CHAPTER 6. ADEQUACY OF THE DATABASE

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

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

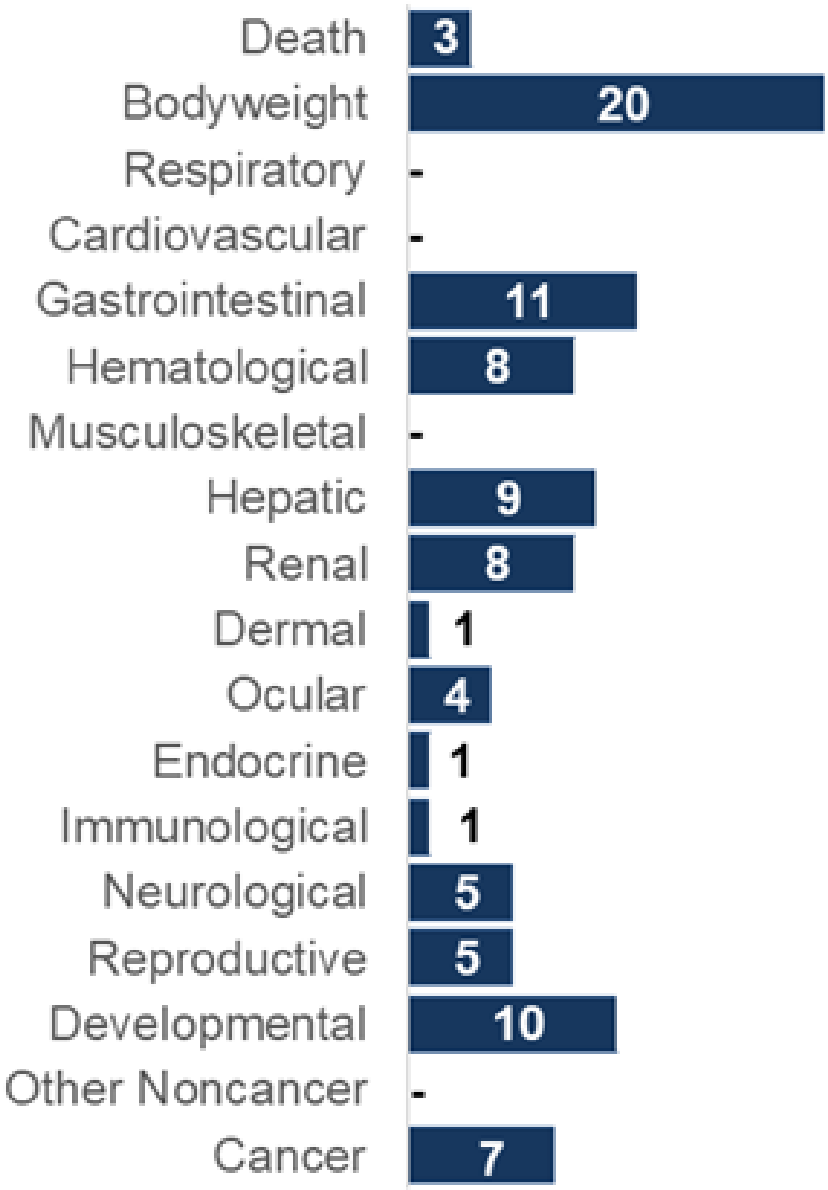
6.1 Information on Health Effects

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

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

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

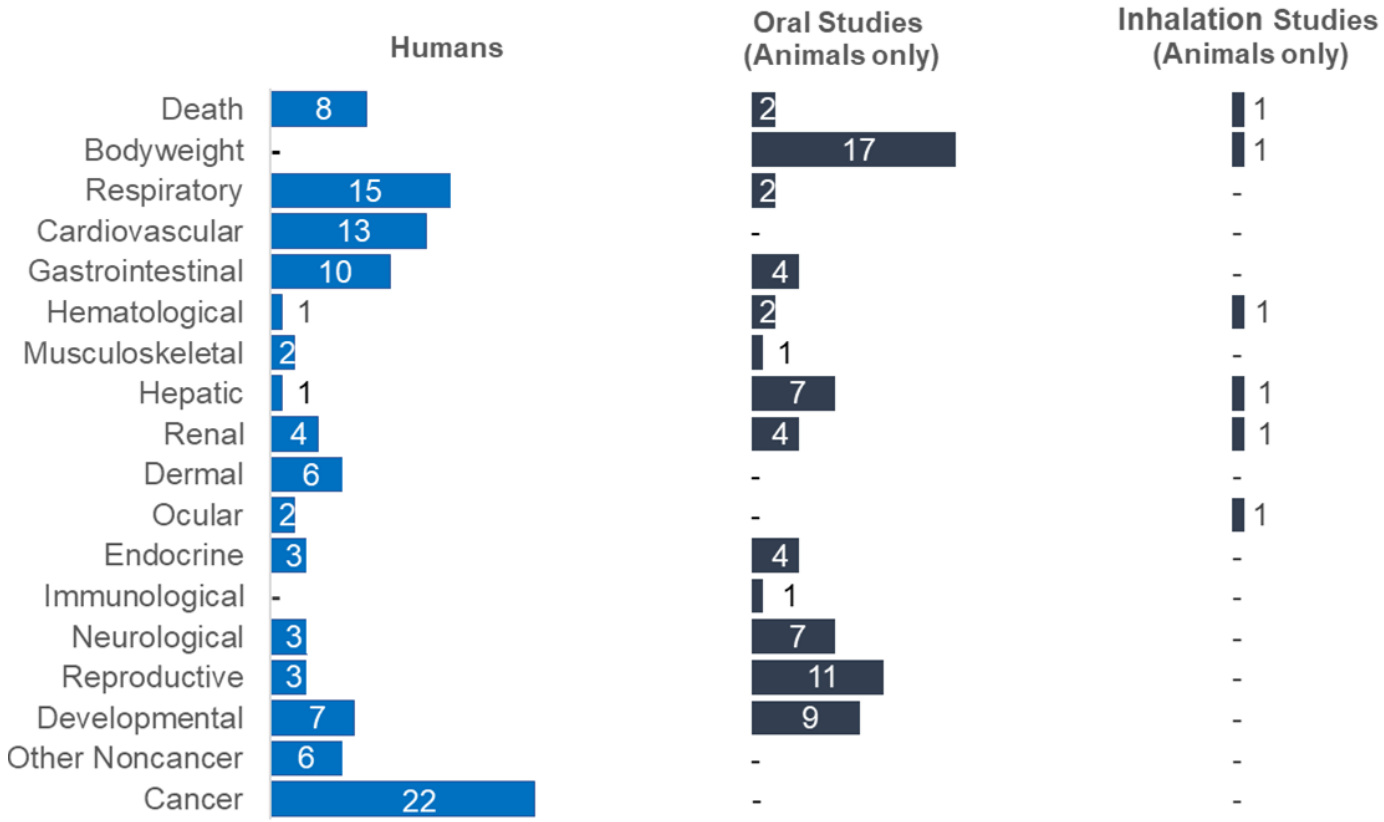
Potential body weight and gastrointestinal effects of glyphosate technical were the most studied endpoints



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

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

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



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

6.2 Identification of Data Needs

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

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

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

As stated previously, most information is available from animal studies submitted to EPA's Office of Pesticides Programs using glyphosate technical (typically >90% purity) to fulfill requirements for the registration of a particular glyphosate formulation for use in the United States. Some animal studies in

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

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

Health Effects

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.3 Ongoing Studies

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

Table 6-1. Ongoing Studies on Glyphosate

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

Source: RePORTER 2020