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.

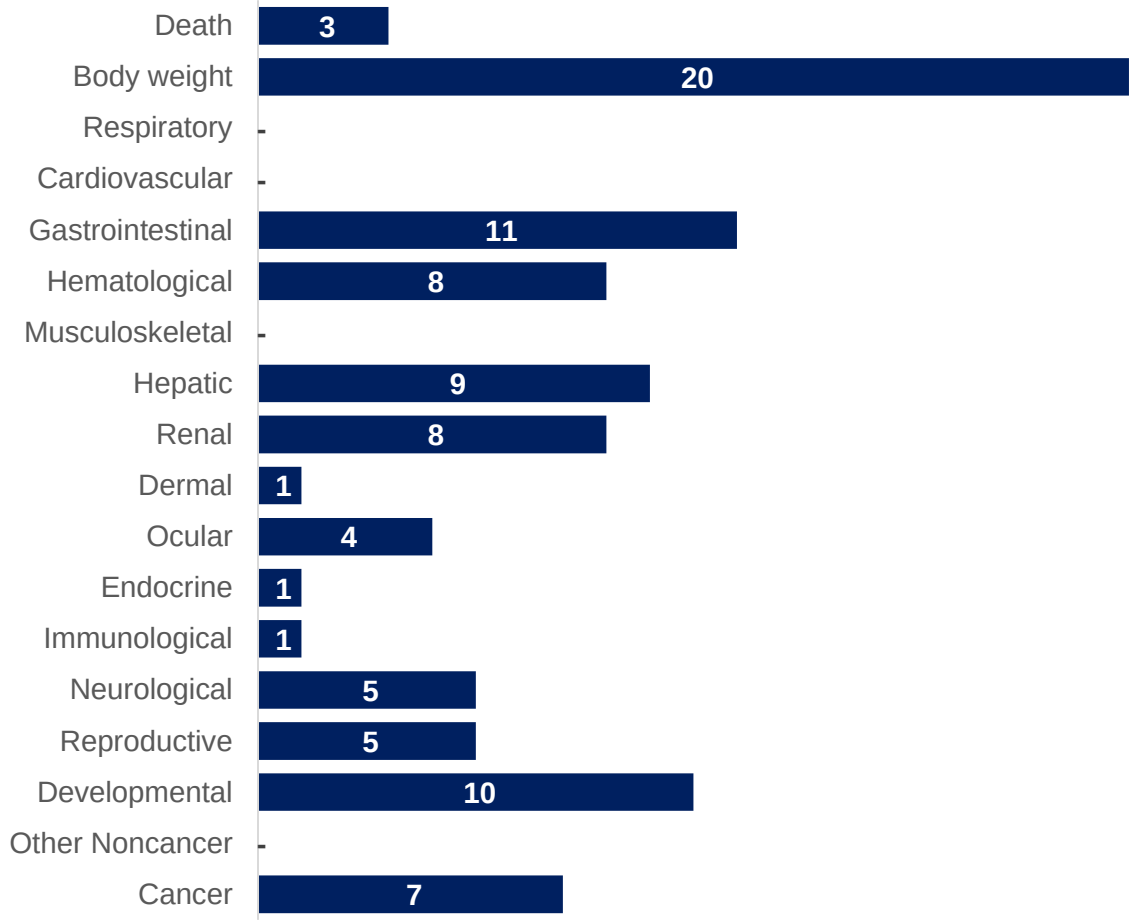
- **Hepatic effects:** Increased serum liver enzyme activity and histopathologic liver lesions were reported in male rats repeatedly gavaged with a glyphosate formulation at 487 mg/kg/day.

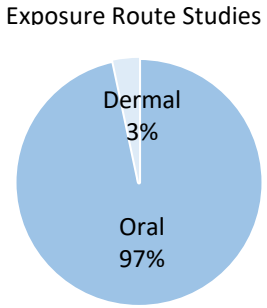
- **Hematological effects:** Decreases in red blood cells, hematocrit, and hemoglobin, and increases in mean corpuscular volume and neutrophils were reported in mice administered a glyphosate formulation orally at 500 mg/kg/day.

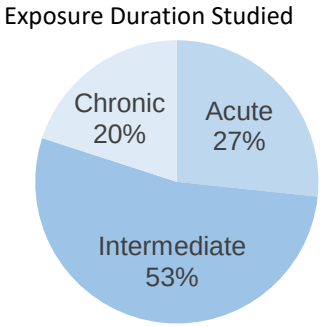
- **Reproductive effects:** Increased percentage of morphologically abnormal sperm was reported among rats receiving a glyphosate formulation from the drinking water for 8 days at 640 mg/kg/day.

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)





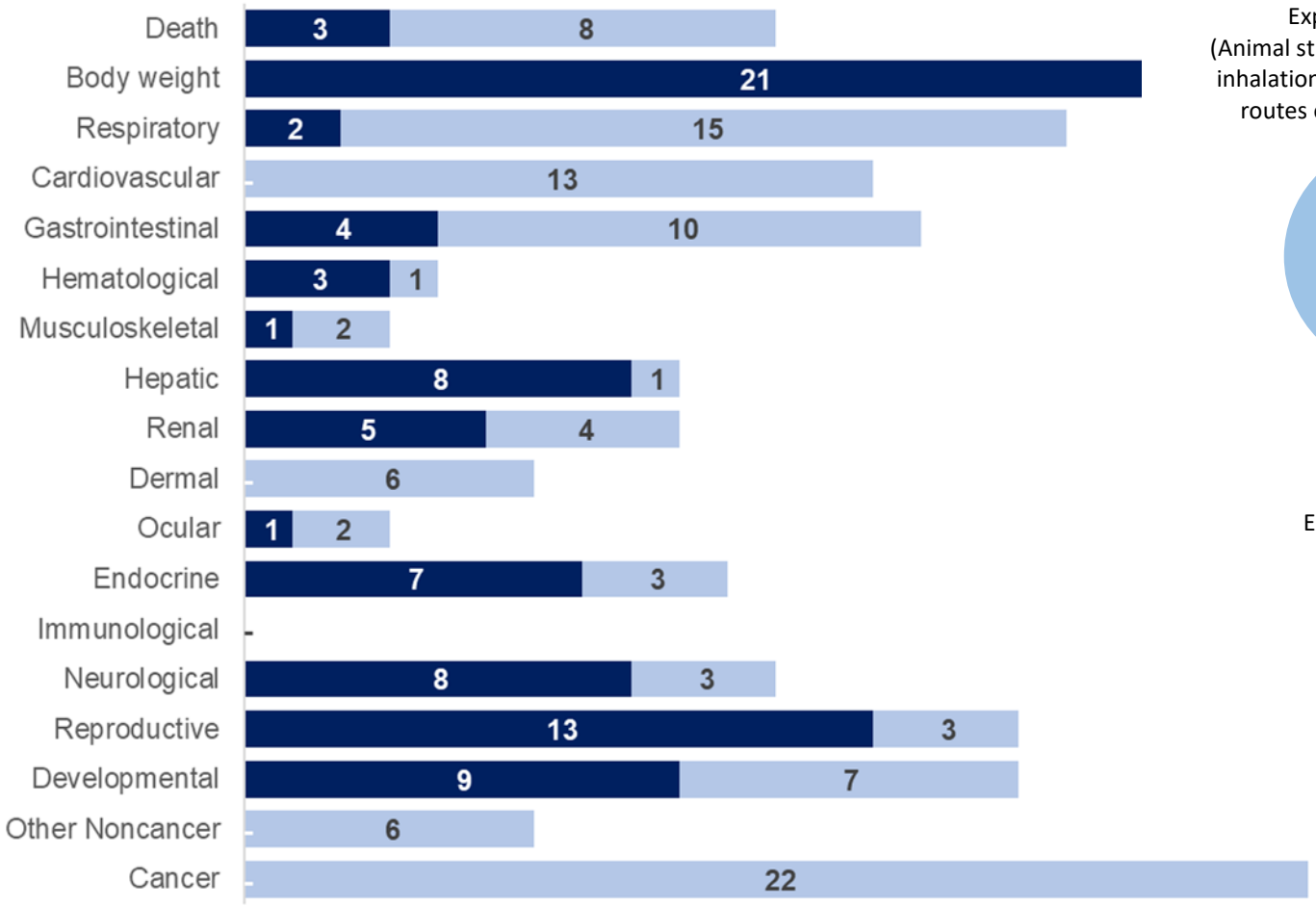


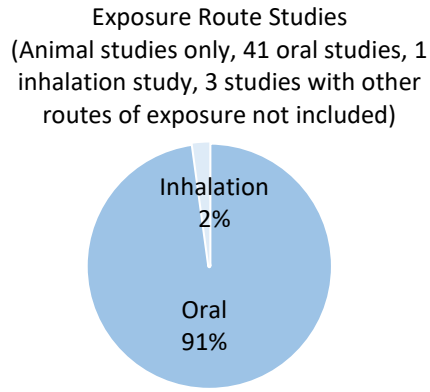
*Includes only animal studies that employed oral exposure to glyphosate technical as discussed in Chapter 2. A total of 30 studies include those finding no effect. Most studies examined multiple endpoints.

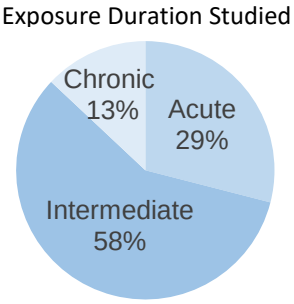
Figure 2-2. Overview of the Number of Studies Examining Glyphosate Formulations Health Effects*

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)

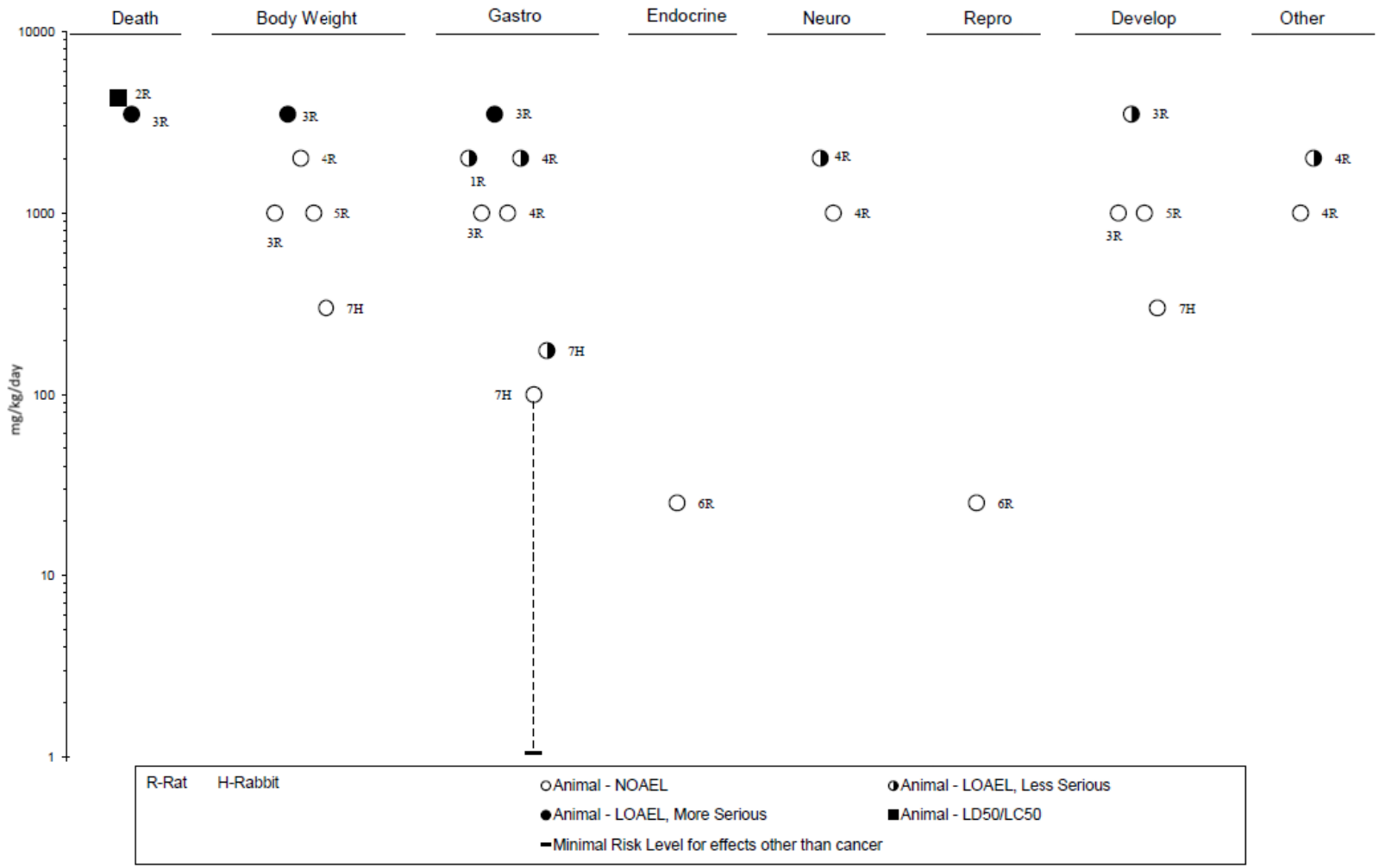


Figure 2-3. Levels of Significant Exposure to Glyphosate Technical – Oral
Intermediate (15-364 days)

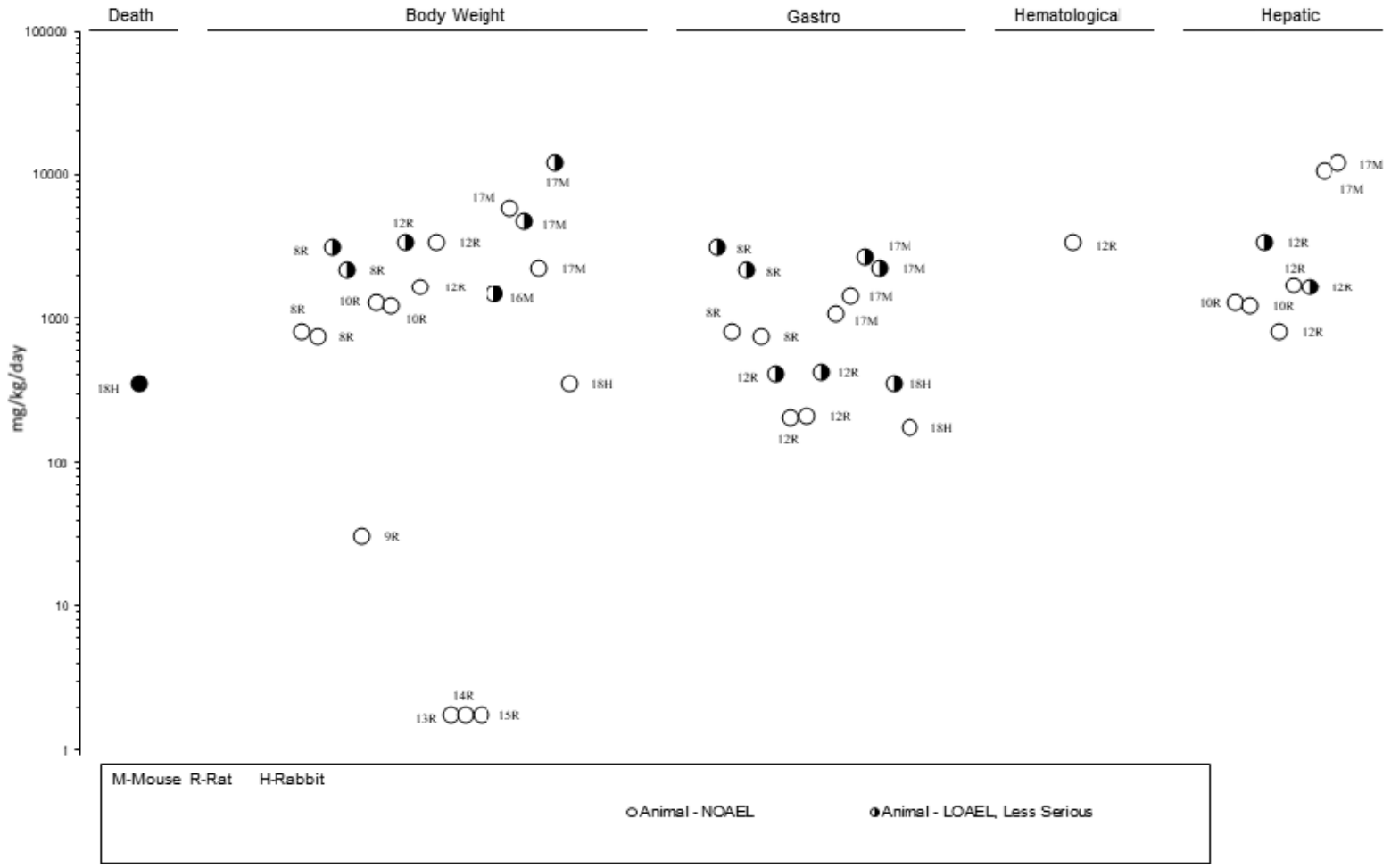


Figure 2-3. Levels of Significant Exposure to Glyphosate Technical – Oral
Intermediate (15-364 days)

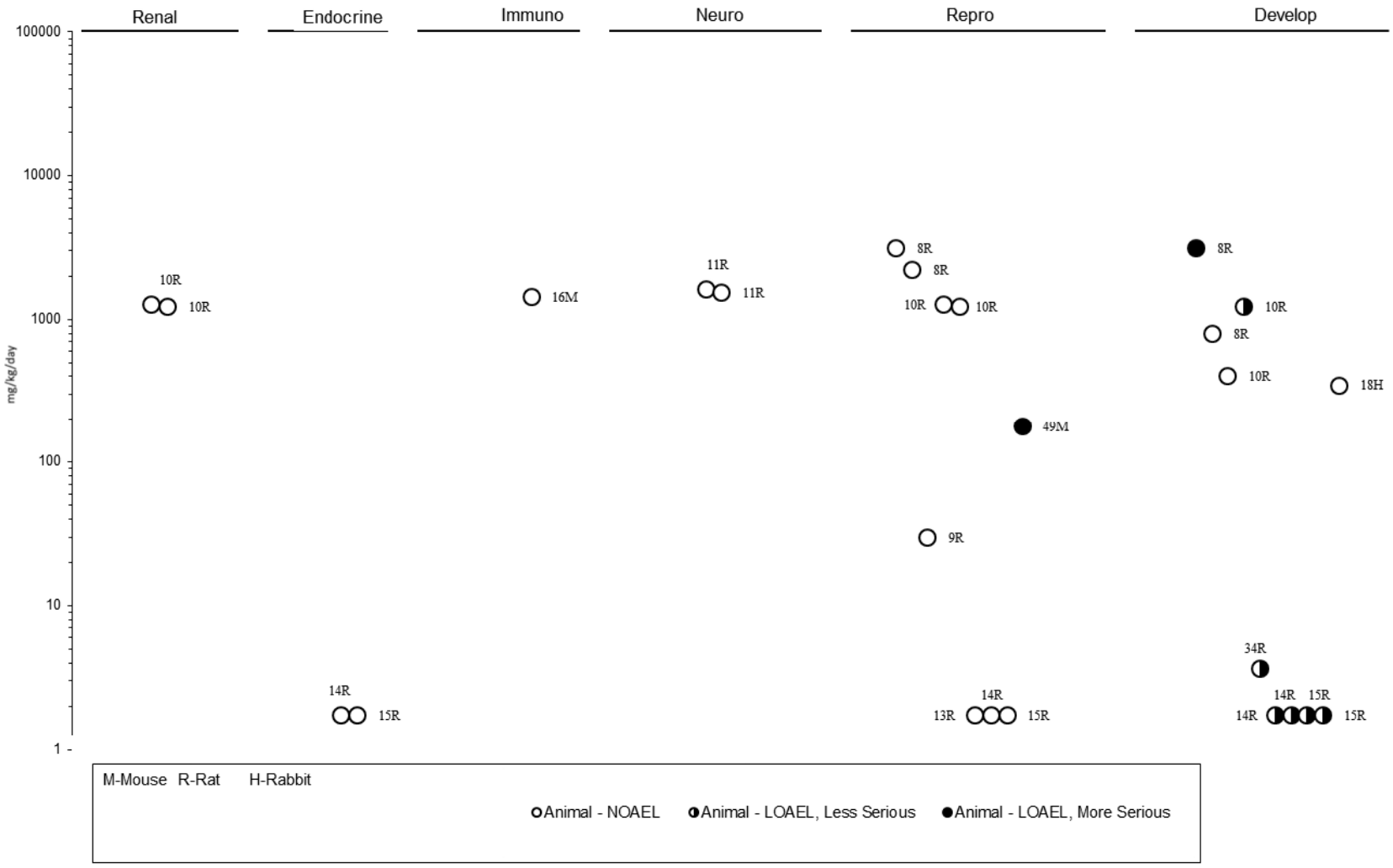


Figure 2-3. Levels of Significant Exposure to Glyphosate Technical – Oral
Chronic (≥365 days)

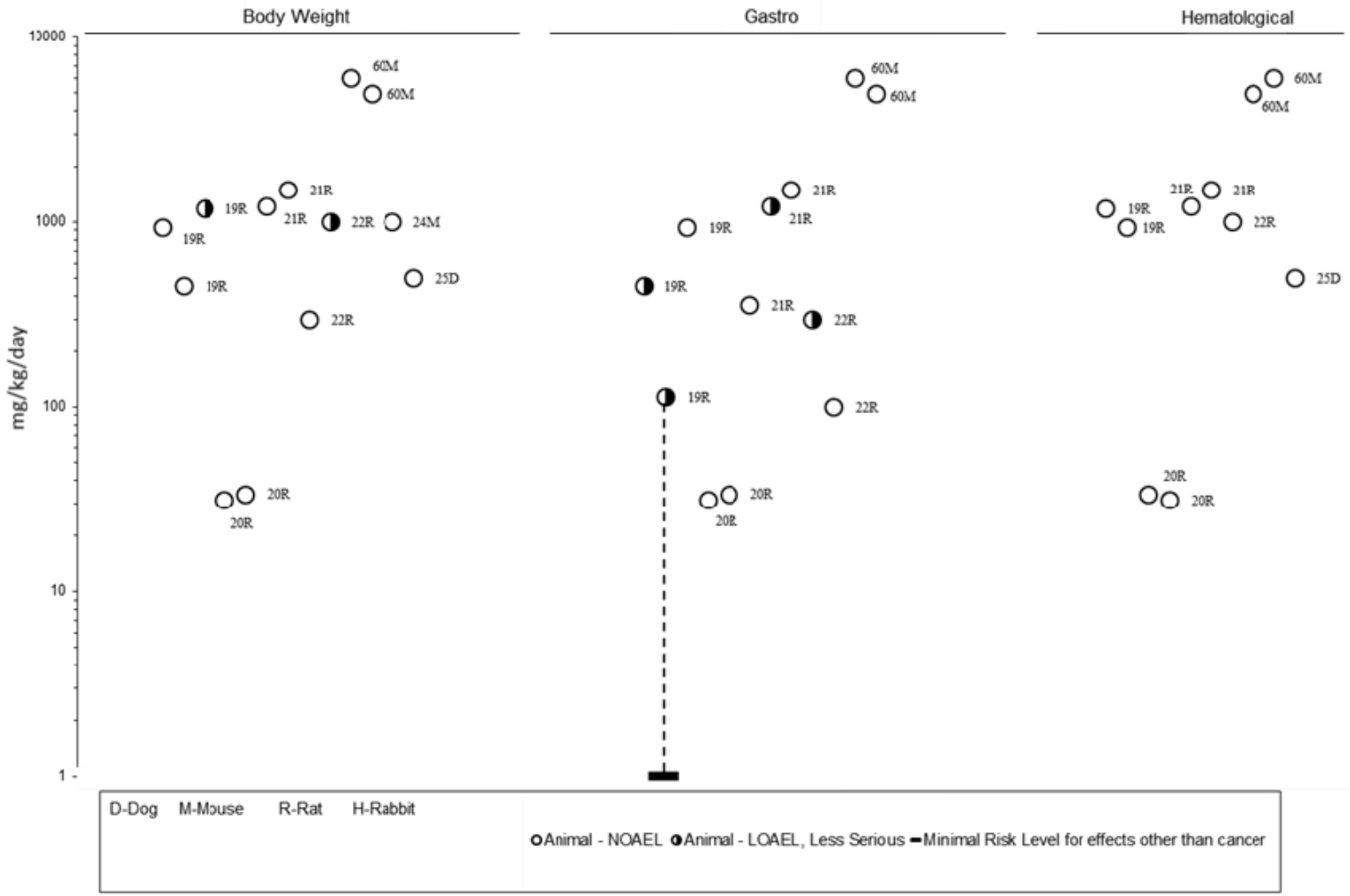


Figure 2-3. Levels of Significant Exposure to Glyphosate Technical – Oral
Chronic (≥365 days)

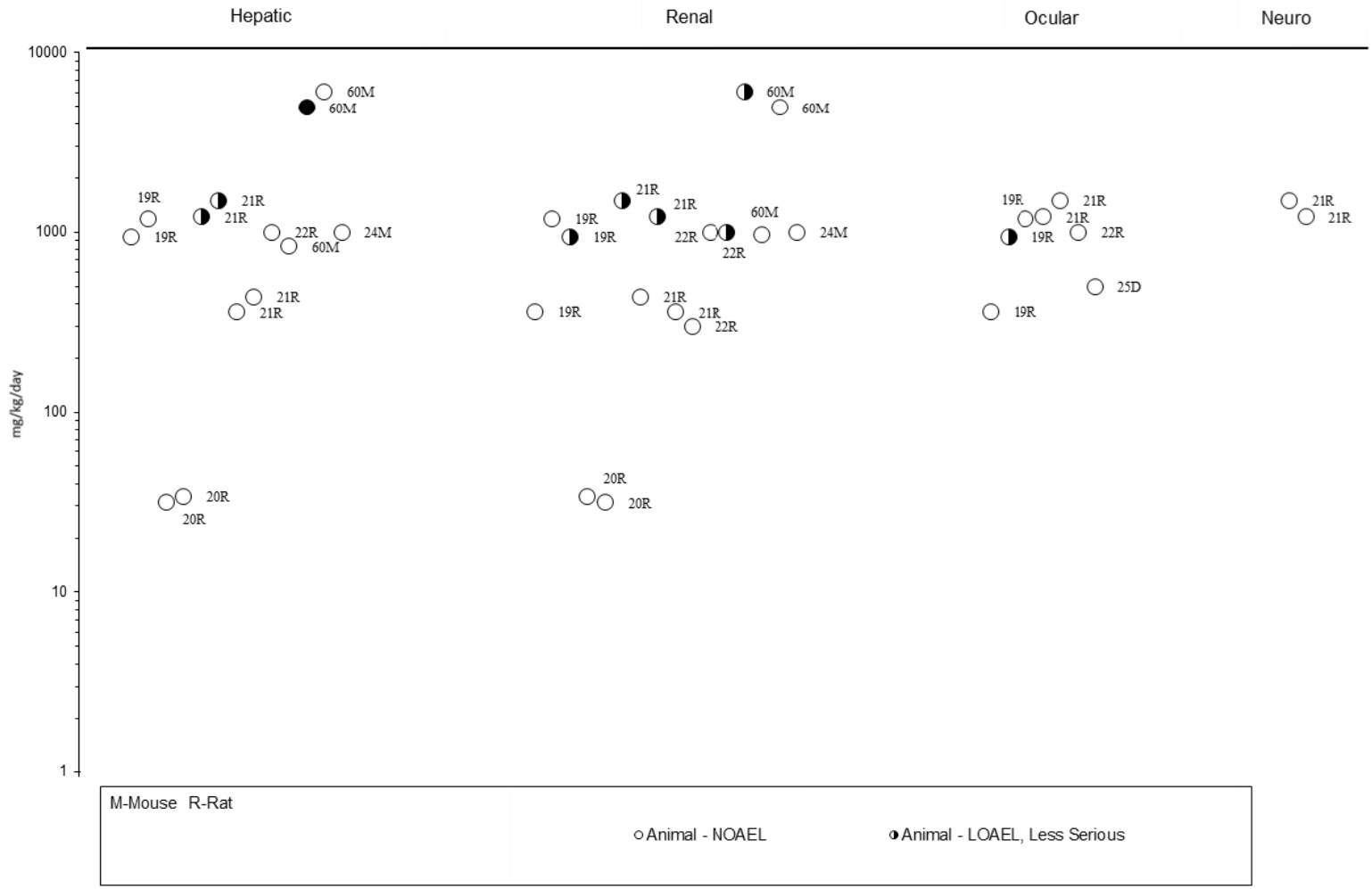


Table 2-3. Levels of Significant Exposure to Glyphosate Formulations[a] – Oral

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 Orsi et al. 2009	517 cases/1,506 controls 244 cases/435 controls	51 cases 12 cases		
B-cell lymphoma	Cocco et al. 2013 Eriksson et al. 2008	2,348 cases/2,462 controls 1,163 cases/1,016 controls	4 cases/2 controls Not stated	2.0 (1.1–3.6) I^2=0.0%, p=0.58 for heterogeneity	Chang and Delzell 2016; Schinasi and Leon 2014
Leukemia	Brown et al. 1990 De Roos et al. 2005a Kaufman et al. 2009	578 cases/1,245 controls 49,211 180 cases/756 controls	15 cases/49 controls 43 cases 1 case/3 controls	1.0 (0.6–1.5) I^2=0.0%[a], p=0.92 for heterogeneity	Chang and Delzell 2016
Multiple myeloma	Brown et al. 1993 De Roos et al. 2005a Kachuri et al. 2013 Orsi et al. 2009 Pahwa et al. 2012 Sorahan 2015	173 cases/650 controls 19 cases 342 cases/1,357 controls 56 cases/456 controls 32 cases/133 controls 40,719	11 cases/40 controls Not stated 32 cases/131 controls 5 cases/24 controls Not stated 24 cases	1.4 (1.0–1.9) I^2=0.0%, p=0.63 for heterogeneity	Chang and Delzell 2016
Multiple myeloma	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 0.87 (0.66–1.15) I^2=0.0%, p=0.95 for heterogeneity	Leon et al. 2019
Hodgkin's lymphoma	Karunanayake et al. 2012 Orsi et al. 2009	316 cases/1,506 controls 87 cases/496 controls	38 cases/133 controls 6 cases/24 controls	1.1 (0.7–1.6) I^2=0.0%, p=0.36 for heterogeneity	Chang and Delzell 2016
Diffuse large B-cell lymphoma	Eriksson et al. 2008 Orsi et al. 2009	955 cases/1,016 controls 456 controls	Not stated 5 cases/24 controls	1.1 (0.5–2.3) I^2=0.0%, p=0.79 for heterogeneity	Chang and Delzell 2016
Diffuse large B-cell 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 1.36 (1.00–1.82) I^2=0.0%, p=0.48 for heterogeneity	Leon et al. 2019

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).

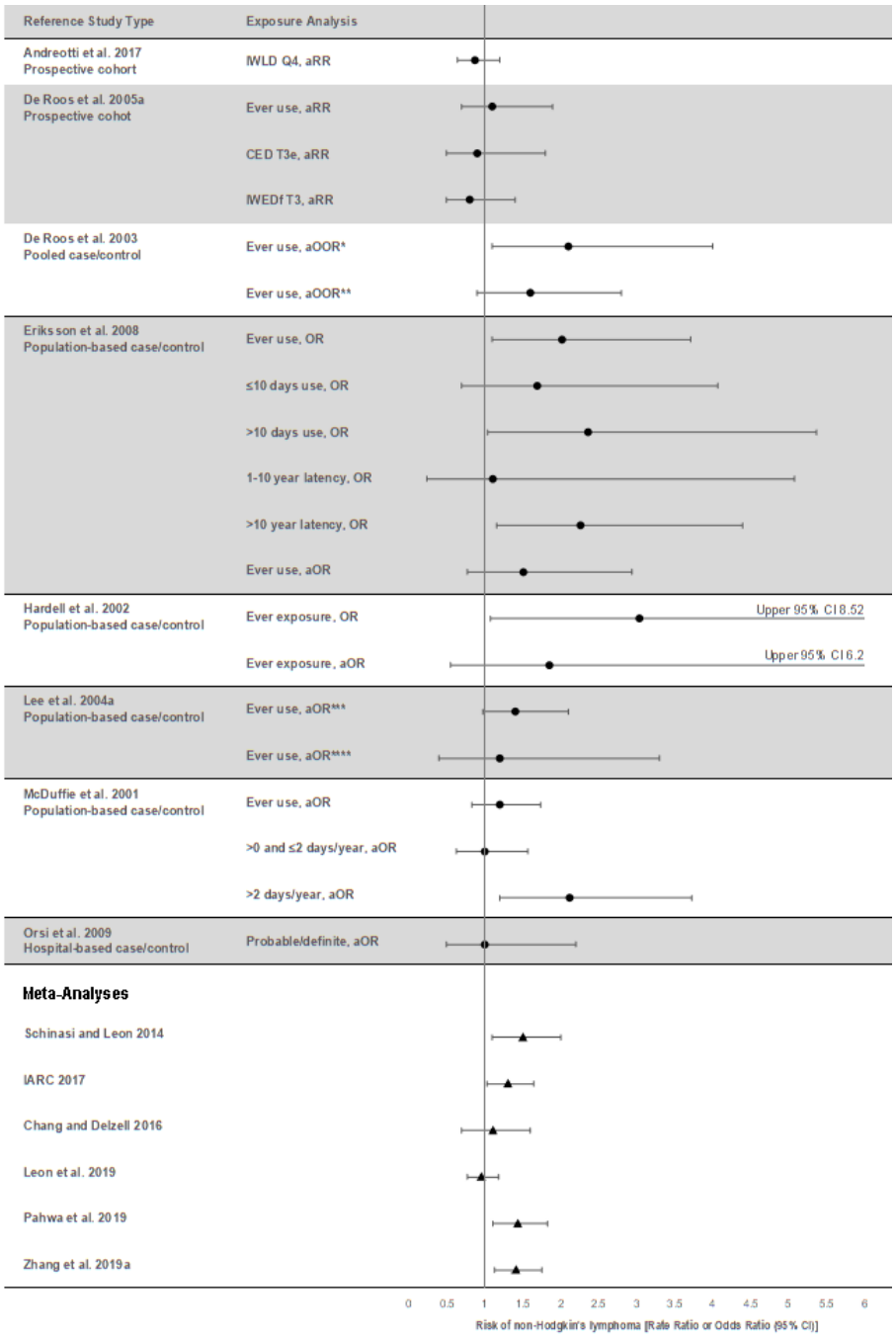
Lymphohematopoietic Cancers. Overviews of epidemiological studies that focused on the association between glyphosate use and lymphohematopoietic cancers are presented in Table 2-8. A majority of the studies did not report statistically significant associations between glyphosate use and many of the lymphohematopoietic 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.

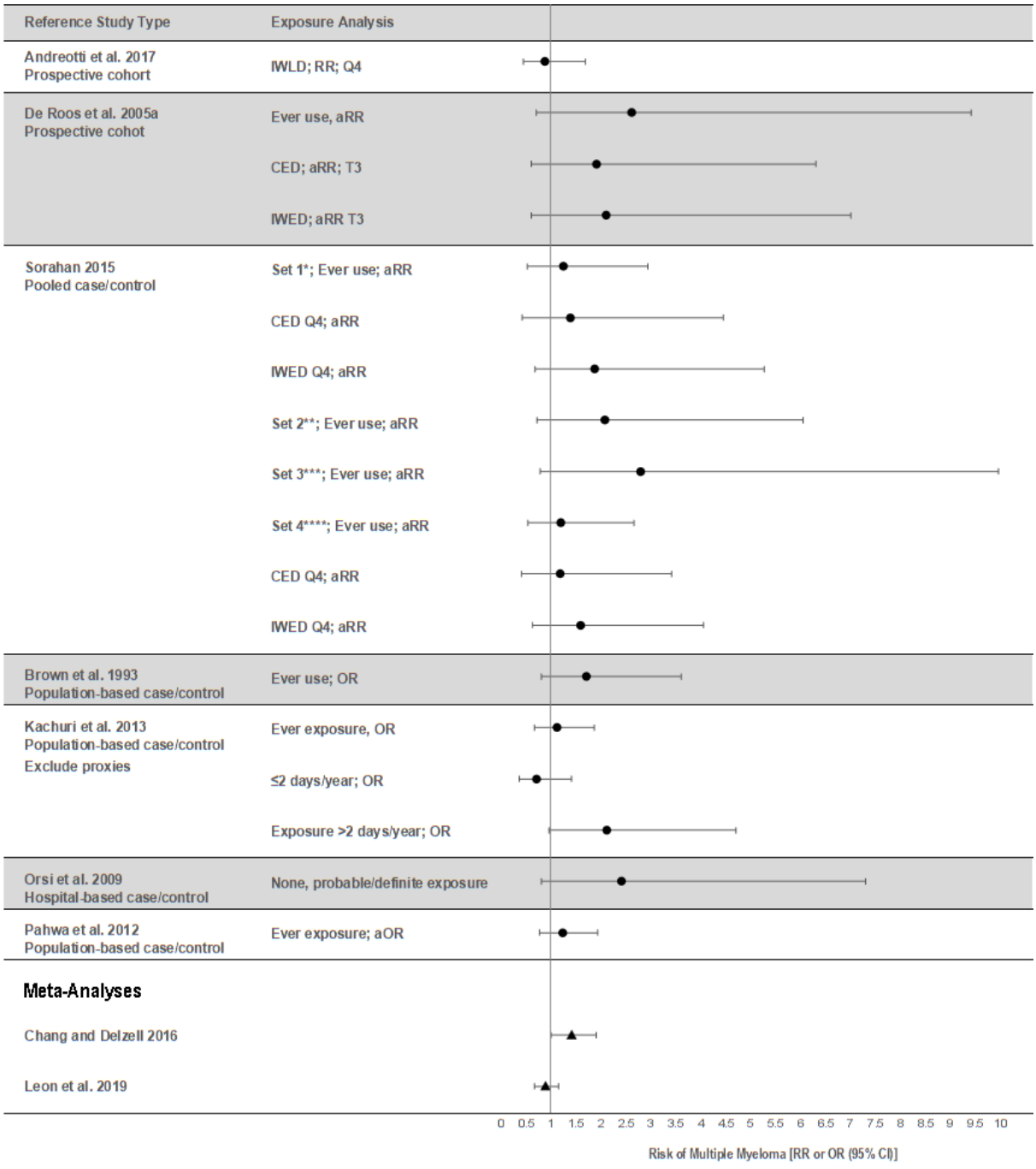
Figure 2-4. Risk of non-Hodgkin's Lymphoma Relative to Self-Reported Glyphosate Use or Exposure



*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*.