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Glyphosate: A review of its global use, environmental impact, and potential health effects on humans and other species

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Abstract
Glyphosate, [N-(phosphonomethyl) glycine], was synthesized in 1950 and patented as a chemical chelator, capable of binding metals such as calcium, magnesium, and manganese. Glyphosate's ability to bind to manganese was later found to inhibit an enzyme used by plants and bacteria for biosynthesis of three amino acids found in all proteins, and the commercial value of this property led to the development and marketing of glyphosate as a broad-spectrum herbicide. In 1974, the Monsanto Chemical Company introduced the herbicide as Roundup™, a formulation of glyphosate and adjuvants. Roundup™ was originally used for weed control in specific farming and landscaping operations and around power lines and train tracks. Following introduction of Roundup Ready™ seeds, in the 1990s, glyphosate use increased significantly. Although Monsanto's patent on glyphosate expired in 2002, the widespread and growing use of Roundup Ready™ seed globally and competitive glyphosate marketing by other chemical companies have led to glyphosate's significant increase in the environment. Concerns about potential adverse effects have also grown. While, at present, many regulatory agencies have determined that there is little risk of adverse health effects to the general public or to farmworkers using proper handling techniques, the International Agency for Research on Cancer (IARC) assessing hazard data on glyphosate identified it in 2016 as a category 2A carcinogen (likely to cause human cancer). Response to this classification has been divided: The agribusiness industry has been forceful in its opposition, while other experts support IARC's classification. The following article examines these issues. It also examines the basis for regulatory decisions, controversies involved, and questions of environmental justice that may or may not be addressed as glyphosate continues to be used.

Keywords Glyphosate · Environmental health · Ecosystem · Environmental justice · Agribusiness

Introduction

Glyphosate, or [N-(phosphonomethyl) glycine], is a broad-spectrum herbicide that is absorbed through the leaves and foliage of growing plants, inhibiting an enzyme involved in the synthesis of tryptophan, phenylalanine, and tyrosine, amino acids that are essential building blocks of proteins. Animals lacking the plant biosynthetic pathway must take these amino acids in through their diet. Thus, glyphosate does not have the same toxic effect on animals.

Glyphosate was originally synthesized and patented as a metal binding agent by a Swiss chemist in 1950. Although not initially used as a herbicide, it became recognized that glyphosate binds to manganese, essential to an enzyme necessary to the biosynthetic pathway for tyrosine, phenyl alanine, and tryptophan formation (amino acids found in all proteins). The biosynthetic pathway for the formation of the amino acids and the specific step in the pathway inhibited by glyphosate are shown in Fig. 1.

Once the inhibitory effect of glyphosate was seen, it was quickly recognized that it could have commercial applications because of its potential to kill unwanted plants, and, in theory, not harming animals. Further investigations demonstrated not only broad-spectrum herbicidal activity (Dill et al. 2010), but also a low acute toxicity, far less toxic than that of several other broad-spectrum herbicides. Glyphosate's high LD_{50} (mean lethal acute dose) is comparable to that of table salt (Fishel et al. 2013). It is water soluble, and, presumably therefore, readily excreted by animals following intake.

Monsanto marketed glyphosate under the trade name Roundup™ and held the patent from 1974 until its

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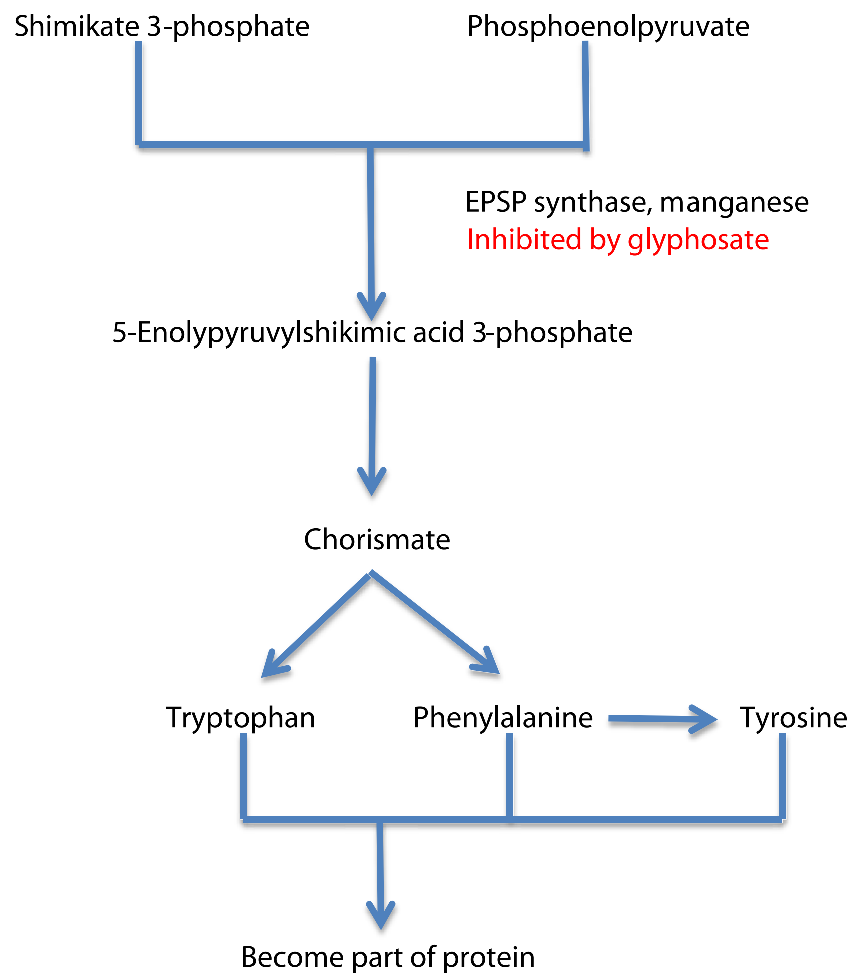

Fig. 1 Biosynthetic pathway for formation of tryptophan, phenylalanine and tyrosine, indicating step inhibited by glyphosate

expiration in 2000. When first marketed, it was heralded as a "breakthrough" in herbicides. Original commercial use was for weed control, including elimination of unwanted plants around power lines and train tracks, in fruit production for elimination of weeds between rows in orchards, and following crop harvest, for removal of unwanted plant growth in fields. However, the volume of glyphosate use increased dramatically with the introduction of Roundup Ready™ genetically engineered commercial crops in the 1990s, making it possible to use glyphosate for weed control before and during crop growth as well as after harvest. It could also be used just prior to harvest in certain applications. The expansion of ways that glyphosate could be used has resulted a dramatic increase in the volume of herbicide used. Today, glyphosate use is global.

Initially, little concern was voiced about its commercial (or other) uses. Nevertheless, as it became consumed more extensively, safety concerns did arise: concerns about safety to the general environment and ecosystem, to the waterways, to animals, and, ultimately, to humans. The following paper discusses each of these issues, examining the growth and global spread of glyphosate use, its short- and long-term effects, its environmental impact, controversies about potential health effects, and other influences that glyphosate use may have on those who are frequently exposed.

Use of glyphosate

Today, a large percentage of glyphosate use is associated with the development and marketing of Roundup Ready™ seed. Initial seed included soybean, corn, and cotton; nevertheless, since the introduction of these original seeds in the mid-1990s, many other glyphosate-resistant seeds have also been developed and marketed. Important commercial crops now include canola, sugar cane, and sugar beets, as well as a number of crops grown on a less wide-scale basis. Glyphosate also continues to be used for weed control in non-farming applications.

Although Monsanto's patent has expired, the development of more glyphosate-resistant seeds; the increased planting of glyphosate-resistant crops; and, because of competition, the decreased cost of the herbicide globally are all major contributors to the larger application of glyphosate/acre and to the increased volume of use worldwide.

Use in the USA

The widespread use of glyphosate use in the USA is expected to increase in the foreseeable future. Although exact data for all uses are not available, relatively precise findings and predictions can be made from available information. Benbrook (2016) analyzed information available through the US Department of Agriculture (USDA) National Agricultural Statistics Service and the US Environmental Protection Agency (EPA) to estimate the volume of use. Taking such information, Benbrook noted the following:

- Overall, in the USA, roughly 67% of the total glyphosate use since its introduction in 1974 has taken place in the decade 2004–2014.[1]
- The overall increase of glyphosate use (1974 to 2014) is estimated to be 200-fold, with agricultural use contributing to 90% of this growth.[1] Breaking this down into sector, agricultural use increased 300-fold and non-agricultural use increased approximately 40-fold.[1]
- From 1974 to 1995, glyphosate use grew from 1,400,000 to 40,000,000 lb (roughly 30-fold). Agricultural use grew from 800,000 to 27,500,000 lb (roughly 34-fold) and non-agricultural use grew from 600 to 12,500 lb (approximately 20-fold).[1]
- From 1995 to 2014, while the volume of use was significantly greater than it was before introduction of GM crops, the rate of growth was less: overall use increased approximately 7-fold with agricultural use expanding at a greater rate (9-fold), and non-agricultural use expanding roughly 2-fold.[1]
- By 2010, agricultural applications accounted for 90% of glyphosate use. This pattern has continued.

Global use

The expiration of the Monsanto's glyphosate patent in 2000 and the rise in glyphosate production by other companies (including Bayer, DuPont, Syngenta, BASF, Crop Science, and Dow as well as several Chinese companies) make it increasingly challenging to access data regarding use or volume of sales. At the present time, major sources of specific data are for-purchase trade reports. Descriptive reports indicate that China is today the major producer of glyphosate (Global Information, Inc. 2013).

A recent growth estimate from a trade report (Transparency Market Research 2014) anticipates a global rate of growth from 2012, rated as US$5.46 billion in 2012, to reach US$8.79 billion by 2019. Other points include the following:

- Globally, soybean is the major glyphosate resistant crop (Benbrook 2016).
- The USA, Argentina, and Brazil are the largest users of glyphosate and glyphosate-resistant seeds (Benbrook 2016).
- Patterns of glyphosate use (frequency of application, pattern of application, strength of herbicide) vary according to farming practices as well as time of introduction of glyphosate and glyphosate-resistant crops in different countries.
- Among Asian/Pacific countries, China and India are the primary users of glyphosate, with much of the use tied to GM seed.
- Use of glyphosate in the European Union has fluctuated within recent years as the result of regulatory issues.
- In sub-Saharan Africa, South Africa is a major user of GM seed and glyphosate.

According to the African Centre for Biodiversity, overall use of glyphosate increased from 12 million to 20 million liters from 2008 to 2012. From 2007 to 2011, glyphosate imports increased by 177% (African Centre for Biodiversity 2015). However, sub-Saharan Africa use varies from country to country, in part because of regulatory considerations, but also because of economic forces. Gabowski and Jayne (2016) found that while overall use is increasing, wide variations exist. Large-scale commercial products such as cotton, maize, and soy are more frequently grown using a combination of GM technology and glyphosate weed control, especially true in South Africa where use is extensive. A recent report from South Africa notes that approximately 85% of both maize (corn) and soy seed are genetically modified, often glyphosate tolerant (Albrecht 2017). Initially approved for use in 1975, glyphosate is now used not only for commercial production of maize and corn but for production of many other crops grown in farms, orchards, and vineyards.

Glyphosate in the environment

Soil, water, and soil organisms

1. Soil: Glyphosate readily attaches to soil following spray application and is released relatively slowly. Release rates depend on soil composition, rainfall, water, and the type of tilling (Vereecken 2005). Depending on soil composition, half-lives of attachment can range anywhere from days to several months (Henderson et al. 2010).

[1] Data based on information from US Department of Agriculture, National Agriculture Statistical Service, and the US Environmental Protection Agency (EPA). Data from EPA includes both farming and non-farming uses, and calculations for non-agricultural use represent adjustments, taking the higher EPA estimates into consideration.

Environmental breakdown is primarily through the action of soil microorganisms. The primary breakdown products are aminomethylphosphonic acid (AMPA) and carbon dioxide. Like glyphosate, AMPA binds tightly to soil and is slowly degraded, ultimately breaking down into phosphate, ammonia, and carbon dioxide.

2. Water: Since they are both polar molecules, glyphosate and AMPA readily dissolve in bodies of water. They may enter rivers and streams as run off or may first enter the atmosphere attached to soil dusts, which subsequently dissolve in rivers and streams. In rivers and streams, the half-life of each compound varies, depending on water composition and pH, as well as composition of bottom sediments which can be a major "sink," especially if the sediments contain metal ions. Henderson et al. (2010) report median half-lives ranging from a few to 91 days. A recent report from the US Geological Survey (Battaglin et al. 2014) that examined water and soil samples from 38 states collected from 2001 to 2010 found glyphosate and AMPA to be widespread in the environment, especially in sediments, soils, precipitation, ditches, drains, rivers, and streams.

Since both glyphosate and AMPA bind tightly to soils allowing break down by soil microorganisms, it is often felt that little glyphosate enters groundwater. Nevertheless, a few studies do report small amounts in groundwater samples (Sanchís et al. 2012; Vereecken 2005). The presence of meaningful amounts seems to reflect periods of heavy precipitation. A study reported by Sanchís and coworkers Sanchís et al. (2012) detailed an analysis of 140 groundwater samples taken in Catalonia, Spain. Roughly 40% of samples analyzed contained glyphosate. Although the mean concentration in groundwater was small (mean concentration 200 ng/L), higher concentrations were found where groundwater samples were taken during a period of heavy precipitation that followed earlier periods of drought, suggesting leaching from soil.

3. Soil organisms: Data on the effects of glyphosate on soil organisms are complex, and findings have been contradictory (Soil Association 2016). Perhaps this is not surprising, given the number of factors that come into play: the composition of different soils which not only determines how strongly glyphosate and AMPA bind, but also the make-up of the microorganism community, the water content of the soil, the pattern of glyphosate use (whether soils tested have been exposed once or on multiple occasions), and whether the soils contain breakdown of plant material treated with glyphosate.

Since glyphosate targets a biosynthetic pathway unique to bacteria and plants, it is to be expected that when first applied, the exudate of root tips into soil would inhibit growth of bacteria dependent on this pathway. However, over time, mutational events may select for bacteria resistant to glyphosate's inhibitory effects. It can be theorized that this selection would change the microbial make-up of the area surrounding plant roots (the rhizosphere), an expectation that has been corroborated in a number of studies (Soil Association 2016). It is, however, difficult to determine specific trends in microbiological changes, or to assess the potential significance of changes. In part, this reflects differences in study design. Some investigations have looked at field changes. Some have compared rhizosphere differences between the rhizospheres of resistant and sensitive plants. Some have examined results of multiple applications. Still others have looked at generational differences. Finally, soil compositions and choice of plants for examination differ from study to study. Looking at glyphosate transfer from the rhizosphere of target (weed) to non-target (crop or landscape) plants, Neumann et al. (2006) found that the transfer inhibited root uptake of essential micronutrients by non-target plants, thus posing a threat to non-target plant growth and nutrition. Kremer and Means (2009) found that the rhizosphere of glyphosate-treated plants supported growth of fungal species; roots of treated plants had fewer nodules.

Consistent with the expectation that glyphosate treatment would select for organisms that are resistant to the inhibitory effects on the enzyme involved in biosynthesis of tyrosine, tryptophan, and phenylalanine, Araújo et al. (2003) found an increase in fungi and particular groups of bacteria as well as an increase in markers of bacterial respiration among organisms found in samples of Brazilian soils treated with glyphosate. Newman et al. (2016), in a controlled experiment over several growth seasons, reported differences in the mix of bacteria found in the rhizosphere of corn and soybean cultures and suggest that some of the shifts might lead changes in the nutrient status of the glyphosate-treated plants.

Weed resistance

As noted by a number of investigators (Benbrook 2016; Cerdiera et al. 2011; Duke 2017; Heap and Duke 2018; Mortensen et al. 2012), the large-scale use of glyphosate has led to growth in glyphosate tolerance among target plants, as well as the evolution of glyphosate-resistant weeds. Weed resistance to glyphosate was first reported in 1996 when *Lolium rigidum* was found in an apple orchard in Australia. Resistance has grown considerably since the first report. Heap and Duke (2017) detailed the evolution of 38 resistant weed species in 37 countries. Resistance has been found in 34 different crops, and glyphosate-resistant weeds have been found growing in several non-crop environments. One response to the evolution of glyphosate-resistant weeds has been the development of GM crops resistant to several herbicides. For example, Monsanto has developed a strain of cotton sold as

Bollgard II® XtendFlex™Cotton that is resistant to dicamba, glufosinate, and glyphosate. A strain of soybean, Roundup Ready 2 XtendTM Soybeans, is resistant to dicamba and glyphosate. Other authorities, responding to the emergence of glyphosate resistance, advocate more integrated approaches such as crop rotation and efficient use (time of use, thoroughness of application, and application to weeds at the appropriate growth/developmental stage) as alternative approaches to glyphosate resistance (Young 2018).

Health effects

Overview

Reports of acute toxic effects resulting from accidental or intentional ingestion of glyphosate can be found in the literature. However, the major concerns about health effects consider adverse outcomes that may arise because of the increasingly ubiquitous presence of glyphosate in the environment. This raises issues about the effects it may have on a variety of animals in the larger ecosystem. Finally, while small in amount, glyphosate may also be found in processed foods, especially foods from soy and corn, and may also be found in milk from cows that have ingested small amounts of the herbicide.

Regarded as the so-called active ingredient in commercially available herbicides, many regulatory agencies focus on the health effects of glyphosate alone and have established toxicological parameters for human exposure based on this approach. However, whether or not the adjuvants used in commercial delivery of glyphosate have toxicological properties per se, adjuvants are usually mixtures of more than one chemical, and mixture components may modulate the effects of glyphosate in "real life." Mesnage et al. (2015) summarize the results of 18 in vitro studies comparing various health end points resulting from exposure to glyphosate alone or glyphosate as part of the commercial product Roundup™ or glyphosate in other commercial products. While these investigations examined a variety of cell/organ lines, had different exposure designs, and did not consistently use Roundup™ as the only adjuvant formulation, the vast majority (16/18) reported more toxic effects from glyphosate plus adjuvant than from glyphosate alone.

Ecosystem health effects

Effects of glyphosate and its various formulations have been studied in a number of organisms present in the larger ecosystem. These include invertebrates, specifically, earthworms; insects; and marine crustaceans. They also include a variety of fish as well as non-human mammals.

Findings from more recent studies are summarized below.

1. Earthworms: A frequently cited advantage of using herbicides such as glyphosate in farming is that their use decreases soil tillage and, with less tillage, earthworm populations will increase. A review study reported by Broines and Schmidt (2017) analyzes data gathered over approximately 65 years to support this claim. Implicit in this finding, however, is that herbicides such as glyphosate would not adversely affect the earthworm populations that have a critical role in maintaining soil health. However, a number of reports suggest that glyphosate does affect earthworms. Findings include avoidance (Verrell and Van Buskirk 2004), bioaccumulation (Contardo-Jara et al. 2009), a decrease in interaction between an earthworm species and mycorrhizal fungi (both essential components of healthy soil; Zailer et al. 2014), changes in burrowing/tunneling behavior (Gaupp-Berghausen et al. 2015; Domínguez et al. 2016), and reproductive capacity (Domínguez et al. 2016). With respect to avoidance, a more recent study did not detect avoidance behavior among earthworms exposed to recommended application doses of glyphosate (Santos et al. 2012).
2. Insects and arthropods: The effects of glyphosate on a number of insect species have been reported in the scientific literature. This includes reports of effects on species of mosquitoes (Morris et al. 2016), aphids (Saska et al. 2016), honeybees (Sol Balbuena et al. 2016; Herbert et al. 2014), and varieties of beetles, including a species that was introduced to control plant predators in sub-tropical environments (Mirande et al. 2010). Herbert et al. (2014) report that glyphosate affects the flight pattern and homing time of honey bees, as well as appetite and foraging behavior. In contrast, Thompson and coworkers (Thompson et al. 2014) report no effect of glyphosate on honeybee brood development.

The effects of glyphosate on arthropod predators that are important for biological control of agricultural pests were reported by two groups. Benamú et al. (2010) reported negative outcomes for prey consumption, web building, fertility, and development of progeny among *Alpaida veniliae*, an orb web weaver spider. Evans et al. (2010) reported behavioral changes in the wolf spider, *Pardosa milvina*, changes that could affect the species' predatory behavior and might have an impact on biological control.

3. Marine animals (fish and amphibians): Recognizing that glyphosate can enter waterways through run-off or from soil dusts, and that very small amounts may also enter the water table, a number of investigators have examined the effects of glyphosate on marine animals and amphibians. Many of these studies have looked at effects on marine

organisms or amphibians at doses related to the LC_{50} (mean lethal concentration) and have used glyphosate alone and glyphosate as part of a herbicide preparation. They have also looked at a variety of marine and amphibian species. These studies, while demonstrating toxicity to marine animals, used concentrations that are unlikely to be found in waterways. Hence, findings, while valuable, may not provide comprehensive information about the present long-term effects of glyphosate in the ecosystem and may not reflect anticipated environmental exposure.

4. Potential effects on farm animals: Glyphosate is widely used in commercial corn and soybean production, two important components of livestock feed. A USDA report notes that glyphosate represented 50% of all herbicides used per acre of planted farmland for a group of 21 crops and 85% of all herbicides used in soybean growth in 2008 (Fernandez-Cornejo et al. 2014). In 2011, the USDA reported glyphosate residues of 1.9 ppm in 90.3% of soybean samples analyzed; however, in 2016, the USDA excluded soybean testing (US Right to Know 2016). Glyphosate use in corn production was somewhat less. Given this use, concerns have been expressed that glyphosate may be found in animal feed, which might, in turn, affect farm animals or milk production. Krüger et al. (2014) report that cattle from eight different Danish dairy farms excreted glyphosate. Several biological markers of cell damage were elevated. In contrast, Donkin and coworkers (Donkin et al. 2003) found no differences in fat-corrected milk production or milk composition among cows fed a diet containing Roundup Ready™ corn product or corn product from conventional corn.

Carcinogenicity

The possibility that long-term exposure to glyphosate alone or in formulations might lead to the development of cancer has been investigated for some time. A large number of controlled exposure animal studies, human epidemiology studies, and in vitro investigations have been conducted, from the early 1990s until the present time. Study findings together with information about glyphosate's environmental presence have been used to assess the basis for regulation by a number of local, national, and international agencies. Most regulation is based on risk assessment, although the focus of other organizations has been on hazard identification.

When glyphosate was first introduced as a herbicide, many regulatory agencies assessing health risk to the general population or to farm/orchard and other field workers concluded that, as used, glyphosate was not a carcinogen and posed little other health risk. Its increased use and greater environmental use over time led to a reassessment of hazards, including carcinogenicity. Tables 1 and 2 provide a summary of up-to-date classifications and regulatory actions, locally, nationally, and internationally.

Controversies about carcinogenicity: IARC and the agrichemical community

In 1994, glyphosate was given a low priority for carcinogenic evaluation by IARC (Viano et al. 1994). However, with ensuing developments, this concern was revisited. In 2014, IARC convened a meeting of 21 scientific advisors representing 13 countries, to prioritize chemicals or groups of chemicals identified through a call for nominations. Organophosphate pesticides/herbicides were listed among a group given moderate or high priority for assessment of health hazard (IARC monographs on the evaluation of the carcinogenic risks to humans 2014; Straif et al. 2014). In selecting this group of compounds, IARC considered new findings, especially those of cancer epidemiology and mechanisms that had been published since prior considerations. As noted in the Guyton article, consideration was also given to addressing cancer incidence in low- and medium-income countries.

Prior to IARC's hazard assessment, a series of review articles, in part commissioned by Monsanto, were published in the peer-reviewed literature. As well as Monsanto-associated contributors, representatives from other chemical industries, members of the Glyphosate Task Force (a consortium of some 20 industrial organizations working together to renew the EU glyphosate registration), academicians, and private consultants participated in the series. As a whole, the articles critiqued studies that were expected to be considered by IARC.

Included in the series were the following articles:

- A critical analysis of animal carcinogenicity studies (Griem et al. Greim et al. 2015)
- A critical analysis of data evaluating genotoxicity to humans exposed to glyphosate (Kier 2015).
- An evaluation of several unpublished animal studies looking at the potential of glyphosate exposure to result in developmental cardiovascular toxicity. (Kimmel et al. 2013)
- A critique of studies looking at glyphosate as a genotoxic agent (Kier and Kirkland 2013)

While each article focuses on a different aspect of glyphosate assessment (genotoxicity, animal studies, developmental toxicity), taken together, the overall conclusion of the reviews was that glyphosate does not present significant genotoxic risks to human populations, nor do animal studies support a finding that it has carcinogenic potential in humans. Analyses in the reviews covered not only articles published in the peer-reviewed literature but also other analyses considered proprietary in nature, not available in open literature. These analyses

Table 1 US agencies: assessment and classification of glyphosate

Agency	Assessment date and ruling	Comments
US Environmental Protection Agency (EPA)	2017 re-evaluation; not likely to be a human carcinogen	Weight-of-evidence assessment of data on glyphosate alone; rat studies est. LOAEL 940 mg/kg/day; chronic dietary intake NOAEL 100 mg/kg/day. "Not likely to be carcinogenic to humans"
Occupational Safety and Health Agency (OSHA)	Advisory information on occupational handling	Primarily address short term occupational exposure effects. TLV (threshold limiting value) not established.
National Institutes of Occupational Safety and Health (NIOSH)	No significant research or assessment	Review on hazardous substances in waste sites
Agency for Toxic Substances and Disease Registry (ATSDR)	Scheduled assessment initiated in 2015	Report release and public comment scheduled for 2018
National Toxicology Program (NTP)	Program to evaluate glyphosate toxicity alone or in formulations and to compare formulation effects scheduled in 2016	No report issued to date. In 1992, NTP determined that glyphosate not a carcinogen risk. Findings in 1992 based on animal and mutagenic studies.
California	In 2017, identified as a hazardous chemical under Proposition 65	Listed under Proposition 65 as causing cancer base; included in hazardous substances list, but based on 2018 court ruling information not listed on glyphosate containing products

were, however, submitted by industry to regulatory agencies as part of approval processes.

In 2015, IARC, using its established risk criteria, classified glyphosate as a category 2A substance (likely to be a human carcinogen). A summary of the IARC assessment can be found in a Lancet Oncology 2015 publication (Guyton et al. 2015). Details of the IARC assessment are published in volume 112 of the IARC Monographs (International Agency for Research on Cancer 2017).

In assessing the carcinogenic potential of glyphosate, the IARC working group considered three areas: epidemiologic studies, animal studies, and in vitro and in vivo studies with various end points of genotoxicity.

1. Epidemiologic studies. Among the evaluated studies were several case control investigations that examined non-Hodgkin's lymphoma (DeRoos, De Roos et al. 2003; McDuffie, McDuffie et al. 2001; and Erikkson, Eriksson et al. 2008) and a prospective cohort investigation which was part of the agricultural health study (DeRoos De Roos et al. 2005). While the IARC working group found the case-control studies, adjusted for confounding effects of other pesticides to show a positive association between glyphosate exposure and the development of non-Hodgkin's lymphoma, this was not found with the agricultural health study (DeRoos, et al., De Roos et al. 2005), a cohort study.
2. Animal studies. IARC found that two animal studies provided strong evidence of carcinogenicity. Included were findings of renal tumors and a rare blood vessel tumor in mice (EPA, 1985; EPA, 1986) as well as benign pancreatic tumors in rats. While several controlled exposure animal studies of the Monsanto-sponsored review articles published prior to deliberations of the IARC working group were cited, it was noted that "The Working Group did not evaluate these studies….because the information

Table 2 International agencies: assessment and classification of glyphosate

Agency	Assessment date and ruling	Comments
International Agency for Research on Cancer (IARC)	Hazard identification of glyphosate as category 2A substance (probable human carcinogen)	Hazard identification not risk assessment; IARC policy to use peer-reviewed published data and other publically available data
European Food Safety Authority (EFSA)	In 2015 determined that glyphosate "unlikely to pose a carcinogenic hazard to humans"	Used peer reviewed literature and analysis of findings and raw data contained in "regulatory guideline studies"
Joint World Health Organization and Food and Agricultural Organization (JMPR)	In 2017 determined dietary intake of glyphosate unlikely to be a carcinogen hazard	Uses published and unpublished data
European Union	In 2017 voted to extend use for five-year period	Extension period "abbreviated." Majority of member nations (18) voted to approve extension. France and Italy opposed. One member-nation abstained.

provided in the review article and its supplement was insufficient"(IARC monographs on the evaluation of the carcinogenic risks to humans 2017).

One controlled exposure animal study (Séralini et al. 2012), published prior to the IARC meeting, warrants attention. The article, which underwent peer review prior to publication, examined and compared the effects over a 24-month period on Sprague Dawley rats fed a diet of GM corn, treated or not treated with Roundup™, rats given water containing Roundup™, and control rats. Reported as a chronic health study, findings were that all treated groups had significantly greater numbers of tumors than control groups. Shortly after it was published, a number of criticisms appeared, coming both from the scientific community and from lay publications. In 2013, Elsevier, the publisher of Food and Chemistry Toxicology, retracted the article (Elsevier 2013) noting that "Ultimately, the results presented (while not incorrect) are inconclusive, and therefore do not reach the threshold of publication for Food and Chemical Toxicology." In its retraction notice, Elsevier provided comments from a large number of authorities, both supporting retraction and supporting the publication. It is noteworthy that while many lay press publications called for retraction, others did not. Ultimately, the Seralini study was re-published in Environmental Sciences Europe (Seralini, et al., Séralini et al. 2014). While cited in the glyphosate monograph, IARC did not consider the later Séralini publication in its consideration of glyphosate, noting that "The Working Group concluded that this study conducted on a glyphosate-based formulation was inadequate for evaluation."

3. Other findings. In addition to epidemiologic and animal studies, the IARC monograph noted studies that described glyphosate metabolites in blood of exposed individuals (Guyton et al. 2015) as well as several findings of genotoxicity, including those seen in residents of areas subject to aerial spraying (Bolognesi et al. 2009)

Response to IARC classification

Response within the scientific and regulatory community Not surprisingly, reaction to the IARC assessment was strong and controversial. The agrichemical industry, facing potential economic challenges as well as litigation, attacked the assessment, and, by extension, US government funding for IARC. IARC and a large number of experts, in turn, responded, pointing out the IARC mission, as well as the strength of the working group observations and its conclusions. Other authorities have responded with an analysis of differences between IARC's approach and analyses by other expert panels, used as risk assessment for regulatory purposes.

1. Industry response in the peer-reviewed literature: Significant response came through Monsanto. Following publication of the IARC monograph, a series of five review articles were published in a supplemental edition of Critical Reviews in Toxicology. The foreword to the review articles notes that [following release of the IARC monograph] "the Monsanto Company engaged Intertek, a scientific and regulatory consulting firm, to convene an independent scientific panel to evaluate and synthesize the scientific evidence of the potential carcinogenic hazard of glyphosate. The activities and conclusions of the independent panel are reported in the five papers in this special issue. Each of the five papers was rigorously reviewed by 5–10 independent reviewers selected by the CRT Editor and anonymous to the authors. A total of 27 different reviewers participated with several of the individuals reviewing all five papers. The authors of each paper were provided the review comments on their paper and asked to make appropriate revisions. The final papers, published here, represented the work product of the authors. Each paper includes an Acknowledgements section and an extensive Declaration of Interest section." (McClellan 2016)

Included in the publication were the following papers:

- "A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment" (Williams et al. 2016a)
- "Glyphosate in the general population and in applicators: a critical review of studies on exposures" (Solomon 2016)
- "Glyphosate epidemiology expert panel review: a weight of evidence systematicreview of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma" (Acquavella et al. 2016)
- "Glyphosate rodent carcinogenicity bioassay expert panel review"(Williams et al. 2016b)
- "Genotoxicity expert panel review: weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid" (Brusick et al. 2016)

The first article in the series (Williams et al. 2016a) summarizes the findings of those participating in the commissioned examination of the IARC review as follows:

> The International Agency for Research on Cancer (IARC) published a monograph in 2015 concluding that glyphosate is "probably carcinogenic to humans" (Group 2A) based on limited evidence in humans and sufficient evidence in experimental animals. It was also concluded that there was strong evidence of

genotoxicity and oxidative stress. Four expert panels have been convened for the purpose of conducting a detailed critique of the evidence in light of IARC's assessment and to review all relevant information pertaining to glyphosate exposure, animal carcinogenicity, genotoxicity, and epidemiologic studies. Two of the panels (animal bioassay and genetic toxicology) also provided a critique of the IARC position with respect to conclusions made in these areas. The incidences of neoplasms in the animal bioassays were found not to be associated with glyphosate exposure on the basis that they lacked statistical strength, were inconsistent across studies, lacked dose-response relationships, were not associated with preneoplasia, and/or were not plausible from a mechanistic perspective. The overall weight of evidence from the genetic toxicology data supports a conclusion that glyphosate (including glyphosate-based formulations and aminomethylphosphonic acid) does not pose a genotoxic hazard and, therefore, should not be considered support for the classification of glyphosate as a genotoxic carcinogen. The assessment of the epidemiological data found that the data do not support a causal relationship between glyphosate exposure and non-Hodgkin's lymphoma while the data were judged to be too sparse to assess a potential relationship between glyphosate exposure and multiple myeloma. As a result, following the review of the totality of the evidence, the panels concluded that the data do not support IARC's conclusion that glyphosate is a "probable human carcinogen" and, consistent with previous regulatory assessments, further concluded that glyphosate is unlikely to pose a carcinogenic risk to humans.

2. IARC reply to critique: IARC's initial response to critiques published in the Critical Reviews in Toxicology articles and other comments that questioned the hazard classification, cited its mission, namely that the agency's focus is on assessing cancer hazards, identifying agents capable of causing cancer under some circumstances, rather than risk assessment. It noted that judgments are qualitative, based on an evaluation of available scientific data in "openly available scientific literature," as well as literature accepted for publication, and openly available government documents. IARC further noted that its focus on qualitative evaluation of data rather than assessment of risk to be an important distinction, since something might presently pose a low hazard, but this hazard might change with "new uses or unforeseen exposures" (IARC, 2006). IARC further noted that decisions of policy or regulation, as well as legislation, are the responsibility of individual agencies and governments.

In January, 2018, IARC issued a more detailed response addressing several specific points that developed after publication of its original hazard classification (IARC 2018). In the introduction to this response, IARC noted the following:

> Since the evaluation of glyphosate by the IARC Monographs Program in March 2015, the Agency has been subject to unprecedented, coordinated efforts to undermine the evaluation, the program and the organization. These efforts have deliberately and *repeatedly misrepresented the Agency's work. The attacks have largely originated from* the agro-chemical industry and associated media outlets. They have taken place in the context of major financial interests relating to: a) the relicensing of glyphosate by the European Commission; b) hundreds of litigation cases in the USA brought by cancer patients against Monsanto, claiming that their malignancies were caused by glyphosate use; c) and the decision by the Californian Environmental Protection Agency to label glyphosate as a carcinogen." (California Office of Environmental Health Hazard Assessment 2017)

The response also clarified several points, including the following:

- IARC did not edit parts of the glyphosate monograph to achieve a particular outcome
- Data from the Agricultural Health Study (AHS) [long-term prospective cohort study] were not deliberately excluded from the Monograph
- IARC Monograph evaluations are transparent and open to scrutiny
- IARC has a strong rationale for inclusion of only publicly available studies in Monograph evaluations
- Monograph Working Group members who evaluated glyphosate were free from conflict of interests; this included a discussion regarding the role of an invited specialist who, while invited, was not a member of the IARC working group.
- IARC evaluates only agents that have some evidence of carcinogenicity; however, of those evaluated, roughly half are found not to present evidence of carcinogenicity; 12% have been classified as human carcinogens; and the remaining have been classified as category 2A (probable) or category 2B (possible) carcinogens.
- The monographs program re-evaluates an agent when a substantial additional body of scientific evidence becomes available
- The monograph evaluations place agents in groups according to the strength of evidence of carcinogenicity, not their potency
- IARC monographs identify carcinogenic hazards and do not include a risk assessment

- IARC evaluations make use of the latest scientific data and methodologies
- The monographs do not exclude research conducted by industry per se. Where industry conducted studies are published in scientific journals they are considered, if available in sufficient detail to allow independent scientific review. Under the same conditions, the monographs also take account of industry-conducted research in summary form or if placed in the public domain by national regulatory agencies.

IARC also noted monograph appraisals take account of "real-world" exposures by evaluation of epidemiological studies. These studies are a central part of monograph evaluations and by definition deal with people exposed in daily life, including work. In addition, when considering scientific evidence of carcinogenicity including biological mechanisms, the Working Groups place special emphasis on whether the observations are relevant to humans.

3. Response from other sources: Articles and presentations from other scientists and regulators considering differences in the IARC evaluation and risk assessments from other regulatory agencies have generally taken a more conciliatory approach, either in detailing differences or by raising questions about approach or conclusions. In the National Toxicology Program (NTP) minutes of June 15–16, 2016, as well as a later presentation (National Toxicology Program 2016; Smith-Roe 2016), it was noted that while IARC evaluated glyphosate as a cancer hazard, evaluations of Joint World Health Organization and Food and Agricultural Organization (JMPR), the European Food Safety Authority (EFSA), and the US Environmental Protection Agency (EPA) are comprehensive risk assessments. One member of the JMPR expert panel evaluating glyphosate, comparing the IARC and JMPR assessments, concluded the following: (1) that the carcinogenicity and/or genotoxicity of glyphosate is heavily dependent upon available information, evaluation criteria, and the weighting system used in evaluating the information available; (2) IARC and JMPR had access to different data (publically available vs. published and unpublished studies, respectively), and conclusions reached by both reflect this access and are consistent with criteria used to classify carcinogens; and (3) the JMPR conclusions reflect both data access and the focus on dietary exposures to glyphosate and glyphosate residues (Eastmond 2016).

An evaluation by the EFSA considering a Renewal Assessment Report for glyphosate concluded that "there is 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"(EFSA, 2015). In response to this conclusion, a group of 97 environmental health specialists, toxicologists, epidemiologists, and cancer researchers representing an array of international organizations developed a response commentary (Portier et al. 2017) pointing out not only the differences in the EFSA statement regarding "unequivocal evidence," but also differences, and, as assessed by the authors, weaknesses in the EFSA use of animal and other studies not available to IARC in its deliberations. The authors noted that the EFSA statement was misleading because IARC did not indicate causality between glyphosate and cancer but used the criteria of sufficient evidence, which the IARC working group and others find to be credible. The commentary authors also questioned the way in which the EFSA used data from unpublished studies (hence not available to IARC) to conclude that animal study findings were essentially negative. In 2017, the lead author of the commentary, Christopher Portier, wrote an open letter to Jean Claude Juncker President of European Commission. The letter raised several issues regarding the EFSA and European Chemical Association's evaluation of glyphosate (Portier CJ, Portier 2017).[2] The executive summary of the letter states the following:

> The European Food Safety Agency IEFSA) and the European Chemical Agency IEChA) have completed their assessments of the carcinogenic potential of glyphosate and concluded that the evidence does not support a classification for glyphosate. The raw data for the animal cancer studies for glyphosate have been released, and a reanalysis of these data show eight instances where significant increases in tumor response following glyphosate exposure were not included in the assessment by either EFSA or EChA. This suggests that the evaluations applied to the glyphosate data are scientifically flawed, and any decisions derived from these evaluations will fail to protect public health. I ask that the evaluations by both EFSA and EChA be repeated for all toxicological endpoints and the data underlying these evaluations be publicly released.

[2] Dr. Portier, now a consulting scientist, was formerly director or associate director of several US environmental agencies and, while not participating as a member of the expert panel in the IARC evaluation of glyphosate, did attend the meeting. In his present consulting role, he has been an expert witness for a US law firm involved in glyphosate litigation. Although at the time he attended the IARC meeting, he was not involved in glyphosate litigation, according to a letter from Reps. Lamar Alexander (R-Tex), Andy Biggs (R-AZ), and Frank Lucas (R-OK) (Smith et al. 2017) to Dr. Christopher Wild, IARC Director, Dr. Portier became involved in glyphosate litigation 9 days after the IARC assessment was announced. A publication by Corporate Europe Observatory (Corporate Europe Observatory 2017) defends Dr. Portier's work, noting that he did not sign a contract until 29 days following the IARC meeting, and that more than 90% of his work as an expert witness was "performed and billed" in 2017.

Lay press discussions

At the time it was announced, the IARC designation was given extensive coverage by the lay press and various advocacy organizations. This attention continues.

A number of publications or news services have looked into questions regarding the role that Monsanto may have played in undermining the IARC designation. Others have questioned the integrity of the IARC working group deliberations. The Huffington Post has published a number of articles supporting concerns about glyphosate carcinogenicity and raising questions and issues specifically related to glyphosate and Monsanto. In contrast, the news agency Reuters has published several articles that are in opposition to the IARC finding, and that suggest IARC's evaluations lacked transparency, suggesting that "a draft of a key section of IARC's assessment of glyphosate underwent significant changes before the report was made public" and that "the chairman of the IARC glyphosate panel [not identified] was aware of new data showing no link between the weed-killer and cancer in humans, but the agency did not take it into account because it had not been published." (Kelland 2017).

Both Bloomberg News (Waldman et al. 2017) and the New York Times (Hakim 2017) reported that in 2017, San Francisco federal Judge Vince Chhabria, during litigation proceedings, ordered that internal Monsanto documents be unsealed. Material in the unsealed documents included communications suggesting that Monsanto had ghostwritten research later attributed to academics.

The disclosures highlighted concerns that the academic research Monsanto underwrites and that it frequently cites to back up its safety claims is compromised. As noted earlier, Monsanto, in response to IARC's designation of glyphosate as a category 2A carcinogen, hired a consulting company to identify experts to write articles that were ultimately published in Critical Reviews in Toxicology. When these were published, it was noted that "Neither any Monsanto company employees nor any attorneys reviewed any of the Expert Panel's manuscripts prior to submission to the journal."(McClellan 2016). However, unsealed documents suggest that Monsanto scientists were heavily involved in organizing, reviewing, and editing drafts submitted by the outside experts. A spokeswoman from Taylor & Francis, publisher of Critical Reviews in Toxicology, noted that an investigation is underway. In October 2017, scientists at the Center for Biological Diversity, Center for Food Safety, Pesticide Action Network and Center for Environmental Health, called for retraction of one of the reviews in the series. The group noted that "These are serious offenses and if left unanswered will ultimately undermine the work of many scientists who view scientific ethics to be sacrosanct"(Center for Biological Diversity 2017).

Litigation

IARC's designation of glyphosate as a category 2A carcinogen has been followed by an increase in lawsuits by plaintiffs who have been exposed to glyphosate and who have developed NHL seeking redress. It is difficult, in the US alone, to determine the number of lawsuits. Attorneys for plaintiffs estimate that approximately 4000 lawsuits have been filed (US Right to Know 2017) although verification is challenging.

Interestingly, the conflict between possibility and probability may play a major role in determining the outcome of many lawsuits. Recently, Judge Vince Chhabria, presiding in federal court in San Francisco, assessing whether the plaintiff's arguments demonstrate an exposure-effect relationship was quoted as saying "I do have a difficult time understanding how an epidemiologist in the face of all the evidence that we saw and heard last week" can conclude that glyphosate "is in fact causing" non-Hodgkin lymphoma in human beings. "The evidence that glyphosate is currently causing NHL in human beings" at current exposure levels is "pretty sparse." (Rosenblatt 2018)

While significant litigation involves lawsuits against Monsanto, other litigation does not. In February 2018, a federal judge ruled against cancer warnings on food that may contain trace amounts of glyphosate. The suit against the state of California was brought by major agricultural producers in California (Polansek 2017).

US government response

The IARC assessment of glyphosate as a category 2A carcinogen has been a subject of on-going activity by the congressional House committee on Science, Space, and Technology. In 2017, two senior committee members sent letters to both Christopher Wild, head of IARC and to Acting Secretary of Health and Human Services (HHS) Eric Hargan regarding what the writers regarded as conflicts of interest, the lack of transparency in the IARC deliberations, and statement about funding and the use of US taxpayer funding of IARC work (Committee on Science, Space, and Technology 2017). These same issues were revisited at a February 6, 2018 hearing of the full committee on Science, Space, and Technology. In his opening remarks, the committee chair, citing food security issues as well as "selective use of data and lack of public disclosure" suggested support for withholding US government funding for IARC work in the future (Committee on Science, Space and Technology 2018). A committee member of the minority party, in opening statements, while supporting the importance of innovation by the chemical industry, outlined concerns about industrial pressure on government agencies that may compromise free and open discussion of work evaluating the potential health hazards of glyphosate.

While it can be expected that the debates and controversies regarding glyphosate will continue, to date, no legislation related to US government funding for IARC or WHO has been enacted.

Environmental justice: agricultural workers and glyphosate

It would be difficult to discuss health and safety questions regarding glyphosate without considering environmental justice. No single definition exists for the term environmental justice; however, for purposes of this discussion, environmental justice is characterized by Berkey (2017a) as a productive definition. Specifically, it is defined as "A form of justice based on addressing the political-economic structures that produce environmental problems, aimed at creating a system within which we focus on causes rather than symptoms. Emphasizes participation in the decisions through which environmental burdens are produced. Characterized by a movement from 'not in my backyard' to a 'not in anyone's backyard' political frame". The EPA further characterizes the term in the following legal definition:

> [Environmental Justice is} [T]he fair treatment and meaningful involvement of all people regardless of race, ethnicity, income, national origin, or educational level with respect to the development, implementation and enforcement of environmental laws, regulations and policies. Fair treatment means that no population, due to policy or economic disempowerment, is forced to bear a disproportionate burden of the negative human health or environmental impacts of pollution or other environmental consequences resulting from industrial, municipal, and commercial operations or the execution of federal, state, local, and tribal programs and policies (United States Environmental Protection Agency 2017).

Within this context, it is important to consider whether acute and chronic health effects of glyphosate on farmworkers has been addressed. To date, information has been relatively limited and confined to workers who have steady employment in the farming sector. This includes a study monitoring urinary excretion of glyphosate or AMPA among glyphosate applicators and their family members (Acquavella et al. 2004) that found little glyphosate in urine after a 48-h period, although somewhat more was excreted among workers who wore less protective gear. The Agricultural Health Study considered by IARC as an epidemiologic study of cancer development from glyphosate exposure studied cancers in a cohort of glyphosate application workers, generally long-term farmworkers who, when applying glyphosate, wore protective gear (De Roos, De Roos et al. 2005). This study did not find a statistical association between cancers and glyphosate exposure, although the study was sufficiently short that it might not be adequate to address latency in cancer development. Several case-control studies that did report a stronger association were considered well executed; however, case-control studies may be subject to selection bias.

Missing in almost all investigations is information about acute or chronic toxicity among a very large group of farmworkers, namely, seasonal or migratory farm and agricultural workers. Agricultural workers (including landscape workers) are, most likely, those most exposed on a continual basis, coming into continual contact with glyphosate, often together with a number of other herbicides and pesticides. This contact is frequently without adequate protection. Rao et al. (2004) point out that farmers believe that, since they most often mix and apply pesticides, they, not farmworkers, are most at risk for any negative health outcomes from this exposure [Rao et al. 2004]. Farmers believe that workers, because they do not mix and apply pesticides or herbicides or enter fields immediately after application, are not vulnerable. That is, residues were not seen as a source of exposure. However, despite regulatory requirements, farmworkers were frequently not given adequate information, nor were they fully aware of how they might be better protected (Rao et al. 2004).

However, as noted by Flocks (Flocks 2012)

> Farmworkers are exempt from many regulations that could afford indirect protection under the system of agricultural `exceptionalism,' which emerged during a historical time in the US when institutional discrimination was accepted and prevalent. Even when protective regulation does exist, however, many employers use a variety of practices-such as hiring labor contractors or a temporary workforce-that allow them to circumvent laws and transfer many of the physical and economic risks of agricultural employment to the workers.

While the USA is not representative of farm worker practices on a global basis, policies in the USA are an effective representation of practices in developed nations. Hence, an examination of issues in the USA provides good insight into farm worker issues in developed countries. To date, little definitive information is available about glyphosate's effects on this group. Not only might such information provide greater power to studies looking at chronic effects of glyphosate in real-life exposure scenarios, but if strong links were found between exposure and outcomes, these should strengthen worker protection measures.

Arcury and coworkers (Acury, et al. Arcury et al. 2006) identify several factors that are challenges in collecting consistent information that could be used to ensure environmental justice for seasonal and migratory farmworkers. Specific challenges include the following:

1. Number of farmworkers at risk. Many workers are seasonal, migratory or both. In the USA, roughly 42 of 50 states employ farmworkers fitting into one or both of these categories. The majority self-identify as Hispanic. The US Department of Labor's National Agricultural Workers Survey provides the following information: (Farmworker Justice 2014)

   - Roughly 48% of farmworkers lack authorization
   - Other sources consider this to be low, estimating that as much or more than 70% of workers may be undocumented
   - Translated to numbers, this means that 1.2 to 1.75 million farmworkers are undocumented
   - Of all farmworkers, roughly 33% are US citizens, 18% are lawful permanent residents, and 1% has work authorization

Given that present immigration policies are unlikely to provide accurate estimations, of undocumented workers, those with seasonal permits, those with residency status, or those who are legal immigrants, and that data cited above have been provided to a US government agency, the actual numbers are unlikely to provide an accurate and current description of farm and agricultural worker composition. Members of many groups may be hesitant to communicate with authorities.

2. Mobility. Documented and undocumented workers move frequently, both within farming season and between seasons.
3. Residence status. Those who are US citizens or permanent residents may, although mobile, be more likely to return to particular work areas and may be more secure to note disparities in health and safety conditions because of work security. Guest workers holding H2 visas are less mobile and, fearing the consequences of reporting, may not report health and safety disparities. Undocumented workers, fearing deportation, are highly unlikely to report adverse health outcomes.
4. Communication obstacles. In the USA, farmworkers speak a variety of languages other than English. Many have not received an education beyond the early secondary level, and some received even fewer years. While Spanish is the most commonly spoken language, many dialects are spoken. In some cases, language is a mixture of indigenous languages and Spanish. Although different in specifics, these same linguistic and obstacles can be found in other developed countries. A study of Kelley (Kelley et al. 2013) examining health care for female farmworkers found that few health clinic workers spoke a language other than English but depended on available translation services for communication.
5. Exposure assessment and bio-monitoring. Typical methods of exposure assessment require that workers donate blood or urine samples or both, that the samples can be properly stored, and that analytic facilities be available for analysis. Equipment limitations, reluctance on the part of workers to donate samples, and, at times, poor cooperation or coordination with local health agencies charged with obtaining samples are often obstacles.
6. Health outcomes: Monitoring short-term acute responses is limited by the availability of health care. Many workers are hesitant to seek health care (Berkey 2017b) because of fears about loss of work or other consequences. Facilities to diagnose and treat long-term chronic conditions are, quite likely, not available, and many health clinicians lack training in occupational health (Kelley et al. 2013). Data about chronic outcomes among workers are also very difficult if not impossible to obtain because of follow-up considerations.

While cancer is often the major focus of long-term effects, it is not the only long-term chronic health outcome. Little or no information is available about such long-term effects as endocrine disruption, pregnancy outcomes, neurotoxicity, or development in children who may be exposed "second hand" from clothing and equipment brought home by parents working in the field. Additionally, agricultural workers are rarely, if ever, exposed only to one herbicide or pesticide. This makes it challenging to attribute any health outcome to glyphosate exposure, and at the same time, it is difficult to predict the synergistic effects of glyphosate in combination with other commonly used pesticides and herbicides.

Addressing many of these issues requires the development of and intervention of advocacy groups. As noted by Reeves and Shafer (Reeves and Schafer 2003) "In many states farmworkers are denied the right to organize, receive no compensation for workplace injuries, and are not paid at a higher rate for overtime work. Farmworkers are specifically excluded from the right to organize under the National Labor Relations Act, which only some states, including California, have redressed by enacting Agricultural Labor Relations acts." Existing advocacy groups include groups such as the California Rural Legal Assistance Foundation, the Pesticide Action Network, and the United Farmworkers, which, although having a voice in California, does not universally have a voice. Despite these limitations, organizations such as the United Farm Workers have worked to address farmworker safety from glyphosate exposure. A letter dated May 08, 2017 from Arturo S. Rodriguez (Rodrigurez, Rodriguez 2017), president of the UFW to Esther Barajas-Ochoa of the

California Office of Environmental Health Hazard Assessment, states:

> On behalf of the United Farm Workers of America, we hereby request that a hearing be held regarding the proposed Safe Harbor for Monsanto's compliance with Proposition 65's required carcinogen warnings for Roundup. We are concerned that the No Significant Risk Level (NSRL) for this Safe Harbor does not take into account the dermal exposure experienced by farm workers. We would like to have a hearing to address appropriate analysis of other studies than the one identified in the Initial Statement of Reasons: Glyphosate Proposition 65 Safe Harbor, and especially to address California Code of Regulations § 25703's requirement that epidemiological data, i.e. human data, be included in the Safe Harbor's NSRL analysis. We believe studies that take into account what our member farm workers endure each day in fields sprayed with Roundup must be part of any Safe Harbor analysis.

The Rodriguez letter is a rare instance in which potential health and safety issues of one agricultural chemical are addressed, an opportunity possible because of California Proposition 65.[3] As noted, however, this is generally not the case. However, key challenges in protecting agricultural workers from potential adverse effects of agricultural chemicals can be identified and addressed. It is also possible to characterize the limitations of immediate health care and follow-up care. Addressing these issues would be a significant step to providing greater protections and addressing injustices.

As IARC notes in its mission statement, in determining the carcinogenic hazard of a substance, its role is to address the issue not only in developed countries but in less developed and developing countries. In such countries, for a variety of reasons, fewer protections may be available (Goldman and Tran 2001). In part, this is because pesticide and herbicide use is not part of traditional agricultural practices, and little training is available about safe use. Farmers are often unaware of the short- and long-term hazards associated with exposure to many pesticide and herbicide products, and they are often used inefficiently and unsafely. This may include excessive use, eating and drinking while working, lack of water and facilities for personal hygiene (often true in developed countries as well), lax storage practices, and careless disposal of empty containers. In addition, poor maintenance facilities for spray equipment can lead to hazardous contamination and use of pesticide mixtures. Occupational health legislation and regulations are often extremely weak in the developing countries. Most developing countries still do not require that imported pesticides be registered.

Discussion and conclusion

Originally introduced in 1974 as the active ingredient in the herbicide Roundup™, glyphosate was considered to be a breakthrough because of its targeted toxicity to bacteria and plants, as well as its very low acute toxicity in humans and other mammals. It was initially used in farming before crops were sown, and following crop harvest, for weed control among fruit trees in orchards, in landscaping, and to remove weeds surrounding in track and power lines. However, its use grew dramatically following the introduction of genetically engineered Roundup-Ready™ seed by the Monsanto Chemical Company in the mid-1990s. It then became possible to use glyphosate during crop growth to minimize invasion of unwanted plants. Today, a variety of Round-Ready™ crops are grown. The use of both GM seed and glyphosate is global.

Available data suggest that the application of glyphosate has grown 200-fold in farming and 300-fold in non-agricultural practices in the USA over the period 1974 to 2014. Although it is possible to locate information about the number and variety of crops grown using from Round-Ready™ seed in developed countries such as the USA, accurate and up-to-date data are more difficult to obtain when looking at developing and less developed countries. Nevertheless, it is clear that global glyphosate use has also grown and spread significantly over this same time period. Interestingly, while not all growth can be attributed to the introduction of Roundup-Ready™ seed, it is quite likely that most can. Thus, while the Monsanto patent on glyphosate expired in the early 2000s, glyphosate continues to be produced not only by Monsanto, but also by a number of other companies, including several in China. Each may use slightly different formulations of the herbicide, formulations that are generally proprietary in nature.

Because of its low acute toxicity, its rapid breakdown, and the low toxicity of breakdown products, it was initially felt that there was little likelihood that glyphosate would persist in the environment. However, an accumulating body of evidence suggests that it can persist, spreading to the atmosphere attached to soil dusts, as run-off in lakes and streams, and, albeit in small quantities, into the water table. The spread has led to two concerns: the overall impact on ecosystems and potential toxicity to animals from long-term low-level exposures. The

[3] In November 2017, a lawsuit was filed in California (National Association of Wheat Growers et al. v. Lauren Zeise, director of OEHHA, et al., US District Court, Eastern District of California), by several farm groups and Monsanto against the California Office of Environmental Health Hazard Assessment to halt labeling under Proposition 65. The suit claims that the requirement would mandate that foodstuffs made from crops grown with glyphosate be labeled, and that such a requirement is an undue burden. According to Scott Partridge, Monsanto Vice President of global strategy, "Such warnings would equate to compelled false speech, directly violate the First Amendment, and generate unwarranted public concern and confusion." (Polansek 2017)

expected continuing growth of glyphosate use can be expected to intensify these concerns.

Glyphosate targets a pathway unique to plants and microorganisms needed for growth. While, as initially used, targeted plants and microorganism "by-standers" cannot grow, both readily undergo mutational changes. The presence of glyphosate in microenvironments thus creates a selective pressure for resistant organisms. In soils, resistant microorganisms have been found to replace other strains. This can change soil composition and may result in less fertile and productive soils. While the precise outcome of these changes is difficult to predict, the increasing number of reports raises concerns. Among plants, the widespread use of glyphosate has also created a selective pressure for resistant weeds. In response to the latter, Monsanto now markets products containing both glyphosate and other herbicides. While each component of these herbicide mixtures may have relatively low toxicity, it is not clear what synergistic effects might result.

An accumulating body of evidence suggests that glyphosate is toxic to a number of animal species found in the environment. Although some studies, focusing on acute toxicity, may not be predictive of long-term outcomes, several studies looking at earthworms found glyphosate in smaller amounts had adverse effects. These may be of concern because of the essential role that earthworms play in maintaining healthy soils.

An equal concern is the potential of adverse human health effects from the continuing and growing use of glyphosate in agriculture. Over time, it is probable that significant and increasing numbers of the general public ingest glyphosate: it is quite likely that commercially processed soy and corn products will contain trace amounts of glyphosate, and it is also likely to be found in a variety of other farm products, especially produce from large-scale industrial farms. It may also, in trace amounts, be found in dairy products. Risk assessment determinations from several regulatory agencies, based on probable dietary intake, find that glyphosate poses no health concerns to the general public. These determinations may not, however, address health concerns for those exposed to larger amounts on a recurrent basis. In the USA and other developed countries, a significant number of those exposed to higher amounts are farm and landscape workers, whose work is seasonal and migratory. Such workers may be undocumented, may face language and literacy challenges, and frequently lack access to consistent health care with any follow-up. Few data are available for these groups.

In 2003, Reeves and Shafer (Reeves and Shaver, Reeves and Schafer 2003) describe an analysis by Pesticide Action Network, United Farmworkers of America, and California Rural Legal Assistance Foundation of government data from California government data on agricultural poisonings and enforcement of worker safety standards that found no evidence of glyphosate carcinogenicity. They note, however, that these data are limited by factors described above and may they not accurately reflect the realities of pesticide exposure, including glyphosate. Another similar study reports an association between cancer and environmental exposure (Avila-Vazquez, Avila-Vazquez et al. 2017). In both cases, the authors point out that more precise information is needed to determine whether or not associations exist.

When initially introduced, both the National Toxicology Program in the USA and IARC as an international agency did not view glyphosate as posing any long-term health threat. This issue has recently been revisited by both agencies. To date, NTP has not issued a final report. The 2016 finding of IARC that glyphosate is a probable carcinogen has been a contentious and polarizing issue. While some of the debates can be found in the peer-reviewed literature and could be regarded as deliberations within the scientific community, others are published in the lay press and have, at times, been accusatory in nature. Scientific integrity has also been questioned in several publications. Recent US congressional hearings, using arguments of food security, suggested that US funding should not be provided to IARC, given their "contested" finding which may "threaten" food security. Within the regulatory community, differences in access to data, and possible differences in use of data, depending on the source can have an impact on risk assessment. Myer and Hilbeck (Meyer and Hilbeck 2013) address this issue with respect to the European Food Safety Agency's risk assessment of glyphosate at that time, noting "critical double standards in acceptance and rigor of the evaluation of feeding studies submitted as proof of safety for regulatory approval to EFSA." The 2013 risk assessment had access both to unpublished data from chronic animal studies as well as articles from peer-reviewed literature; differences in the data may have led to differences in weight given in the final assessment.

Many believe that glyphosate is now ubiquitous in the environment. While it might be argued that given its low acute toxicity and controversies surrounding chronic health and environmental effects, this issue is not of paramount importance. However, the ubiquitous presence makes it challenging to carefully assess negative effects. It is also important to note that the global presence, because it is under corporate control of several agribusiness giants, means that, on a global basis, farmers face higher prices. As noted by Bratspies (2017), farmers now face higher prices (an increase of 143% for GE soy seed between 2000 and 2010). Profits from sales did not keep up with seed cost. As noted earlier, more glyphosate is needed to control weed growth, and, at the same time, more unwanted plants are glyphosate resistant, which has led to industry development of GM seed with resistance to glyphosate and other herbicides. While it may be premature to anticipate global spread of such seed and the use of a mixture of herbicides on the same global basis as glyphosate use today, the possibility of such a development, the potential for overuse of such mixtures, and the likelihood of global circulation of products could lead to closure of what Faber (1993) describes as "the circle of poison."

It may be worthwhile as the debates about glyphosate continue to consider other so-called breakthroughs. A particularly compelling example is the discovery and development of antibiotics. When they were originally introduced, many believed that infectious disease would be a thing of the past. However, their "over-use" coupled with the ability of bacteria to develop resistance mutations has led, rather than to the eradication of infectious disease, to increasing challenges for infectious disease treatment. Although the pharmaceutical industry is able to develop new antibiotics, no "master strategy" exists. Judiciously used, antibiotics are a powerful tool. Improperly used, they have negative effects, not only on those potentially affected but on the ecosystem as a whole. By comparison, when introduced, few felt that glyphosate created a health hazard. This is now a significant question, and, at the same time, more and more plants are resistant, moving the agri-business community to develop herbicide mixtures that, taken together, may be more toxic.

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