load"[tw] OR "Roundup PRODry"[tw] OR "70393-85-0"[tw] OR "MON 8000"[tw] OR "Monsanto 8000"[tw] OR "Polado"[tw] OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr]) AND (2017/01/01 : 3000[dp])
	("39600-42-5"[tw] OR "Glyphosate potassium"[tw] OR "Glyphosate monopotassium salt"[tw] OR "Glyphosate potassium"[tw] OR "Glyphosate-potassium"[tw] OR "Monopotassium glyphosate"[tw] OR "Roundup Attack"[tw] OR "Roundup Energy"[tw] OR "Roundup Maxload"[tw] OR "Roundup Original Max"[tw] OR "Roundup Power Max"[tw] OR "Roundup Ultramax II"[tw] OR "Roundup Weathermax"[tw] OR "Touchdown Forte HiTech"[tw] OR "Transorb R"[tw] OR "Weathermax"[tw] OR "Zapp Qi"[tw] OR "70901-12-1"[tw] OR "Glyphosate-potassium"[tw] OR "Potassium glyphosate"[tw] OR "Potassium N-(phosphonomethyl)glycine"[tw] OR "Uragan Forte"[tw] OR "VisionMAX"[tw] OR "N-(phosphonomethyl)glycine potassium salt"[tw] OR "114370-14-8"[tw] OR "Glyphosate ammonium"[tw] OR "N-(phosphonomethyl)glycine ammonium salt"[tw] OR "69254-40-6"[tw] OR "Glyphosate-diammonium"[tw] OR "Diammonium N-(phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)glycine diammonium salt"[tw]) NOT (("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh]

Table B-4. Database Query Strings Post-Public Comment Searches

Database search date	Query String
	OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb]) OR ("Roundup"[tw] AND (monsanto[tw] OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR "antifungal"[tw] OR "anti-fungal"[tw] OR "enzyme inhibitors"[Pharmacological Action] OR "enzyme inhibitors"[MeSH Terms] OR ("enzyme"[tw] AND inhibitor*[tw]) OR "enzyme inhibitors"[tw] OR "enzyme inhibitor"[tw] OR "herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[tw] OR "herbicide"[tw] OR "uncoupling agents"[Pharmacological Action] OR "uncoupling agents"[MeSH Terms] OR ("uncoupling"[tw] AND agent*[tw]) OR "uncoupling agent"[tw] OR "uncoupling agents"[tw] OR "pesticides"[mh] OR pesticide*[tw]))) AND (2017/01/01 : 3000[dp])
	((("glyphosate, isopropyl amine salt"[nm]) OR ("N-(phosphonomethyl)glycine trimethylsulfonium salt"[nm])) NOT (("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic

Table B-4. Database Query Strings Post-Public Comment Searches

Database search date	Query String
	acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb]) OR ("Roundup"[tw] AND (monsanto[tw] OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR "antifungal"[tw] OR "anti-fungal"[tw] OR "enzyme inhibitors"[Pharmacological Action] OR "enzyme inhibitors"[MeSH Terms] OR ("enzyme"[tw] AND inhibitor*[tw]) OR "enzyme inhibitors"[tw] OR "enzyme inhibitor"[tw] OR "herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[tw] OR "herbicide"[tw] OR "uncoupling agents"[Pharmacological Action] OR "uncoupling agents"[MeSH Terms] OR ("uncoupling"[tw] AND agent*[tw]) OR "uncoupling agent"[tw] OR "uncoupling agents"[tw] OR "pesticides"[mh] OR pesticide*[tw])))) OR (("38641-94-0"[tw] OR "Glyphosate-isopropylammonium"[tw] OR "Glyphosate isopropylamine salt"[tw] OR "Azural AT"[tw] OR "CP 70139"[tw] OR "Fosulen"[tw] OR "Glifosato estrella"[tw] OR "Glycel"[tw] OR "Glycine, N-(phosphonomethyl)-, cmpd with 2-propanamine (1:1)"[tw] OR "Glyfos AU"[tw] OR "Glyfos BIO"[tw] OR "Glyphosate isopropylamine salt"[tw] OR "Glyphosate mono(isopropylamine) salt"[tw] OR "Glyphosate-isopropylammonium"[tw] OR "Glyphosate-mono(isopropylammonium)"[tw] OR "Landmaster"[tw] OR "MON 139"[tw] OR "MON 39"[tw] OR "N-(Phosphonomethyl)glycine isopropylamine salt"[tw] OR "N-(Phosphonomethyl)glycine isopropylammonium salt"[tw] OR "N-(Phosphonomethyl)glycine monoisopropylamine salt"[tw] OR "Nitosorg"[tw] OR "Ron-do"[tw] OR "Utal"[tw] OR "Utal (herbicide)"[tw] OR "Vision (herbicide)"[tw] OR "2-Propanamine, compd, with N-(phosphonomethyl)glycine (1:1)"[tw] OR "Glycine, N-(phosphonomethyl)-, compd. with 2-propanamine (1:1)"[tw] OR "N-(Phosphonomethyl)glycine, compound with 2-propylamine (1:1)"[tw] OR "Isopropylamine glyphosate"[tw] OR "81591-81-3"[tw] OR "Glyphosate-trimesium"[tw] OR "Glyphosphate-trimesium"[tw] OR "Avans 330"[tw] OR "Glyphosate mono(trimethylsulfonium) salt"[tw] OR "Glyphosate trimethylsulfonium salt"[tw] OR "Glyphosate-trimesium"[tw] OR "Medallon"[tw] OR "Ouragan"[tw] OR "R 50224"[tw] OR "SC 0224"[tw] OR "Sulfosate"[tw] OR "Sulphosate"[tw] OR "Touchdown herbicide"[tw] OR "Trimethylsulfonium carboxymethylamino-methylphosphonate"[tw] OR "Trimethylsulfonium glyphosate"[tw] OR "Glycine, N-(phosphonomethyl)-, ion(1-), trimethylsulfonium"[tw] OR "Sulfosate"[tw]) NOT (("glyphosate"[nm]) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone

Table B-4. Database Query Strings Post-Public Comment Searches	
Database search date	Query String
	antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR cancer[sb] OR "pharmacology"[Majr])) OR (("1071-83-6"[tw] OR "(Carboxymethylamino)methylphosphonic acid"[tw] OR "Carboxymethylaminomethanephosphinic acid"[tw] OR "C-K Yuyos FAV"[tw] OR "CP 67573"[tw] OR "Folusen"[tw] OR "Forsat"[tw] OR "Glialka"[tw] OR "Glifoglex"[tw] OR "Glifosan 747"[tw] OR "gliphosate"[tw] OR "Gliz"[tw] OR "Glyfos"[tw] OR "GlyGran"[tw] OR "Glyphodin A"[tw] OR "Glyphomax"[tw] OR "Glyphosate"[tw] OR "Glyphosphate"[tw] OR "Ground Bio"[tw] OR "Herbatop"[tw] OR "HM 2028"[tw] OR "Kickdown"[tw] OR "Lancer herbicide"[tw] OR "MON 2139"[tw] OR "MON 3539"[tw] OR "MON 6000"[tw] OR "N-(Phosphonomethyl)glycine"[tw] OR "N-(phosphonomethyl)-Glycine"[tw] OR "N-Phosphomethylglycine"[tw] OR "N-Phosphonomethylglycine"[tw] OR "Phorsat"[tw] OR "Phosphonomethylglycine"[tw] OR "Phosphonomethyliminoacetic acid"[tw] OR "Pondmaster"[tw] OR "Rebel Garden"[tw] OR "Roundup Max"[tw] OR "Safal"[tw] OR "Scout herbicide"[tw] OR "Silglif"[tw] OR "yerbimat"[tw]) NOT medline[sb]) OR ("Roundup"[tw] AND (monsanto[tw] OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[MeSH Terms] OR "antifungal"[tw] OR "anti-fungal"[tw] OR "enzyme inhibitors"[Pharmacological Action] OR "enzyme inhibitors"[MeSH Terms] OR ("enzyme"[tw] AND inhibitor*[tw]) OR "enzyme inhibitors"[tw] OR "enzyme inhibitor"[tw] OR "herbicides"[Pharmacological Action] OR "herbicides"[MeSH Terms] OR "herbicides"[tw] OR "herbicide"[tw] OR "uncoupling agents"[Pharmacological Action] OR "uncoupling agents"[MeSH Terms] OR ("uncoupling"[tw] AND agent*[tw]) OR "uncoupling agent"[tw] OR "uncoupling agents"[tw] OR "pesticides"[mh] OR pesticide*[tw]))))) AND (2017/01/01 : 3000[dp])
BIOSIS 9/2019	CH=(Glyphosate OR "glyphosate isopropylamine" OR Glyphosphate OR "N-(phosphonomethyl)glycine " OR "glycine, N-(phosphonomethyl)-, compound with 2-propanamine (1:1)" OR "phosphonomethyliminoacetic acid" OR "glyphosate acid" OR "glyphosate-isopropylammonium" OR "glyphosate mono(isopropylamine) salt" OR "glyphosate-mono(isopropylammonium)" OR "N-(phosphonomethyl)glycine, isopropylamine salt" OR Pondmaster OR "Roundup Max" OR Glifoglex OR Glycel OR ((Muster) AND (pesticide OR herbicide)) OR Rondo OR ((Sonic) AND (pesticide OR herbicide)) OR Spasor OR ((Sting) AND (pesticide OR herbicide)) OR Tumbleweed OR "MON-0573" OR "CP 67573" OR Roundup OR ((Rodeo) AND (pesticide OR herbicide)) OR Glifonox OR "MON-0139" OR "CP 70139" OR ((Shackle) AND (pesticide OR herbicide)) OR "1071-83-6" OR "38641-94-0") Indexes=BCI Timespan=2017-2019
MEDLINE 9/2019	("glyphosate" OR "1071-83-6" OR "(Carboxymethylamino)methylphosphonic acid" OR "Carboxymethylaminomethanephosphinic acid" OR "C-K Yuyos FAV" OR "CP 67573" OR "Folusen" OR "Forsat" OR "Glialka" OR "Glifoglex" OR "Glifosan 747" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "GlyGran" OR "Glyphodin A" OR "Glyphomax" OR "Glyphosate" OR "Glyphosphate" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown" OR "Lancer herbicide" OR "MON 2139" OR "MON 3539" OR "MON 6000" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phorsat" OR "Phosphonomethylglycine" OR "Phosphonomethyliminoacetic acid" OR "Pondmaster" OR "Rebel Garden" OR "Roundup Max" OR "Safal" OR "Scout herbicide" OR "Silglif" OR

Table B-4. Database Query Strings Post-Public Comment Searches	
Database search date	Query String
	"yerbimat" OR "Roundup" OR "34494-03-6" OR "MON 0459" OR "40465-66-5" OR "MON 14420" OR "MON 8750" OR "Roundup Hi-Load" OR "Roundup PRODry" OR "70393-85-0" OR "MON 8000" OR "Monsanto 8000" OR "Polado" OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate" OR "39600-42-5" OR "Glyphosate potassium" OR "Glyphosate monopotassium salt" OR "Glyphosate potassium" OR "Glyphosate-potassium" OR "Monopotassium glyphosate" OR "Roundup Attack" OR "Roundup Energy" OR "Roundup Maxload" OR "Roundup Original Max" OR "Roundup Power Max" OR "Roundup Ultramax II" OR "Roundup Weathermax" OR "Touchdown Forte HiTech" OR "Transorb R" OR "Weathermax" OR "Zapp Qi" OR "70901-12-1" OR "Glyphosate-potassium" OR "Potassium glyphosate" OR "Potassium N-(phosphonomethyl)glycine" OR "Uragan Forte" OR "VisionMAX" OR "N-(phosphonomethyl)glycine potassium salt" OR "114370-14-8" OR "Glyphosate ammonium" OR "N-(phosphonomethyl)glycine ammonium salt" OR "69254-40-6" OR "Glyphosate-diammonium" OR "Diammonium N-(phosphonomethyl)glycine" OR "N-(phosphonomethyl)glycine diammonium salt") AND MH (("neoplasms" OR "carcinogenicity tests" OR "carcinogens" OR "cell division/drug effects" OR "cell cycle/drug effects" OR "cell line, tumor/drug effects" OR "gene expression regulation, neoplastic" OR "neoplasm proteins/drug effects" OR "angiogenesis inducing agents" OR "myelodysplastic-myeloproliferative diseases") OR AB (cancer* OR carcinog* OR carcinom* OR cocarcinog* OR lymphoma* OR neoplas* OR oncogen* OR precancer* OR tumor* OR tumour*))
	("glyphosate, isopropyl amine salt" OR "N-(phosphonomethyl)glycine trimethylsulfonium salt" OR "38641-94-0" OR "Glyphosate-isopropylammonium" OR "Glyphosate isopropylamine salt" OR "Azural AT" OR "CP 70139" OR "Fosulen" OR "Glifosato estrella" OR "Glycel" OR "Glycine, N-(phosphonomethyl)-, cmpd with 2-propanamine (1:1)" OR "Glyfos AU" OR "Glyfos BIO" OR "Glyphosate isopropylamine salt" OR "Glyphosate mono(isopropylamine) salt" OR "Glyphosate-isopropylammonium" OR "Glyphosate-mono(isopropylammonium)" OR "Landmaster" OR "MON 139" OR "MON 39" OR "N-(Phosphonomethyl)glycine isopropylamine salt" OR "N-(Phosphonomethyl)glycine isopropylammonium salt" OR "N-(Phosphonomethyl)glycine monoisopropylamine salt" OR "Nitosorg" OR "Ron-do" OR "Utal" OR "Utal (herbicide)" OR "Vision (herbicide)" OR "2-Propanamine, compd, with N-(phosphonomethyl)glycine (1:1)" OR "Glycine, N-(phosphonomethyl)-, compd. with 2-propanamine (1:1)" OR "N-(Phosphonomethyl)glycine, compound with 2-propylamine (1:1)" OR "Isopropylamine glyphosate" OR "81591-81-3" OR "Glyphosate-trimesium" OR "Glyphosphate-trimesium" OR "Avans 330" OR "Glyphosate mono(trimethylsulfonium) salt" OR "Glyphosate trimethylsulfonium salt" OR "Glyphosate-trimesium" OR "Medallon" OR "Ouragan" OR "R 50224" OR "SC 0224" OR "Sulfosate" OR "Sulphosate" OR "Touchdown herbicide" OR "Trimethylsulfonium carboxymethylamino-methylphosphonate" OR "Trimethylsulfonium glyphosate" OR "Glycine, N-(phosphonomethyl)-, ion(1-), trimethylsulfonium" OR "Sulfosate") AND (MH ("neoplasms" OR "carcinogenicity tests" OR "carcinogens" OR "cell division/drug effects" OR "cell cycle/drug effects" OR "cell line, tumor/drug effects" OR "gene expression regulation, neoplastic" OR "neoplasm proteins/drug effects" OR "angiogenesis inducing agents" OR "myelodysplastic-myeloproliferative diseases") OR AB(cancer* OR carcinog* OR carcinom* OR cocarcinog* OR lymphoma* OR neoplas* OR oncogen* OR precancer* OR tumor* OR tumour*))
	AB ("glyphosate" OR "1071-83-6" OR "(Carboxymethylamino)methylphosphonic acid" OR "Carboxymethylaminomethanephosphinic acid" OR "C-K Yuyos FAV" OR "CP 67573" OR "Folusen" OR "Forsat" OR "Glialka" OR "Glifoglex" OR "Glifosan 747" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "GlyGran" OR "Glyphodin A" OR "Glyphomax" OR "Glyphosate" OR "Glyphosphate" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown" OR "Lancer herbicide" OR "MON 2139" OR "MON 3539" OR "MON 6000" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phorsat" OR "Phosphonomethylglycine" OR "Phosphonomethyliminoacetic acid" OR "Pondmaster" OR

Table B-4. Database Query Strings Post-Public Comment Searches

Database search date	Query String
	"Rebel Garden" OR "Roundup Max" OR "Safal" OR "Scout herbicide" OR "Silglif" OR "yerbimat") AND (MH ("humans" OR "animals" OR "environmental exposure" OR "endocrine system" OR "hormones, hormone substitutes, and hormone antagonists" OR "endocrine disruptors" OR "Computational biology" OR "Medical Informatics" OR Genomics OR Genome OR Proteomics OR Proteome OR Metabolomics OR Metabolome OR Genes OR "Gene expression" OR Phenotype OR genetics OR genotype OR Transcriptome OR "Systems Biology") OR AB ("toxicity" OR "poisoning" OR "adverse effects" OR "pharmacokinetics" OR "metabolism" OR "chemically induced" OR "blood" OR "cerebrospinal fluid" OR "urine")) AND MH (("Environmental Exposure" OR "Epidemiological Monitoring" OR "Transcription, Genetic " OR "Reverse transcription" OR "Transcriptional activation" OR "Transcription factors") OR AB (Analysis OR Biosynthesis)) AND MH ((RNA OR DNA OR "RNA, Messenger" OR "RNA, Transfer" OR "peptide biosynthesis" OR "protein biosynthesis" OR "Reverse Transcriptase Polymerase Chain Reaction" OR "Base Sequence" OR "Trans-activators" OR "Gene Expression Profiling" OR "pharmacology") OR AB (cancer OR "1071-83-6" OR "Carboxymethylamino)methylphosphonic acid" OR "Carboxymethylaminomethanephosphinic acid" OR "C-K Yuyos FAV" OR "CP 67573" OR "Folusen" OR "Forsat" OR "Glialka" OR "Glifoglex" OR "Glifosan 747" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "GlyGran" OR "Glyphodin A" OR "Glyphomax" OR "Glyphosate" OR "Glyphosphate" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown" OR "Lancer herbicide" OR "MON 2139" OR "MON 3539" OR "MON 6000" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phorsat" OR "Phosphonomethylglycine" OR "Phosphonomethyliminoacetic acid" OR "Pondmaster" OR "Rebel Garden" OR "Roundup Max" OR "Safal" OR "Scout herbicide" OR "Silglif" OR "yerbimat"))
	AB ("Roundup") AND (AB ((monsanto OR "antifungal agents" OR "antifungal" OR "anti-fungal" OR ("enzyme" AND inhibitor*) OR "enzyme inhibitors" OR "enzyme inhibitor" OR "herbicides" OR "herbicide" OR ("uncoupling" AND agent*) OR "uncoupling agent" OR "uncoupling agents" OR pesticide*) OR MH ("antifungal agents" OR "enzyme inhibitors" OR herbicides OR "uncoupling agents" OR pesticides)) (NOT (("glyphosate" OR "1071-83-6" OR "(Carboxymethylamino)methylphosphonic acid" OR "Carboxymethylaminomethanephosphinic acid" OR "C-K Yuyos FAV" OR "CP 67573" OR "Folusen" OR "Forsat" OR "Glialka" OR "Glifoglex" OR "Glifosan 747" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "GlyGran" OR "Glyphodin A" OR "Glyphomax" OR "Glyphosate" OR "Glyphosphate" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown" OR "Lancer herbicide" OR "MON 2139" OR "MON 3539" OR "MON 6000" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phorsat" OR "Phosphonomethylglycine" OR "Phosphonomethyliminoacetic acid" OR "Pondmaster" OR "Rebel Garden" OR "Roundup Max" OR "Safal" OR "Scout herbicide" OR "Silglif" OR "yerbimat")) AND AB ("toxicity" OR "poisoning" OR "adverse effects" OR "pharmacokinetics" OR "metabolism") AND (MH ("humans" OR "animals" OR "environmental exposure" OR "endocrine system" OR "hormones, hormone substitutes, and hormone antagonists" OR "endocrine disruptors" OR (("Computational biology" OR "Medical Informatics" OR Genomics OR Genome OR Proteomics OR Proteome OR Metabolomics OR Metabolome OR Genes OR "Gene expression" OR Phenotype OR genetics OR genotype OR Transcriptome OR "Transcription, Genetic " OR "Reverse transcription" OR "Transcriptional activation" OR "Transcription factors" OR "RNA, Messenger" OR "RNA, Transfer" OR "protein biosynthesis" OR "Reverse Transcriptase Polymerase Chain Reaction" OR "Base Sequence" OR "Trans-activators" OR "Gene Expression Profiling" OR "pharmacology") OR AB ("chemically induced" OR "blood" OR "cerebrospinal fluid" OR "urine" OR cancer OR "1071-83-6" OR "(Carboxymethylamino)methylphosphonic acid" OR

Table B-4. Database Query Strings Post-Public Comment Searches	
Database search date	Query String
	"Carboxymethylaminomethanephosphinic acid" OR "C-K Yuyos FAV" OR "CP 67573" OR "Folusen" OR "Forsat" OR "Glialka" OR "Glifoglex" OR "Glifosan 747" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "GlyGran" OR "Glyphodin A" OR "Glyphomax" OR "Glyphosate" OR "Glyphosphate" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown" OR "Lancer herbicide" OR "MON 2139" OR "MON 3539" OR "MON 6000" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phorsat" OR "Phosphonomethylglycine" OR "Phosphonomethyliminoacetic acid" OR "Pondmaster" OR "Rebel Garden" OR "Roundup Max" OR "Safal" OR "Scout herbicide" OR "Silglif" OR "yerbimat" OR "peptide biosynthesis") OR (AB("biosynthesis") AND MH(RNA OR DNA)) OR MH ("Systems Biology" AND ("Environmental Exposure" OR "Epidemiological Monitoring"))
	AB ("34494-03-6" OR "MON 0459" OR "40465-66-5" OR "MON 14420" OR "MON 8750" OR "Roundup Hi-Load" OR "Roundup PRODry" OR "70393-85-0" OR "MON 8000" OR "Monsanto 8000" OR "Polado" OR "Trisodium hydrogen bis(N-(phosphonatomethyl)aminoacetate") AND AB ("toxicity" OR "poisoning" OR "adverse effects" OR "pharmacokinetics" OR "metabolism") AND (AB ("chemically induced" OR "blood" OR "cerebrospinal fluid" OR "urine") OR MH ("humans" OR "animals" OR "environmental exposure" OR "endocrine system" OR "hormones, hormone substitutes, and hormone antagonists" OR "endocrine disruptors" OR "Computational biology" OR "Medical Informatics" OR Genomics OR Genome OR Proteomics OR Proteome OR Metabolomics OR Metabolome OR Genes OR "Gene expression" OR Phenotype OR genetics OR genotype OR Transcriptome OR "Systems Biology")) AND MH (("Environmental Exposure" OR "Epidemiological Monitoring" OR analysis)) OR "Transcription, Genetic " OR "Reverse transcription" OR "Transcriptional activation" OR "Transcription factors" OR ("biosynthesis" AND (RNA OR DNA)) OR "RNA, Messenger" OR "RNA, Transfer" OR "peptide biosynthesis" OR "protein biosynthesis" OR "Reverse Transcriptase Polymerase Chain Reaction" OR "Base Sequence" OR "Trans-activators" OR "Gene Expression Profiling" OR "pharmacology") OR AB (cancer))
	("39600-42-5" OR "Glyphosate potassium" OR "Glyphosate monopotassium salt" OR "Glyphosate potassium" OR "Glyphosate-potassium" OR "Monopotassium glyphosate" OR "Roundup Attack" OR "Roundup Energy" OR "Roundup Maxload" OR "Roundup Original Max" OR "Roundup Power Max" OR "Roundup Ultramax II" OR "Roundup Weathermax" OR "Touchdown Forte HiTech" OR "Transorb R" OR "Weathermax" OR "Zapp Qi" OR "70901-12-1" OR "Glyphosate-potassium" OR "Potassium glyphosate" OR "Potassium N-(phosphonomethyl)glycine" OR "Uragan Forte" OR "VisionMAX" OR "N-(phosphonomethyl)glycine potassium salt" OR "114370-14-8" OR "Glyphosate ammonium" OR "N-(phosphonomethyl)glycine ammonium salt" OR "69254-40-6" OR "Glyphosate-diammonium" OR "Diammonium N-(phosphonomethyl)glycine" OR "N-(phosphonomethyl)glycine diammonium salt") NOT (("glyphosate") OR (("1071-83-6" OR "(Carboxymethylamino)methylphosphonic acid" OR "Carboxymethylaminomethanephosphinic acid" OR "C-K Yuyos FAV" OR "CP 67573" OR "Folusen" OR "Forsat" OR "Glialka" OR "Glifoglex" OR "Glifosan 747" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "GlyGran" OR "Glyphodin A" OR "Glyphomax" OR "Glyphosate" OR "Glyphosphate" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown" OR "Lancer herbicide" OR "MON 2139" OR "MON 3539" OR "MON 6000" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phorsat" OR "Phosphonomethylglycine" OR "Phosphonomethyliminoacetic acid" OR "Pondmaster" OR "Rebel Garden" OR "Roundup Max" OR "Safal" OR "Scout herbicide" OR "Silglif" OR "yerbimat") AND AB ("toxicity" OR "poisoning" OR "adverse effects" OR "pharmacokinetics" OR "metabolism") AND MH (("humans" OR "animals" OR "environmental exposure" OR

Table B-4. Database Query Strings Post-Public Comment Searches	
Database search date	Query String
	"endocrine system" OR "hormones, hormone substitutes, and hormone antagonists" OR "endocrine disruptors" OR (("Computational biology" OR "Medical Informatics" OR Genomics OR Genome OR Proteomics OR Proteome OR Metabolomics OR Metabolome OR Genes OR "Gene expression" OR Phenotype OR genetics OR genotype OR Transcriptome OR ("Systems Biology" OR (AB ("chemically induced" OR "blood" OR "cerebrospinal fluid" OR "urine")) AND MH("Environmental Exposure" OR "Epidemiological Monitoring" OR analysis)) OR "Transcription, Genetic " OR "Reverse transcription" OR "Transcriptional activation" OR "Transcription factors") OR AB ("biosynthesis")) AND (RNA OR DNA OR "RNA, Messenger" OR "RNA, Transfer" OR "peptide biosynthesis" OR "protein biosynthesis" OR "Reverse Transcriptase Polymerase Chain Reaction" OR "Base Sequence" OR "Trans-activators" OR "Gene Expression Profiling" OR "pharmacology" OR "antifungal agents"[Pharmacological Action] OR "antifungal agents"[Terms] OR "antifungal" OR "anti-fungal" OR "enzyme inhibitors" OR AB (cancer OR "1071-83-6" OR "(Carboxymethylamino)methylphosphonic acid" OR "Carboxymethylaminomethanephosphinic acid" OR "C-K Yuyos FAV" OR "CP 67573" OR "Folusen" OR "Forsat" OR "Glialka" OR "Glifoglex" OR "Glifosan 747" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "GlyGran" OR "Glyphodin A" OR "Glyphomax" OR "Glyphosate" OR "Glyphosphate" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown" OR "Lancer herbicide" OR "MON 2139" OR "MON 3539" OR "MON 6000" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phorsat" OR "Phosphonomethylglycine" OR "Phosphonomethyliminoacetic acid" OR "Pondmaster" OR "Rebel Garden" OR "Roundup Max" OR "Safal" OR "Scout herbicide" OR "Silglif" OR "yerbimat" OR "Roundup") AND AB (monsanto OR "enzyme") AND AB ((inhibitor* OR "enzyme inhibitors" OR "enzyme inhibitor" OR "herbicides" OR "herbicide" OR "uncoupling agents" OR "uncoupling") OR MH (herbicides OR "uncoupling agents")) AND AB (agent* OR "uncoupling agent" OR "uncoupling agents" OR Pesticide*) OR MH (Pesticides)
	(TX ("glyphosate, isopropyl amine salt" OR "N-(phosphonomethyl)glycine trimethylsulfonium salt")) NOT TX ("glyphosate") OR (TX ("1071-83-6"OR "(Carboxymethylamino)methylphosphonic acid" OR "Carboxymethylaminomethanephosphinic acid"OR "C-K Yuyos FAV" OR "CP 67573" OR "Folusen" OR "Forsat" OR "Glialka" OR "Glifoglex" OR "Glifosan 747" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "GlyGran" OR "Glyphodin A" OR "Glyphomax" OR "Glyphosate" OR "Glyphosphate" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown" OR "Lancer herbicide" OR "MON 2139" "MON 3539" OR "MON 6000" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phorsat" OR "Phosphonomethylglycine" OR "Phosphonomethyliminoacetic acid" OR "Pondmaster" OR "Rebel Garden"OR "Roundup Max" OR "Safal" OR "Scout herbicide" OR "Silglif" OR "yerbimat")) AND (MH ("humans" OR "animals") OR MH ("environmental exposure" OR "endocrine system" OR "hormones, hormone substitutes, and hormone antagonists" OR "endocrine disruptors") OR MH ("Computational biology" OR "Medical Informatics" OR Genomics OR Genome OR Proteomics OR Proteome OR Metabolomics OR Metabolome OR Genes OR "Gene expression" OR Phenotype OR genetics OR genotype OR Transcriptome OR "Transcription, Genetic " OR "Reverse transcription" OR "Transcriptional activation" OR "Transcription factors" OR "RNA, Messenger" OR "RNA, Transfer" OR "peptide biosynthesis" OR "protein biosynthesis" OR "Reverse Transcriptase Polymerase Chain Reaction" OR "Base Sequence" OR "Trans-activators" OR "Gene Expression Profiling") OR MH ("Systems Biology")) AND (MH ("Environmental Exposure" OR "Epidemiological Monitoring") OR MW (analysis) OR MW ("biosynthesis")) AND (MH (RNA OR DNA) OR AB (cancer) OR MM ("pharmacology")) AND (MH ("humans" OR "animals") OR MH ("environmental exposure" OR "endocrine system" OR "hormones, hormone substitutes, and hormone antagonists" OR "endocrine disruptors" OR (("Computational biology" OR "Medical Informatics" OR Genomics

Table B-4. Database Query Strings Post-Public Comment Searches	
Database search date	Query String
	OR Genome OR Proteomics OR Proteome OR Metabolomics OR Metabolome OR Genes OR "Gene expression" OR Phenotype OR genetics OR genotype OR Transcriptome OR ("Systems Biology" AND ("Environmental Exposure" OR "Epidemiological Monitoring") OR MW (analysis) OR MH ("Transcription, Genetic" OR "Reverse transcription" OR "Transcriptional activation" OR "Transcription factors") OR MW ("biosynthesis")) AND (MH ((RNA OR DNA) OR "RNA, Messenger" OR "RNA, Transfer" OR "peptide biosynthesis" OR "protein biosynthesis" OR "Reverse Transcriptase Polymerase Chain Reaction" OR "Base Sequence" OR "Trans-activators" OR "Gene Expression Profiling") OR AB (cancer) OR MM ("pharmacology") OR TX (("1071-83-6" OR "(Carboxymethylamino)methylphosphonic acid" OR "Carboxymethylaminomethanephosphinic acid" OR "C-K Yuyos FAV" OR "CP 67573" OR "Folusen" OR "Forsat" OR "Glialka" OR "Glifoglex" OR "Glifosan 747" OR "gliphosate" OR "Gliz" OR "Glyfos" OR "GlyGran" OR "Glyphodin A" OR "Glyphomax" OR "Glyphosate" OR "Glyphosphate" OR "Ground Bio" OR "Herbatop" OR "HM 2028" OR "Kickdown" OR "Lancer herbicide" OR "MON 2139" OR "MON 3539" OR "MON 6000" OR "N-(Phosphonomethyl)glycine" OR "N-(phosphonomethyl)-Glycine" OR "N-Phosphomethylglycine" OR "N-Phosphonomethylglycine" OR "Phorsat" OR "Phosphonomethylglycine" OR "Phosphonomethyliminoacetic acid" OR "Pondmaster" OR "Rebel Garden" OR "Roundup Max" OR "Safal" OR "Scout herbicide" OR "Silglif" OR "yerbimat") OR TX ("Roundup" AND (Monsanto)) OR MH ("antifungal agents")OR TX ("antifungal" OR "anti-fungal") OR MH ("enzyme inhibitors") OR TX ("enzyme" AND inhibitor*) OR TX ("enzyme inhibitors" OR "enzyme inhibitor")OR MH ("herbicides") OR TX ("herbicides" OR "herbicide") OR MH ("uncoupling agents") OR TX ("uncoupling" AND agent*) OR TX ("uncoupling agent" OR "uncoupling agents") OR MH ("pesticides" OR pesticide*))
SciFinder 9/2019	Substance Identifier "1071-83-6; 38641-94-0; Glyphos...">substances (27)>get references (19597)>refine "2017-2019" (2591)>refine "Clinical Trial Dissertation Jo..." (1111)>remove 198 references (913)

The results of the 2019 updated literature review were:

- Number of records identified (after duplicate removal): 2,636
- Number of records identified from government websites: 0
- Total number of records to undergo literature screening: 2,636

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on glyphosate:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and/or abstract clearly indicated that the study was not relevant to the toxicological profile.

2015/2017 literature review:

- Number of titles and abstracts screened: 5,803
- Number of studies considered relevant and moved to the next step: 628

2019 literature review

- Number of titles and abstracts screened: 2,636
- Number of studies considered relevant and moved to the next step: 135

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

2015/2017 literature review:

- Number of studies undergoing full text review: 628
- Total number of studies cited in the profile: 329

2019 literature review:

- Number of studies undergoing full text review: 135
- Total number of studies cited in the profile: 60

A summary of the results of the literature search and screening is presented in Figure B- and Figure B-2..

Figure B-1. February 2015 and September 2017 Literature Search Results and Screen for Glyphosate

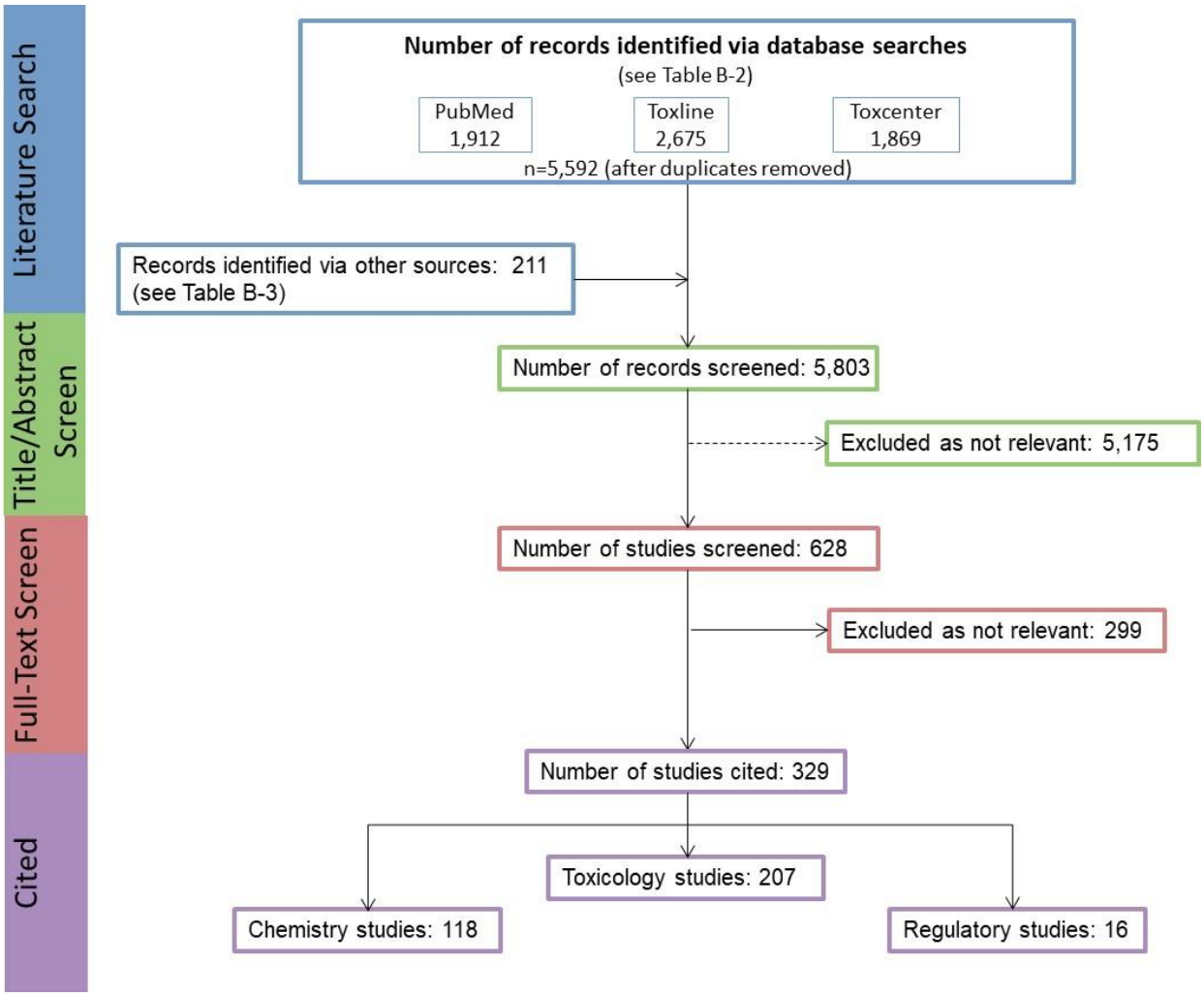
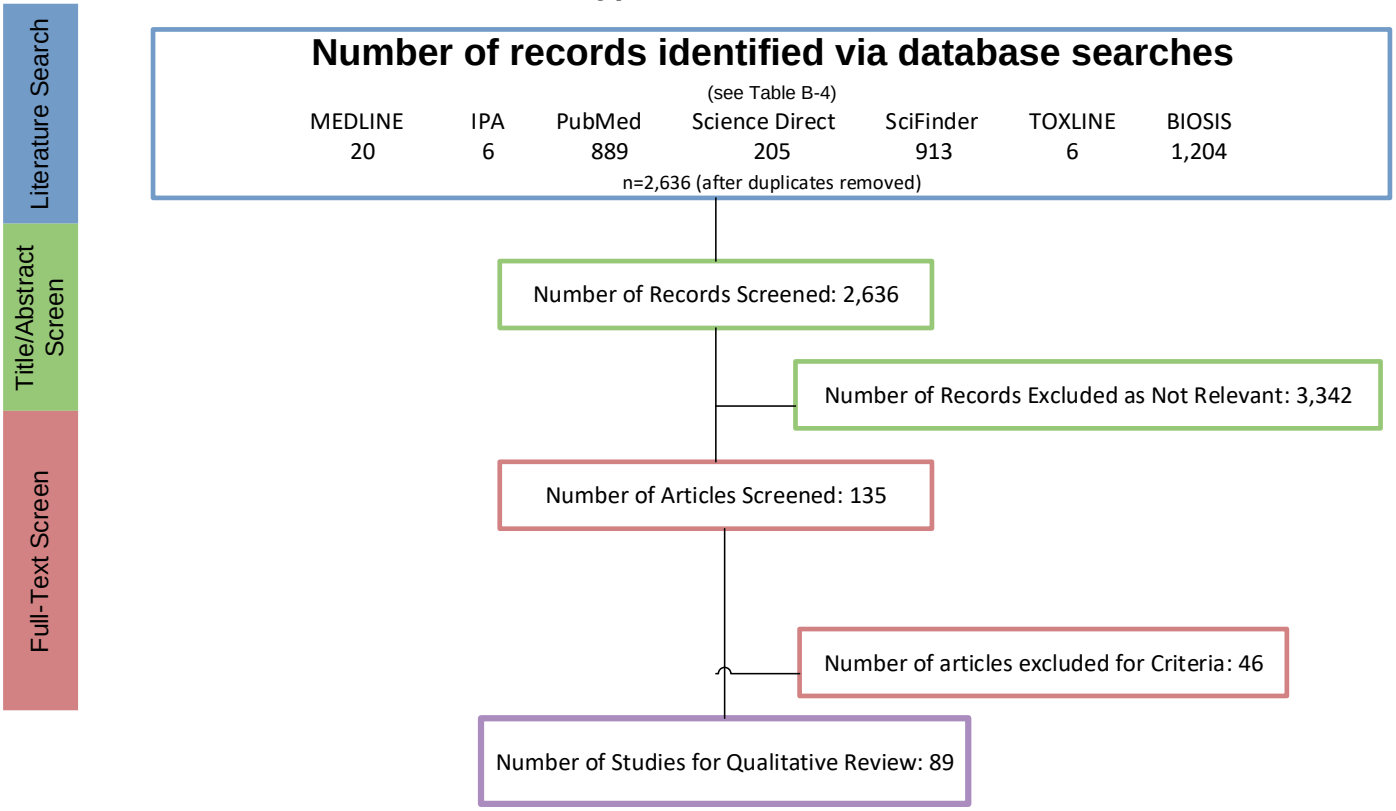


Figure B-2. September 2019 Supplemental Literature Search Results and Screen for Glyphosate



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL,

these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX C

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

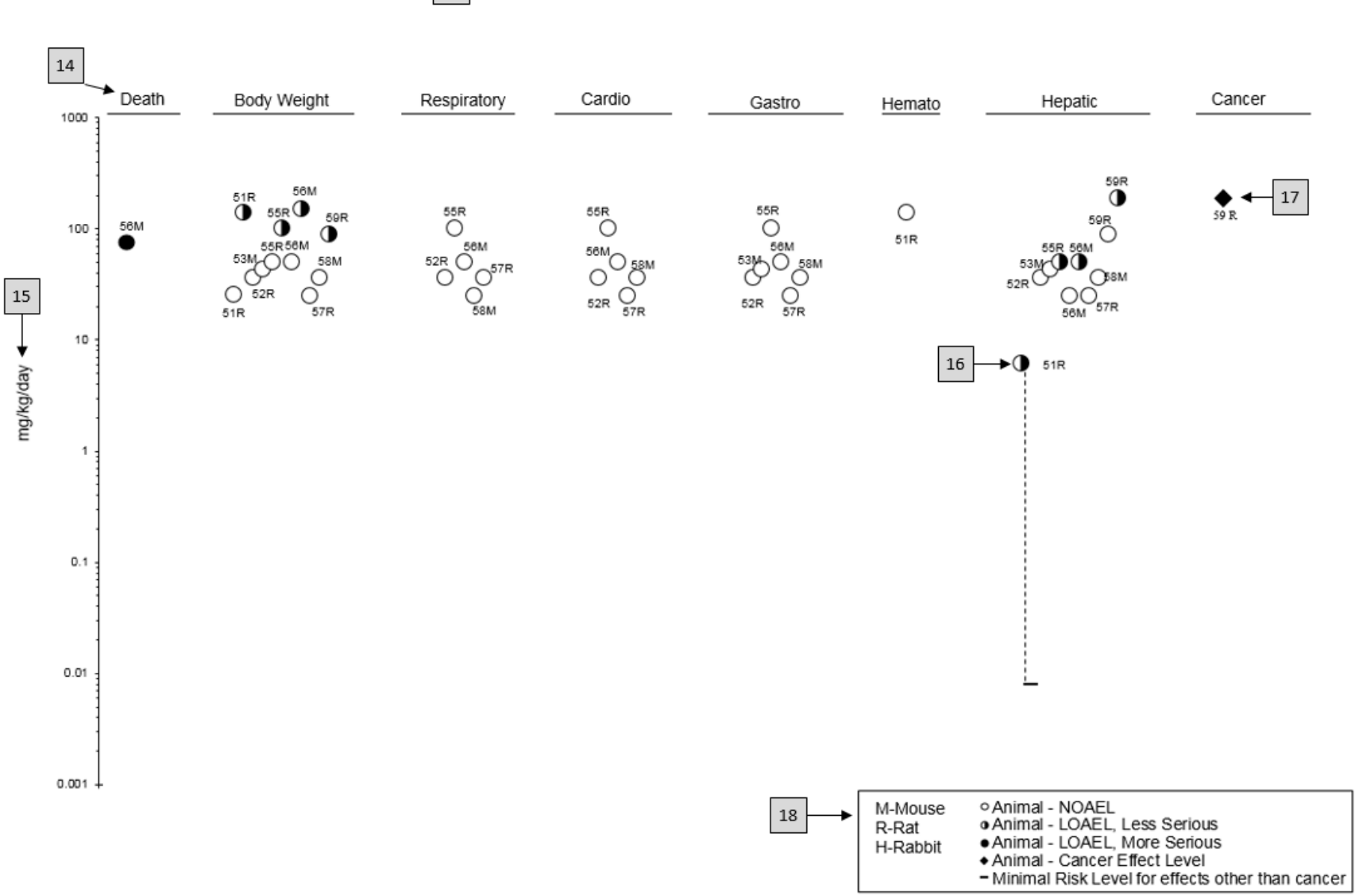
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) $\geq$1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration

FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram

NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PEHSU	Pediatric Environmental Health Specialty Unit
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture

USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result