



Controversies over human health and ecological impacts of glyphosate: Is it to be banned in modern agriculture?*



Islam Md. Meftaul ^{a,b}, Kadiyala Venkateswarlu ^c, Rajarathnam Dharmarajan ^a,
Prasath Annamalai ^a, Md Asaduzzaman ^e, Aney Parven ^{a,b}, Mallavarapu Megharaj ^{a,d,*}

^a Global Centre for Environmental Remediation (GCER), Faculty of Science, The University of Newcastle, Callaghan, NSW 2308, Australia

^b Department of Agricultural Chemistry, Sher-e-Bangla Agricultural University, Dhaka 1207, Bangladesh

^c Formerly Department of Microbiology, Sri Krishnadevaraya University, Anantapuramu 510003, India

^d Cooperative Research Centre for Contamination Assessment and Remediation of the Environment (CRC CARE), The University of Newcastle, Callaghan, NSW 2308, Australia

^e NSW Department of Primary Industries, Pine Gully Road, Wagga Wagga, NSW 2650, Australia

ARTICLE INFO

Article history:

Received 17 November 2019

Received in revised form

9 February 2020

Accepted 12 March 2020

Available online 14 March 2020

Keywords:

Glyphosate

Aminomethylphosphonic acid (AMPA)

Polyethoxylated tallow amine (POEA)

Human and ecological health

Herbicide resistance

ABSTRACT

Glyphosate, introduced by Monsanto Company under the commercial name Roundup in 1974, became the extensively used herbicide worldwide in the last few decades. Glyphosate has excellent properties of fast sorption in soil, biodegradation and less toxicity to nontarget organisms. However, glyphosate has been reported to increase the risk of cancer, endocrine-disruption, celiac disease, autism, effect on erythrocytes, leaky-gut syndrome, etc. The reclassification of glyphosate in 2015 as 'probably carcinogenic' under Group 2A by the International Agency for Research on Cancer has been broadly circulated by anti-chemical and environmental advocacy groups claiming for restricted use or ban of glyphosate. In contrast, some comprehensive epidemiological studies involving farmers with long-time exposure to glyphosate in USA and elsewhere coupled with available toxicological data showed no correlation with any kind of carcinogenic or genotoxic threat to humans. Moreover, several investigations confirmed that the surfactant, polyethoxylated tallow amine (POEA), contained in the formulations of glyphosate like Roundup, is responsible for the established adverse impacts on human and ecological health. Subsequent to the evolution of genetically modified glyphosate-resistant crops and the extensive use of glyphosate over the last 45 years, about 38 weed species developed resistance to this herbicide. Consequently, its use in the recent years has been either restricted or banned in 20 countries. This critical review on glyphosate provides an overview of its behaviour, fate, detrimental impacts on ecological and human health, and the development of resistance in weeds and pathogens. Thus, the ultimate objective is to help the authorities and agencies concerned in resolving the existing controversies and in providing the necessary regulations for safer use of the herbicide. In our opinion, glyphosate can be judiciously used in agriculture with the inclusion of safer surfactants in commercial formulations sine POEA, which is toxic by itself is likely to increase the toxicity of glyphosate.

© 2020 Elsevier Ltd. All rights reserved.

1. Introduction

Glyphosate (N-(phosphonomethyl) glycine) is the world's most common commercial synthetic phosphonate herbicide introduced by Monsanto Company, USA under the commercial name Roundup

in 1974 (Bento et al., 2016; Duke, 2018). It has been extensively used as a broad-spectrum, nonselective systemic herbicide for broadleaf weed control and as plant growth regulator for lawns/turfs, home gardens, parks and agricultural crops (Botero-Coy et al., 2013; Bento et al., 2016). Several glyphosate-based herbicide formulations are widely used on more than 100 crops for controlling both annual and perennial weeds in areas of agriculture, residences, forests, greenhouse and industrial sectors over 130 countries (Monsanto, 2009; Mink et al., 2011). In USA, about 750 products of glyphosate mostly in the form of acid and several salts are available for sale. Among them, the most frequently applied commercial

* This paper has been recommended for acceptance by Da Chen.

* Corresponding author. Global Centre for Environmental Remediation (GCER), Faculty of Science, The University of Newcastle, ATC Building, University Drive, Callaghan, NSW 2308, Australia.

E-mail address: megh.mallavarapu@newcastle.edu.au (M. Megharaj).

formulations contain isopropylamine (IPA) salt of glyphosate, surfactants like polyethoxylated tallow amine (POEA), and water (Giesy et al., 2000; Saunders and Pezeshki, 2015). The molecule of this organophosphate contains three polar functional groups such as $-NH_2$, $-COOH$ and $-PO_3H_2$ (Ren et al., 2014). Phosphonomethyl derivative of glycine is the free acid that exists as a zwitterionic amphoteric substance containing three acidic sites for deprotonation and one amino group for protonation (Sheals et al., 2001). The main function of the widely used surfactant, POEA, is to facilitate the entry of glyphosate across the cuticle of target plants (Guilherme et al., 2012; Mesnage et al., 2013).

The Monsanto Company marketed several herbicide formulations such as Roundup Pro®, Roundup PowerMAX™, Roundup WeatherMAX®, Roundup^{CT} and AquaMaster® (Monsanto, 2005). Some other companies like Zeneca, SinoHarvest, DuPont Dow AgroSciences, Syngenta, Nufarm, etc. have also been marketing this herbicide. The salt formulations contain the active ingredient in variable concentrations and cations such as monoammonium, dimethylammonium, isopropylammonium, sodium and potassium as the counter ions, or dianionic form paired with one protic cation like diammonium salt or more than one cation including potassium/ammonium salt (Tomlin, 2009; Nufarm, 2014; Pernak et al., 2014). Fig. 1 presents several special features of glyphosate such as rapid soil binding, biodegradation, non-volatility, stability in sunlight, complete solubility in water, easy applicability on crops, and less toxic to a wide array of living organisms (Borggaard and Gimsing, 2008; Valavanidis, 2018).

The use of glyphosate has been successfully extended globally ever since the introduction and approval for cultivation of glyphosate-resistant (GR) crops in 1996 (Ge et al., 2012; James, 2016; Duke, 2018). In fact, genetically modified (GM)-GR crops play a vital role in economic benefits in the US agricultural sector contributing an increase up to 22 and 68% in crop yields and profits, respectively, over non-GM crops (Klüpper and Qaim, 2014). Consequent to the continuous application of glyphosate over the last 45 years, selective GR populations evolved and approximately 38 GR weed species have been reported in the fields planted to transgenic GR crops worldwide (Powles and Yu, 2010; Heap, 2011). Also, there is a growing concern about the possible health and environmental impacts of glyphosate caused during the manufacture, transportation and application of this herbicide (Relyea, 2005a; Meftaul et al., 2020). Indeed, the effluents with high

concentrations of glyphosate and NaCl released during manufacturing are extremely hard to purify (Ren et al., 2014), posing a potential long-term threat to the ecological and human health due to its persistence in water and soils (Bai and Ogbourne, 2016).

Glyphosate has been shown to induce multiple antibiotic resistance in bacteria such as *Escherichia coli* and *Salmonella enterica* serovar Typhimurium (Kurenbach et al., 2015). Very recently, Ramakrishnan et al. (2019) highlighted the global implications, in terms of developing antimicrobial resistance in soil bacteria, as a result of local applications of pesticides like glyphosate. Glyphosate-based formulations have also been considered toxic to other living organisms such as amphibians, fishes, reptiles, birds, etc. (Giesy et al., 2000; Howe et al., 2004; Oliveira et al., 2007; Moore et al., 2012; Carpenter et al., 2016; Lugowska, 2018). Several other studies also indicated that glyphosate in commercial formulations even at concentrations below regulatory limits cause carcinogenic, hepatorenal, teratogenic and tumorigenic effects, besides posing endocrine disruption, metabolic alterations and oxidative stress, depending on dose and exposure time (Mesnage et al., 2015b; Myers et al., 2016). Such health concerns were considered more alarming after the reclassification of glyphosate as a possible carcinogen (Group 2A) in 2015 by IARC (Valavanidis, 2018). In view of the adverse effects on ecological and human health as well as the development of resistance in several weeds and antimicrobial resistance in bacteria, the use of glyphosate-based formulations in the recent years has been either restricted or banned in approximately 20 countries including Malawi, Thailand, Sri Lanka, Vietnam, Oman, Saudi Arabia, Kuwait, United Arab Emirates, Bahrain, Qatar, Bermuda, Costa Rica, St Vincent and the Grenadines, Austria, Belgium, Denmark, France, The Netherlands, Czech Republic, and Italy (Saunders and Pezeshki, 2015; Sustainable Pulse 2019).

Researchers as well as regulatory authorities such as the US Environmental Protection Agency (USEPA), the Canadian Pest Management Regulatory Agency, and the European Commission reviewed the safety of glyphosate and concluded that judicious applications of glyphosate do not pose carcinogenic or genotoxic threat to the humans (Kier and Kirkland, 2013; Authority, 2015; Canada, 2015; Williams et al., 2016). Moreover, many investigations concerning glyphosate toxicity to higher animal including birds, dogs, fish, mice, rabbits, rats and other animals

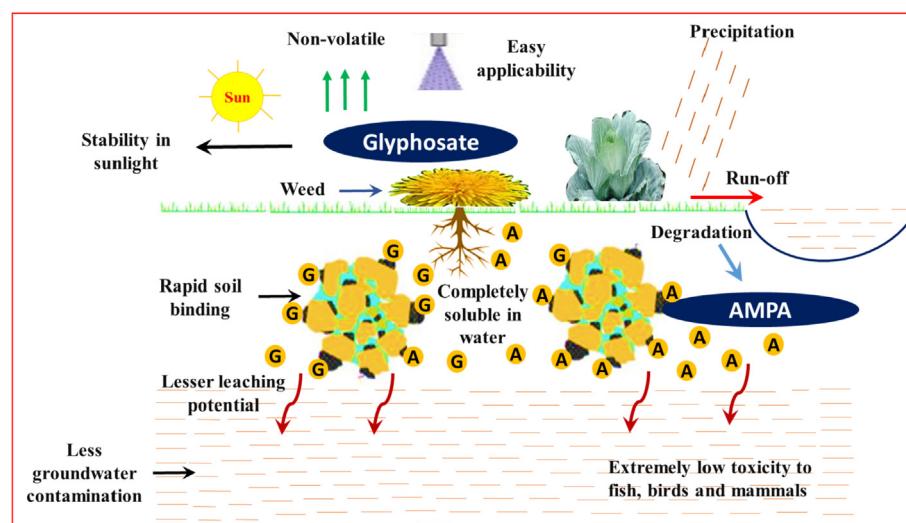


Fig. 1. Properties par excellence of glyphosate in the environment. G = glyphosate and A = Aminomethylphosphonic acid (AMPA).

suggested that glyphosate active ingredient is mostly non-toxic or least toxic and the adverse effects could be observed only at higher concentrations (Giesy et al., 2000; Monheit, 2007; NTP, 2007; Borggaard and Gimsing, 2008; Battaglin et al., 2014; Saunders and Pezeshki, 2015; Valavanidis, 2018). The surfactant, POEA, contained in Roundup has been reported to be relatively more toxic compared to the adjuvants present in other formulations of glyphosate (Mesnage et al., 2013; Kwiatkowska et al., 2014b; Mesnage et al., 2015b; Carpenter et al., 2016; Van Bruggen et al., 2018). In fact, both the surfactants, POEA and MON 0818 (75% POEA), were found to have an adverse impact on aquatic and terrestrial animals (Van Bruggen et al., 2018). Moreover, the toxicity of the primary metabolite of glyphosate, aminomethylphosphonic acid (AMPA), is either similar or less as compared to the parent compound (Borggaard and Gimsing, 2008; Howe et al., 2004; Moore et al., 2012). However, some other studies indicated that the toxicity risk of AMPA, in view of its longer persistence in the environment, is higher when compared with glyphosate (Bonnet et al., 2007; Daouk et al., 2013; Guilherme et al., 2014; Domínguez et al., 2016). All these controversies raise a question as to whether glyphosate, a potent herbicide widely applied in modern agriculture, should be used with restrictions or banned. In this direction, a clear understanding of the overall controversial scenario about the behaviour and fate, and the adverse impacts of glyphosate on humans, terrestrial and aquatic animals is greatly warranted. Therefore, the aim of the present critical review is to consolidate the extant literature in a single source on (a) the fate of glyphosate and its residues in the environment, (b) the extent of glyphosate resistance in weed species and microorganisms, and (c) the potential threat of this herbicide to ecological and human health. Thus, this review will aid the regulatory organizations and other authorities in providing the necessary precautions and guidelines for the future use of glyphosate.

2. Behaviour and fate of glyphosate in the environment

The fate and behaviour of glyphosate in soil depend on the interactions between herbicide and soil under the specific local environmental conditions (e.g., precipitation, temperature, wind speed, etc.), and are influenced by diverse soil factors and processes (Gimsing et al., 2004b; Locke and Zablotowicz, 2004). In addition, the application rates and formulations also have a potential influence on the fate and behaviour of a pesticide (Rampazzo et al., 2013).

2.1. Sorption–desorption

Sorption-desorption behaviour of glyphosate is important for understanding its potential environmental health risks as well as the fate and distribution in the waterways as well as (Ruiz-Toledo et al., 2014). The soil physico-chemical properties such as organic matter content, acidity, and texture largely influence the irreversible or reversible reaction of glyphosate in soil (Laitinen, 2009; Ortiz et al., 2017). Because glyphosate is a small molecule with carboxyl, amino and phosphonate groups, it is strongly sorbed by minerals in soils (Gimsing et al., 2007). Also, glyphosate is strongly sorbed onto clay and organic matter and relatively immobile in the soil, making it somewhat inaccessible for microbial degradation and consequently accumulating in soils over time (Cassagneul et al., 2016; Sidoli et al., 2016; Okada et al., 2017). Thus, in clay soils, glyphosate and AMPA can persist for more than a year and quickly wash out in sandy soils (Sidoli et al., 2016; Okada et al., 2017). Glyphosate and its primary metabolite AMPA have >96 and >78% sorption affinities, respectively, to clay mineral, soil organic matter, mud sediments and particularly soil oxides and hydroxides, which

act as a sink for the herbicide (Gimsing et al., 2004a; Skeff et al., 2018).

Glyphosate can bind to humic substances through its phosphonic acid moiety and react with polyvalent cations sorbed on organic matter and clays (Piccolo et al., 1996; Ortiz et al., 2017). Sandy sediments showed a weak sorption capacity to glyphosate and AMPA, whereas silty sediments exhibited a higher tendency to these compounds (Skeff et al., 2018). Glyphosate contains low Henry's constant value ($<1.44 \times 10^{-12}$ atm·m³ mole⁻¹) which indicates its tendency to partition in water-air and is readily adsorbed onto soil particles (Schuette, 1998). Sorption capacity of both the parent compound and its metabolite is considerably reduced with increased pH, salinity or temperature of the soil solution (Skeff et al., 2018). Soil minerals, particularly Fe and Al oxides/hydroxides as well as broken surfaces of silicate minerals have strong influences on sorption of glyphosate by its phosphonate, carboxyl, and amino groups whereas inorganic phosphorus competes with glyphosate for sorption sites, and hence mobility of glyphosate is higher (Si et al., 2013; Norgaard et al., 2014; Padilla and Selim, 2019). In soils with a pH range of 4–8, glyphosate acts as a polyprotic acid with high affinity to mono- and divalent anions as well as trivalent cations like Al³⁺ and Fe³⁺ (Barja and dos Santos Afonso, 2005). Sorption of glyphosate is not entirely permanent since desorption occurs after certain contact time. For instance, 15–81% desorption of sorbed glyphosate was observed after two steps, each with a contact period of 2 h (Piccolo et al., 1994), and desorption of 6–23% was also found in batch experiments during five successive steps, each with a contact time of 16 h (WHO, 1994).

2.2. Mobility

Mobility of glyphosate in different environment settings is limited theoretically due to its high sorption capacity in soils (Borggaard and Gimsing, 2008; Sidoli et al., 2016). The amount of glyphosate available for leaching is governed by the dose, prevalence, preferential flow, sorption and degradation (Norgaard et al., 2014). Glyphosate is strongly sorbed into soil particles because of its high soil sorption coefficient ($K_d = 61 \text{ g cm}^{-3}$) and is less mobile in soil due to its very low octanol/water partition coefficient ($K_{ow} = 0.00033$) (Skeff et al., 2018). Glyphosate leaching is generally determined by rainfall and soil structure, whereas sorption and degradation affect glyphosate mobility in soils (Borggaard and Gimsing, 2008). It may be transported either in dissolved or particle form and therefore reach surface waters (Coupe et al., 2012; Aparicio et al., 2013). Since the primary metabolite of glyphosate, AMPA, is more mobile than the parent compound, it is frequently detected in both surface and groundwaters globally (Kolpin et al., 2006; Skeff et al., 2015). The volatilization of glyphosate into the atmosphere is negligible because of its less mobility in the soil and low vapour pressure (9.8×10^{-8} mmHg at 25 °C) (Giesy et al., 2000). Besides, runoff is another source of glyphosate movement to waterways from the agricultural field and urban areas as in impervious and connected paved surfaces (Hanke et al., 2010; Grandcoin et al., 2017). Hence, glyphosate application is prohibited on such impervious and connected surfaces in some countries of Europe (Rosenbom et al., 2010, 2015). Although glyphosate residues have been frequently detected in different settings of the environment globally, its potential risk in the ecosystem, in terms of groundwater ubiquity score (GUS), leachability index (LIX) and hysteresis index (HI), has not been fully understood.

2.3. Degradation

Glyphosate degradation involves biotic and abiotic pathways in

the environment. Microbial degradation of glyphosate is the major pathway affecting its fate and behaviour in the soil, whereas photodegradation and chemical degradation play a minor role (Alexa et al., 2009; Sviridov et al., 2015). The degradation rates for glyphosate were higher within the first four days, and the range in per cent degradation, in terms of the amount initially applied in different agricultural soils, was 7–70 (Nguyen et al., 2018). Microbial degradation of glyphosate proceeds in an initial formation of intermediates like sarcosine and glycine, and subsequent release of AMPA (Borggaard and Gimsing, 2008). However, both biotic and abiotic degradation pathways yield AMPA as the major metabolite of glyphosate (Borggaard and Gimsing, 2008; Al-Rajab and Hakami, 2014) which is phytotoxic in nature and have negative effects on plant physiology, but the underlying mechanisms of these effects have not been clearly elucidated (Gomes et al., 2014). Microbial activities in soils are strongly regulated by soil moisture and temperature, organic matter content, pH and soil texture, consequently affecting glyphosate degradation and AMPA formation (Zhang et al., 2015). Glyphosate mineralization rate increases with increased temperature and soil moisture (Schroll et al., 2006; Grundmann et al., 2008). Manganese oxide or other metals present in soils strongly influence the abiotic degradation of glyphosate (Barrett and McBride, 2005; Ascolani Yael et al., 2014). The glyphosate degradation also depends on its structural affinity to certain transformations as well as some environmental conditions (Fenner et al., 2013). Although AMPA is more persistent with a half-life of 23–958 days in soil than glyphosate (1–197 days), most of the studies focussed only on glyphosate (Laitinen et al., 2006; Bergström et al., 2011; Sihtmäe et al., 2013; Yang et al., 2015a). Soil properties and environmental conditions strongly influence the persistence of glyphosate and AMPA in the environment. In clay soils of Sweden, glyphosate and AMPA exhibited half-lives up to 151 and 98 days, respectively, whereas in a loamy soil of China the half-life was only up to 10 days (Zhang et al., 2015; Fishel, 2017). Thus, the extended half-life and long-term environmental contamination of glyphosate and AMPA might pose a potential risk to the human and ecological health (Al-Rajab and Schiavon, 2010).

3. Glyphosate residues in the environment

Due to its low toxicity and less mobility in the environment (Saunders and Pezeshki, 2015; Skeff et al., 2018; Valavanidis, 2018), glyphosate is applied widely on genetically modified cotton, soybean and corn with no-till farming practices (Battaglin et al., 2014). Globally, the application of glyphosate-based herbicides has increased around 100-fold since the late 1970s, mostly after the introduction of genetically modified glyphosate-tolerant crops (Benbrook, 2016; Myers et al., 2016). For instance, in USA alone over 1.6 billion kg active ingredient (a.i.) of glyphosate has been used since 1974, which is about 19% of the estimated global use (Benbrook, 2016). In 2014, farmers worldwide applied approximately 0.53 kg ha⁻¹ a.i. of glyphosate on all croplands, while its usage in USA was about ~1.0 kg ha⁻¹ (Benbrook, 2016). Consequently, glyphosate has been frequently detected in a diverse section of the environment including soil, water, dust particle and air due to its extensive use during the past three decades (Krüger et al., 2014).

3.1. Glyphosate residues in soil, dust particle and air

Soil contamination with pesticide residues is considered not only a major problem to sustainable development but also a raising concern worldwide. Glyphosate-based herbicides can contaminate soils in and around the application site (Van Bruggen et al., 2018).

For instance, in 45 soils and sediment samples collected from seven sites in Indiana and Mississippi states of USA, the range of median-maximum concentrations of glyphosate and AMPA were 9.6–476 and 18–341 µg kg⁻¹, respectively (Battaglin et al., 2014). In Argentina, analysis of soils from sixteen agricultural sites during 2012 following UPLC-MS/MS ESI(+) revealed concentrations of glyphosate and AMPA at 35–1502 and 299–2256 µg kg⁻¹, respectively (Aparicio et al., 2013). The concentrations of glyphosate and AMPA detected in soil were 8105 and 38,939 µg kg⁻¹ in the Mesopotamic Pampas agroecosystem, Argentina (Primost et al., 2017). The above data on the occurrence of residues in soils clearly suggest that glyphosate is incompletely degraded to yield AMPA. Due to its strong affinity to solid surfaces, glyphosate also contaminates dust particles and air in the environment. Thus, glyphosate residues have been detected at concentrations up to 2.5 µg L⁻¹ in rainwater and air in agricultural areas of Iowa and Mississippi (Chang et al., 2011).

3.2. Glyphosate residues in waterways

Surface waterways are highly polluted with urban wastewaters, agricultural runoff, and through mining and industrial activities during the last decades. Initially, glyphosate-based herbicide was not considered as a potential threat for surface and groundwater contamination due to its limited mobility from soil (Sihtmäe et al., 2013; Monsanto, 2014). Glyphosate-based herbicides and their metabolites were frequently detected as contaminants in rivers and surface waters (Gasnier et al., 2009). For instance, glyphosate residues were detected in surface waters at a concentration of 4.15 µg L⁻¹ in Switzerland (Hanke et al., 2010). While the freshwater aquatic life standard for glyphosate is only 65 µg L⁻¹, the residues detected in a sample from Riley Spring Pond in Rock Creek National Park, Washington, DC, were at the highest concentration of 328 µg L⁻¹ (Battaglin et al., 2009). Glyphosate residue levels detected in surface and groundwater samples in Europe (50 and 24 mg L⁻¹, respectively), and USA (427 and 4.7 mg L⁻¹, respectively) were much higher than the EU drinking water limit of 0.1 mg L⁻¹ but far below the EPA maximum protective level of human health (700 mg L⁻¹) (Scribner et al., 2007; Horth and Blackmore, 2009; Wang et al., 2016).

Although glyphosate and AMPA are strongly bound to clay and organic matter, a portion of them may transfer to groundwater via rainfall (Maqueda et al., 2017; Rendón-von Osten and Dzul-Caamal, 2017). Not only rain but also an erosion of soil particles into surface water are responsible for carrying glyphosate and AMPA and remain in the dissolved or particulate phase and settle at the bottom sediment (Yang et al., 2015b; Wang et al., 2016; Maqueda et al., 2017). The concentrations of glyphosate and AMPA detected in water or sediment samples, collected from as many as 1341 sites in 38 states of the US and the District of Columbia, were 476 and 397 µg L⁻¹, respectively (Battaglin et al., 2014). Also, the concentrations of glyphosate and AMPA detected in samples of stormwater overflows, sewage, wastewater treatment plant outlets, bottled water and drinking water were very low (Grandcoin et al., 2017; Rendón-von Osten and Dzul-Caamal, 2017; Van Bruggen et al., 2018). While analyzing 44 stream water and sediment samples during 2012 in Argentina using UPLC-MS/MS ESI(+/-), Aparicio et al. (2013) detected the residues of glyphosate and AMPA at concentrations of 15 and 12% in water and 66 and 88.5% in sediments, respectively. Because of the extensive use of glyphosate on genetically modified and glyphosate-resistant (GM-GR) crops in USA, both glyphosate and AMPA have been frequently detected in stream, surface and ground waterways at concentrations ranging from 2 to 430 µg L⁻¹ (Coupe et al., 2012; Battaglin et al., 2014;

Mahler et al., 2017). On the other hand, very low concentrations ($<0.1\text{--}2.5 \mu\text{g L}^{-1}$) of glyphosate were observed in surface waters in Switzerland, Germany, Hungary and Spain, but comparatively higher concentrations (up to $165 \mu\text{g L}^{-1}$) were found in those from Denmark and France (Villeneuve et al., 2011; Sanchís et al., 2012; Mörtl et al., 2013; Poiger et al., 2017). The concentrations of glyphosate and AMPA detected in environmental compartments including sediment, suspended particulate matter and surface water in the Mesopotamic Pampas agroecosystem, Argentina were 3294 and 7219, 584 and 475 $\mu\text{g kg}^{-1}$, and 1.80 and 1.90 $\mu\text{g L}^{-1}$, respectively (Primost et al., 2017). These observations support the fact that the degradation of glyphosate in sediments and water is rapid than in soils. However, Wang et al. (2016) reported that microbial degradation of glyphosate was considerably slower in sediments than in water.

3.3. Glyphosate residues in the food chain

Globally, the widespread cultivation of GM-GR crops including soybean, corn, maize, cotton, canola, rapeseed and sugar beet varieties led to a dramatic increase in the use of glyphosate (Cerdeira et al., 2007; Duke, 2018). Consequently, glyphosate residues have been frequently detected in food (Zoller et al., 2018). According to the Food and Agriculture Organisation (FAO), both glyphosate and its primary degradation product, AMPA, raised a potential toxicological concern particularly for their accumulation in the food chain (Bai and Ogbourne, 2016). After the development of genetically modified glyphosate-tolerant edible plants, application of this herbicide resulted in its increased presence by 75% in the food chain (Clive, 2009). Following enzyme-linked immunosorbent assay (ELISA), Zhao et al. (2018) detected glyphosate in 18 commercial animal feeds from eight manufacturers in the USA in a range of $7.83 \times 10^{-1}\text{--}2.14 \times 10^{-3} \text{ mg kg}^{-1}$, on a dry weight basis. In Switzerland, glyphosate and AMPA were also detected in 243 samples of diverse foodstuffs including beer, wine, milk, fruit juice, mineral water, potatoes and vegetables, baby food, honey, egg, meat and fish, pulses, oilseeds and vegetable oil, pseudocereals, breakfast cereals, wheat, durum, pastry and snacks, flour and baking mixtures, bread, and other cereal products using LC/MS/MS method at concentrations of $<0.0005\text{--}2.948$ and $0.0005\text{--}0.0025 \text{ mg kg}^{-1}$, respectively (Zoller et al., 2018). However, it is not yet clear whether glyphosate is partially degraded to AMPA in living plants, and both glyphosate and AMPA are toxic to living organisms (Kwiatkowska et al., 2014a, 2014b; Gomes et al., 2016). The range of total concentration (mg kg^{-1}) of glyphosate and AMPA in agricultural products varied widely from 0.1 to 25 in cereals, 0.1–100 in legumes, 0.1–28 in oilseeds and 1–344 in fodders (Alimentarius, 2013; USEPA, 2013; Bøhn et al., 2014; Cuhra, 2015; Çetin et al., 2017). According to FAO, the dietary risk of glyphosate and AMPA is quite unlikely provided the maximum daily intake does not exceed 1 mg kg^{-1} body weight (Bai and Ogbourne, 2016).

In Europe, animals and humans consuming GM soybean as feed and food accumulate unknown amounts of glyphosate (Krüger et al., 2014). The influence of glyphosate residues on the quality of animal products consumed by humans is almost unknown because the residues likely to be present in tissues and organs of animals fed with GM corn or soybean are not considered or neglected in the legislation (Krüger et al., 2014). The colour of broiler breast muscles is considerably affected due to the inclusion of GM soybean as feed (Stadnik et al., 2011). On the other hand, Erickson et al. (2003) did not find any effects on the feedlot performance of steers and carcass characteristics. Moreover, glyphosate acts as a strong chelating agent to fix trace and macro elements

(Zobole et al., 2010; Krüger et al., 2013a).

4. Toxicity of glyphosate and environmental impacts

The mode of glyphosate's action in weeds is blocking the shikimic acid pathway by inhibiting enolpyruvylshikimic phosphate (EPSP) synthase to prevent the synthesis of the three essential aromatic amino acids, viz., tyrosine, tryptophan and phenylalanine (Gimsing et al., 2004a; Monheit, 2007; Morini et al., 2018). After exposure to the herbicide, the target plant experiences stunted growth, loss of green coloration, leaf wrinkling/malformation, tissue damage, and eventually death within 7–21 days (Saunders and Pezeshki, 2015; Morini et al., 2018). The pathway for the aromatic amino acid synthesis through shikimic acid is limited to plants, fungi and some microorganisms (Saunders and Pezeshki, 2015). Since the shikimic acid pathway is absent in animals, the aromatic amino acids must be supplemented through diets. Thus, the lack of this pathway is the basis for underlying low toxicity of glyphosate in animals although certain adverse effects of exposure to higher doses for longer periods have been very well documented (Borggaard and Gimsing, 2008; Mesnage et al., 2015b; Saunders and Pezeshki, 2015; Morini et al., 2018). Therefore, the maximum contaminant level (MCL) set in the USA for glyphosate is $700 \mu\text{g L}^{-1}$ in drinking water which is higher than the MCLs of other pesticides (Contaminants, 2003; MDH, 2017). Glyphosate, with its very low acute toxicity, seems to have very limited or no harmful effects on populations of microorganisms and their processes (Busse et al., 2001; Ratcliff et al., 2006). But, glyphosate-based formulations exhibited differential toxic effects to nontarget aquatic and terrestrial organisms (Giesy et al., 2000; Howe et al., 2004; Oliveira et al., 2007; Moore et al., 2012; Carpenter et al., 2016; Lugowska, 2018). In particular, the surfactant, POEA, present in Roundup formulations is responsible for the observed toxicity toward human and ecological health (Mesnage et al., 2013; Kwiatkowska et al., 2014b; Mesnage et al., 2015b; Carpenter et al., 2016; Van Bruggen et al., 2018). The major routes of human exposure to glyphosate formulations applied to agricultural or non-agricultural settings and the associated different toxic effects on human and ecological health are presented in Fig. 2.

4.1. Human health effects

Human and environmental health risks associated with glyphosate have been evaluated by both academic researchers and regulatory agencies (WHO, 1994; Solomon and Thompson, 2003). Although the German Federal Institute for Risk Assessment, a lead regulatory authority, recommended an increase in acceptable daily intake (ADI) of glyphosate from 0.3 to 0.5 mg kg^{-1} body wt day $^{-1}$, signs of oxidative stress, damages in liver and kidneys occurred at concentrations below the regulatory limits (Mesnage et al., 2015b; Myers et al., 2016). In fact, a wide array of human disorders and diseases, such as metabolic alterations, DNA damage, kidney damage, reproduction toxicity, mental conditions like attention deficit hyperactivity disorder (ADHD), Alzheimer's, Parkinson's, celiac disease, autism, effect on erythrocytes, leaky gut syndrome, cancers, etc. are also associated with glyphosate-based herbicide formulations (Mink et al., 2012; Swanson et al., 2014; Mesnage et al., 2015b; Fluegge and Fluegge, 2016; Fortes et al., 2016; Myers et al., 2016). Different toxic effects associated with the use of glyphosate formulations on human health are presented in Table 1. It has been established that glyphosate is toxic only at higher concentrations (Saunders and Pezeshki, 2015; Bai and Ogbourne, 2016; Valavanidis, 2018). In contrast, very recently USEPA opined that glyphosate is non-carcinogenic, and its use as a herbicide can be continued (Erickson, 2020). However, mention may be made

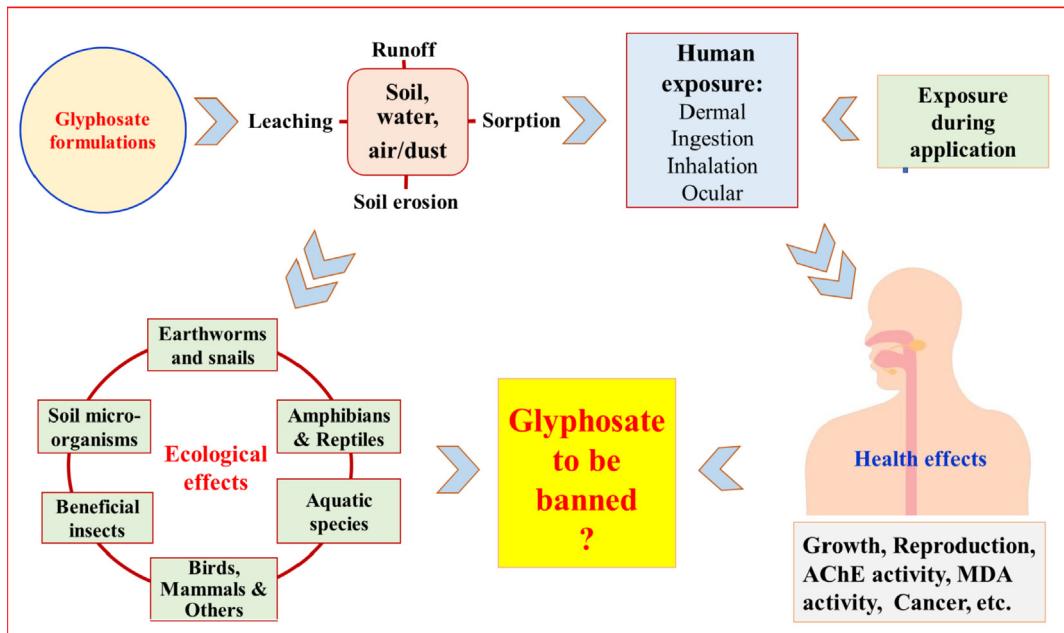


Fig. 2. Human health and ecological effects of glyphosate-based formulations.

Table 1

Human health effects of glyphosate-based herbicide formulations.

Toxic effect	Organ/cells	Glyphosate concentration	References
Breast cancer	T47D cells	10^{-12} – 10^{-6} M	Thongprakaisang et al. (2013)
Endocrine disruption	Human cell lines (HepG2 and MDA-MB453-kb2)	0.5–10 ppm	Gasnier et al. (2009)
Effect on erythrocytes	Human erythrocytes	0.01–5 mM	Kwiatkowska et al. (2014a, b)
DNA damage	Human-derived buccal epithelial cells	>20 mg L ⁻¹ to >80 mg L ⁻¹	Koller et al. (2012)
	Hep-2 cells	3–7.5 mM	Manas et al. (2009)
Effect on placental cell	Human placental JEG3 cells	1–2% in water	Richard et al. (2005)
Effects on oxidative balance	HepG2 cell line	<1000 mg L ⁻¹	Chaufan et al. (2014)
Induction of apoptosis and necrosis	Umbilical cord vein cells, 293 embryonic kidney and JEG3 placental cell lines	Far below from agricultural concentration	Benachour and Séralini (2008)
Gluten intolerance	Intestine	NA	Samsel and Seneff (2013a)
Neurological disorders	Neural cells and axons in rats	4000 mg L ⁻¹	Čolović et al. (2013); Coullery et al. (2016)
Blood disorder	DNA in leucocytes	85–1690 mg L ⁻¹	Kwiatkowska et al. (2017)
Liver damage	Liver in laboratory rats	56 mg kg ⁻¹	Çağlar and Kolankaya (2008)
Liver and kidney damage and tumours	Liver and kidney in laboratory rats	50 ng L ⁻¹ ; 4 ng kg ⁻¹ bwt d ⁻¹ (chronic)	Séralini et al. (2014); Mesnage et al. (2015a)
Human cell toxicity	Hepatic (Hep G2), embryonic (HEK 293) and placental (JEG 3) cell lines	1–3 ppm	Mesnage et al. (2013)
Effect on cell physiology	3T3-L1 cell line	36–178 ppm	Martini et al. (2016)
Disruption of CYP enzymes	Cytochrome P450	NA	Samsel and Seneff (2013b)

NA = Not available.

here that there must be a general consensus between the researchers and regulatory agencies while establishing the ecotoxicity of an environmental pollutant (Fagin, 2012). In certain instances, improper handling of the herbicides and the resulting spray drifts can severely affect the farmworkers, besides causing environmental pollution to a great extent (Harrison, 2008; Bain et al., 2017).

It has been established that the oral absorption of glyphosate and AMPA in rats, rabbits, goats and chicken or dermal penetration through skin of humans and monkeys was minimal, and the transient irritation in rabbit eyes was due to the direct ocular exposure of concentrated Roundup formulation (Williams et al., 2000). They observed no significant experimental evidence on bioaccumulation through animal tissue, direct *in vitro* or *in vivo* DNA damage and heritable/somatic mutations. On the other hand, glyphosate

residues were detected in urine and some organs of humans, dairy cows and rabbits, and the concentrations were significantly higher in the urine of cows in areas where genetically modified crops are grown than in conventional husbandry (Krüger et al., 2014). According to the acute toxicity classification system, USEPA classified glyphosate as a practically non-toxic and non-irritant chemical to humans and animals (Mink et al., 2012; Bai and Ogbourne, 2016). Safety studies on glyphosate and its commercial formulation, Roundup, also accompanied by several scientific institutions and regulatory agencies worldwide did not find any indication of human health concern (Williams et al., 2000). Likewise, glyphosate was considered as a non-carcinogenic chemical (Borggaard and Gimsgaard, 2008). On the other hand, concerns have periodically increased worldwide regarding their potential adverse health effects on humans and animals. The surfactants may amplify the

toxicity through increasing glyphosate uptake in cells, or by adding their own toxicity via cell membrane disruption (Mesnage et al., 2015b). Moreover, the IARC a research wing of World Health Organisation (WHO) reclassified glyphosate after re-evaluation as 'probably carcinogenic' of Group 2A to humans (IARC, 2015; Van Bruggen et al., 2018; Zoller et al., 2018). This reclassification has been based on data from the studies conducted with technical grade glyphosate on experimental animals and limited evidence on the incidence of cancer in humans really exposed to the herbicide (IARC, 2016). However, the IARC decision has not been confirmed through evaluation by EU or the recent joint FAO/WHO assessment (Tarazona et al., 2017). Although the reclassification by IARC attracted greater attention, glyphosate is not the first topic of its disagreement with other regulatory evaluations (Tarazona et al., 2017).

In most cases, glyphosate and AMPA residues present in water and agricultural products are taken up by humans and animals, excreted through their faeces and urine (Krüger et al., 2014; Niemann et al., 2015; Von Soosten et al., 2016). Also, residues of glyphosate were detected in urine of 60–80% general public, including children, in the USA at 2–3 and 233 µg L⁻¹ mean and maximum concentrations, respectively, whereas in 44% of the general public in Europe the mean and maximum concentrations were <1 and 5 µg L⁻¹, respectively (Krüger et al., 2014; Niemann et al., 2015). Gasnier et al. (2009) observed that glyphosate-based herbicides were also endocrine disruptors at sub-agricultural doses (0.5–10 ppm) in human cell lines (HepG2 and MDA-MB453-kb2). Glyphosate formulations induced morphological changes in human erythrocytes as well as hemolysis, haemoglobin oxidation and formation of reactive oxygen species (ROS) at different concentrations (0.01–5 mM) during 1–24 h, whereas the metabolites and impurities caused more damage than glyphosate (Kwiatkowska et al., 2014a). Thongprakaisang et al. (2013) opined that glyphosate causes the growth of T47D cells and human hormone-dependent breast cancer. After a single exposure to glyphosate formulations, the acute toxicity to amphibians, reptiles and mammals was more at relatively higher doses, and the median lethal doses were dependent on the nature of surfactants (Durkin, 2011; Moore et al., 2012; Weir et al., 2016). In addition, lethal doses for many toxic formulations varied among species and ranged from 175 to 540 mg glyphosate acid equivalent (a.e.) kg⁻¹ body weight in terrestrial animals and from 1 to 52 mg a.e. L⁻¹ of water in aquatic organisms (Durkin, 2011). Moreover, no clear distinction was made between the effects of glyphosate and POEA in the experiments conducted with Roundup although the acute oral toxicity of POEA determined was higher ($LD_{50} = 1.2 \text{ g kg}^{-1}$) than that of glyphosate ($LD_{50} = 4.8 \text{ g kg}^{-1}$) (Diamond and Durkin, 1997).

4.2. Toxicity to other organisms

Glyphosate is largely considered as non-toxic to the aquatic and terrestrial animal, while detrimental effects of exposure have been documented at higher concentrations (Monheit et al., 2004). Table 2 presents the negative effects of glyphosate-based formulations on different terrestrial and aquatic organisms. According to Annett et al. (2014), glyphosate is non-toxic or less toxic to birds and mammals, while they are non-toxic to moderately toxic to aquatic invertebrates. Glyphosate is also considered to be slightly to moderately toxic to amphibians, and AMPA is less toxic than glyphosate to these organisms (Giesy et al., 2000; Howe et al., 2004; Moore et al., 2012). Domínguez et al. (2016) also reported that glyphosate might have neutral or negative effects on soil biota, whereas field-relevant concentrations of AMPA had no significant effects on mortality in acute or chronic assays. However, a

significant biomass loss was observed in the chronic assay compared to controls at the highest concentration used. Both the surfactants, POEA and MON 0818, were found to have adverse effects on such animals in the aquatic food chain as crustaceans, frogs and fish, mussels, protozoa, and terrestrial animals as well (Moreno et al., 2014; Rissoli et al., 2016; Li et al., 2017; Prosser et al., 2017; Zhang et al., 2017), but terrestrial animals (mammals, reptiles and birds) seem to be less sensitive to POEA than aquatic animals (Van Bruggen et al., 2018). Moreover, POEA-containing glyphosate formulations were more toxic than the formulations without this surfactant (Bringolf et al., 2007; Prosser et al., 2017). Studies revealed that the toxic effects of glyphosate formulations and of the surfactants like POEA used in the Roundup were severe to amphibians (Brausch and Smith, 2007). In addition, the lethal effect of POEA was observed in amphibians (Annett et al., 2014). Lugowska (2018) also reported that POEA is more toxic to fish than glyphosate itself. Several adverse effects of Roundup to aquatic organisms particularly on growth, biomass, behaviour, metabolism, histopathological changes, oxidative status and gene expression, haematological parameters, metamorphosis and mortality have been well documented (Relyea, 2005a,b; Moore et al., 2012; Fan et al., 2013; Jofré et al., 2013; Nwani et al., 2013; Yadav et al., 2013; Velasques et al., 2016; Tapkir et al., 2019). The negative effects of Roundup on vertebrates and invertebrates are also not uncommon (Balbuena et al., 2015). In pigs, infertility and malformation were related to glyphosate residues detected in the liver and kidneys as well as in the feed (Krüger et al., 2014).

4.3. Ecological impacts in sustainable agriculture

The soil rhizosphere microbial community plays a vital role in improving soil quality through its involvement in biogeochemical and nutrient cyclings, long-term soil sustainability, and resistance to perturbations (Topp, 2003; Prashar et al., 2014). It also improves plant health through a wide range of mechanisms, such as disease suppression, nutrients mineralization, phytohormones production and plant stress tolerance (Figueiredo et al., 2011; Berendsen et al., 2012). Glyphosate applied to control weeds ultimately reaches the soil, and potentially affect the soil microbial community (Haney et al., 2000). The availability of a herbicide to soil microorganisms depends on diverse environmental factors, such as soil temperature, moisture, pH and nutrient status (Weber et al., 1993). Soil temperature and moisture have a direct role on some important biological processes including plant metabolism, microbial degradation and persistence of a particular herbicide (Weber et al., 1993). Heterotrophic soil microorganisms obtain C and N to maintain their growth and development through the decomposition of organic matter (Haney et al., 2000). Soil application of glyphosate showed no significant effect on microbial activity, as measured by C mineralization, or had only transitory effects at higher concentrations (Wardle and Parkinson, 1990, 1992; Olson and Lindwall, 1991; Hart and Brookes, 1996). Glyphosate considerably stimulated soil microbial activity, as measured by C and N mineralization, but microbial biomass remained unaffected besides increasing the rate of C mineralization with increasing glyphosate concentrations, indicating that glyphosate has a direct influence in enhancing microbial activity (Haney et al., 2000).

Rapid microbial degradation of glyphosate occurred even at higher concentrations, without affecting the microbial activity (Haney et al., 2000). Araújo et al. (2003) measured microbial activity in soil, in terms of respiration (evolution of CO₂) and fluorescein diacetate (FDA) hydrolysis, in presence of glyphosate at a concentration of 2.16 mg kg⁻¹ over 32 days and observed an increase in 10–15% CO₂ evolution as well as 9–19% FDA hydrolysis

Table 2

Toxicity of glyphosate-based herbicide formulations to a wide range of living organisms.

Scientific name	Common name	Glyphosate concentration	Toxic effects	References
<i>Aporrectodea caliginosa</i> , <i>Eisenia fetida</i>	Earthworms	0.1–10 mg L ⁻¹	Defects in growth and reproduction	Springett and Gray (1992); Correia and Moreira (2010)
<i>Daphnia magna</i> , <i>Daphnia spinulata</i>	Daphnia	1.4–250 mg L ⁻¹	Chronic toxicity	Alberdi et al. (1996); Cuhra et al. (2013)
<i>Apis mellifera</i>	Honeybee	2.5–10 mg L ⁻¹	Adaptation in agricultural environments	Boily et al. (2013); Herbert et al. (2014); Balbuena et al. (2015)
<i>Trichogramma pretiosum</i>	Wasps	960 g ha ⁻¹	Harmful to eggs of parasite	Bueno et al. (2008)
<i>Pseudosuccinea columella</i> , <i>Helix aspersa</i>	Snails	0.1–10 mg L ⁻¹	Body growth	Tate et al. (1997); Balbuena et al. (2015); Druart et al. (2011)
<i>Danio rerio</i> <i>Cyprinus carpio L.</i>	Zebrafish Common carp	10 mg L ⁻¹ 20.0 mg L ⁻¹	Reproductive toxicity Effect on gametes, and embryo development	Uren Webster et al. (2014) Lugowska (2018)
<i>Lepidocephalichthys thermalis</i> <i>Jenynsia multidentata</i>	Common spiny loach Killifish	0.5 mg L ⁻¹ 5–100 mg L ⁻¹	Chronic toxicity Effect on liver, blood cells, gills, sexual activity, etc.	Tapkir et al. (2019) Hued et al. (2012)
<i>Tilapia zillii</i> <i>Carassius auratus</i>	Tilapia fish Goldfish	108–540 mg L ⁻¹ 32 µg L ⁻¹	Lethal toxicity Effects on OH ⁻ , malondialdehyde (MDA) and acetylcholinesterase (AChE) in liver	Nwani et al. (2013) Fan et al. (2013)
<i>Hypomesus transpacificus</i>	Delta Smelt	0.46 and 4.2 µM	Non-monotonic effect on estradiol levels in males	Jin et al. (2018)
<i>Rhamdia quelen</i>	Silver catfish	0–5 mg L ⁻¹	Changes in enzymatic activity, vacuolization, leukocyte, cytoplasm and melanomacrophages	Murussi et al. (2016)
<i>Cnesterodon decemmaculatus</i>	Ray-finned fish	1–35 mg L ⁻¹	AChE activity	Menéndez-Helman et al. (2012)
<i>Salmo trutta</i>	Brown trout	0–10 mg L ⁻¹	Cell proliferation and cellular turnover	Webster and Santos (2015)
<i>Anguilla Anguilla</i>	European eel	58 and 116 mg L ⁻¹	Oxidative stress, breaks in chromosomes and DNA strands	Guilherme et al. (2010)
<i>Bufo americanus</i> , <i>Bufo fowleri</i> , <i>Euphlyctis cyanophlyctis</i> , <i>Hyla chrysoscelis</i> , <i>Hyla versicolor</i> , <i>Leptodactylus latrans</i> , <i>Lithobates catesbeianus</i> , <i>Rana sylvatica</i> , <i>Rana pipiens</i> , <i>Rana clamitans</i> , <i>Rana catesbeiana</i> , <i>Rhinella arenarum</i> , <i>Caiman latirostris</i> , <i>Oligosoma polychroma</i> , <i>Salvator merianae</i>	Amphibians	1.5–684 mg L ⁻¹	Chronic toxicity	Relyea (2005a,b); Howe et al. (2004); Moore et al. (2012); Yadav et al. (2013); Lajmanovich et al. (2015); Dornelles and Oliveira (2016); Soloneski et al. (2016); Pérez-Iglesias et al. (2016)
<i>Agelaius phoeniceus</i> , <i>Anas platyrhynchos</i> , <i>Cistothorus palustris</i> , <i>Empidonax alnorum</i> , <i>Geothlypis trichas</i> , <i>Melospiza lincolni</i> , <i>Xanthocephalus xanthocephalus</i>	Reptiles	144 mg L ⁻¹	Physiological stress, DNA damage, decrease in WBC, increase in heterophils and total protein content	Carpenter et al. (2016); Schaumburg et al. (2016); Siroski et al. (2016)
<i>Rattus norvegicus</i> <i>Landrace piglets</i>	Birds	Wetland with 50–90% areal spray coverage of glyphosate	Affected male genital organs, reduced natural habitats and bird population	Santillo et al. (1989); Linz et al. (1996); Oliveira et al. (2007)
	Wistar rat Pig	14.4–375 mg kg ⁻¹ (body wt.) 41% of IPAG and 15% surfactant	Effects on physiology and reproduction Cardiovascular effects	Tizhe et al. (2014a,b) Lee et al. (2009)

compared to the soil with no glyphosate. Populations of fungi and actinomycetes increased in soil treated with glyphosate whereas the number of bacteria decreased slightly. Following HPLC, AMPA was detected, indicating microbial degradation of glyphosate (Araújo et al., 2003). Lane et al. (2012) reported stimulation of microbial respiration in glyphosate-treated soils with no significant effect on functional diversity measured in terms of ester-linked fatty acid methyl ester (EL-FAME), microbial biomass or exchangeable potassium. Lane et al. (2012) reported a shift in soil microbial community that could readily degrade glyphosate. In GR soybean plants treated with glyphosate, Fan et al. (2017) observed reduction in chlorophyll content, root and nodule mass, total plant N, and nitrogenase activity. The relative abundance of dominated soil microbial community belonging particularly to *Gamma proteobacteria* was found to increase due to glyphosate exposure in GT

corn and soybean, whereas the abundance of *Acidobacteria* decreased indicating significant changes in nutrient status of the rhizosphere (Newman et al., 2016). Glyphosate mineralization capacity of soil could be modified by phosphorus availability and the presence of exogenous inorganic phosphorus that may be utilized by microorganisms as a preferred alternative P source (Susana and Silvia, 2015). The activities of alkaline phosphomonoesterase (ALP), acid phosphomonoesterase (ACP), phosphodiesterase (PD) and phosphotriesterase (PT) were measured spectrophotometrically in soils treated with glyphosate and observed that ALP and PD were the most susceptible to glyphosate (Piatkowski and Telesiński, 2016). A comparison of the impact of glyphosate and its formulations showed that Roundup 360 SL was the most toxic due to the presence of POEA (Piatkowski and Telesiński, 2016).

5. Development of resistance to glyphosate

Globally, diverse weed populations were under glyphosate selection since 1974 (Duke and Powles, 2008). Because of its non-selective nature, glyphosate is applied for controlling a wide array of weeds before crop sowing/transplanting or between the established rows of vine crops, nuts and trees (Duke and Powles, 2009). During the recent years of the traditional application of this herbicide, only a very limited number of weeds developed resistance to glyphosate (Powles, 2008a,b). After the development of GM-GR crops, application of glyphosate in agricultural fields drastically increased worldwide because of its excellent weed control properties (Duke and Powles, 2009). In addition, more than 80% of the transgenic crops planted on the vast and ever-increasing farming areas are glyphosate-resistant (Duke, 2010). For diversified weed control, glyphosate use is the most sustainable, and this diversity has been provided by many different factors such as alternative herbicides, mechanical tools like tillage, hand-weeding, mowing, etc., and biological factors including crop competition and grazing animals (Duke and Powles, 2009). Development of resistance in diverse weed species to glyphosate is widely possible due to cultivation of GM-GR crops with continuous and repeated application of this herbicide (Gaines et al., 2011).

5.1. Glyphosate-resistant crops and shortcomings

The development of herbicide-tolerant (HT) crops certainly allowed the farmers to simplify their weed control programs. In the absence of other control measures, cultivation of HT crops has now been common that resulted in the repeated use of the same herbicide at higher doses which led to the evolution of herbicide-resistant (HR) weeds (Beckie et al., 2011). For instance, the extensive use of triazines on triazine-tolerant (TT) canola cultivars resulted in an increase in triazine-resistant populations of annual ryegrass and wild radish in Australia (Heap, 2006). Growing imidazolinone-tolerant canola greatly improved the profits by avoiding the yield-penalty linked with TT canola, but many imidazolinone-resistant weed populations developed particularly in Australia (Hudson and Richards, 2014), thus making this Clearfield® technology less attractive. Use of another cultivar, Roundup Ready (RR) canola, significantly reduced the use of other herbicides and provided the growers with a simple and efficient solution for weed control. Although glyphosate was earlier thought to be the 'bullet-proof' herbicide, this paradigm was changed in 1996 with the discovery of GR annual ryegrass in Australia (Pratley et al., 1996). Some classical examples for the development of resistance to glyphosate in different crop plants are provided in Table 3. The flexibility in the application of glyphosate on a crop has often resulted in a delay to ensure the emergence of as many weeds as

possible prior to herbicide use (Asaduzzaman et al., 2014a). Unfortunately, such delayed application allows the weeds to compete with the canola cultivars for resources (Asaduzzaman et al., 2014b). Thus, the intensive and repeated application of a single herbicide leads to resistance in weed species, as reported for GM-RR corn and GM-RR soybeans (Marshall et al., 2000). Species of *Amaranthus*, *Commelina*, *Ipomoea*, *Cyperus* as well as annual grasses were more problematic weeds in glyphosate-tolerant cotton and soybean in 11 states of Brazil (Culpepper et al., 2006).

The potential for the 'escape' of genes via pollen transfer is significant in canola (Vencill et al., 2012), and it became an important issue while determining the possible environmental impacts and the longevity of HT canola (Beckie et al., 2011). Evidence from the field experiments showed that genes could move through pollen to both conventional canola and related weed species such as wild mustard (Simard et al., 2006). Consequently, canola gene flow via pollen can result in multiple HR volunteer plants. Thus, *Brassica napus* was shown to hybridize, at a very low frequency in the open environment, with Indian mustard (*Brassica juncea*), Ethiopian mustard (*Brassica carinata*), black mustard (*Brassica nigra*), annual wall rocket (*Diplotaxis muralis*) and wild radish (*Raphanus* sp.) (Chèvre et al., 1997; Green, 2009). Only four years after the introduction of HT canola in Western Canada, Hall et al. (2000) observed multiple resistances such as double (glyphosate-glufosinate or glyphosate-imazethapyr) and triple (glyphosate-imazethapyr-glufosinate) in canola volunteers in a commercial field. It is therefore important to carry out studies to determine how the effects of pollen-mediated gene movement can be eliminated especially from volunteer plants. Agronomic practices like crop rotation, rotating mode of action of herbicides, destroying volunteers, regular tillage, etc. must be evaluated for effective control of volunteers. Such a pollen escape phenomenon can be minimized by giving much attention to different parameters such as vegetative propagation (apomixes), self-fertilization, male sterility and seed sterility (Liu et al., 2013).

5.2. Glyphosate-resistant weeds and risks

Weeds are one of the most important factors in crops that determine the yields because they compete for the common resources like light, water and nutrients, and significantly affect crop growth and yield (Preston and Baker, 2009; Rajabifard and Aghalikhani, 2011). Since herbicides are the main weed management toolboxes, this system often exerts strong selection pressures for the development of resistance in weeds. Weeds resistant to herbicides is an inherited ability of a plant to survive an application of the herbicide at the recommended use (Gressel and Roehrs, 1991). In this evolutionary process, the resistant alleles in a population are enriched for the survival of individuals in the presence of

Table 3
Glyphosate-tolerant crop plants reported in the literature.

Family	Scientific name	Common name	Region	References
Amaranthaceae	<i>Beta vulgaris</i> L.	Sugarbeet	North America	Duke (2005); Duke and Powles (2009)
Brassicaceae	<i>Brassica napus</i> L.	Rape seed	North and South America	Cerdeira et al. (2007)
Brassicaceae	<i>B. napus</i> L.	Canola	USA	Duke (2005); Duke and Powles (2009)
Fabaceae	<i>Medicago sativa</i>	Alfalfa	North America	Duke (2005); Duke (2005); Nandula et al. (2005)
Fabaceae	<i>Glycine max</i> L.	Soybean	Brazil	Cerdeira et al. (2007)
Malvaceae	<i>Gossypium hirsutum</i> L.	Cotton	USA	Duke (2005); Duke and Powles (2009)
Poaceae	<i>Zea mays</i> L.	Maize	North and South America	Duke (2005); Cerdeira et al. (2007)

herbicide (Powles and Yu, 2010). In fact, the dynamics and enrichment rate of resistant alleles in a population are greatly influenced by genetic factors such as gene mutation rate, dominance, additivity, epistasis, pleiotropy, inheritance mode, ploidy, etc. and biological factors like reproduction and mating system, population size, number of generations, etc. (Jasienski et al., 1996) as well as environmental conditions (Vila-Aiub et al., 2014). Although resistance to herbicides in weeds a potent more than six decades ago, warnings and reports were ignored until a mutation was detected during 1970s in D1 protein of photosystem II (Keshtkar et al., 2018). It is believed that overreliance on herbicides of the same chemical class or targeting the same site of action is a

major contributor to the development of herbicide resistance (Powles and Gaines, 2016). In fact, focusing on confirmation of resistance and characterisation of resistance mechanisms in weeds rather than management failed to mitigate the problem of weed control (Neve, 2007).

Though conservation agriculture dramatically increased productivity in Australia, the consequence is the widespread evolution of HR weeds across grain-producing regions (Broster et al., 2013; Owen et al., 2014). Over the years, many weed species developed resistance towards glyphosate (Table 4). Indeed, glyphosate resistance was reported in 38 weed species across 70 different countries (Heap, 2006). The occurrence of genetically diverse and well-

Table 4
Global reports on evolution of glyphosate-resistant (GR) weed species.

Family of the weed	Scientific name	Common name	Crop field	Country	References
Acanthaceae	<i>Dicliptera chinensis</i> L.	Chinese foldwing	Orchard	Unknown	Yuan et al. (2002)
Amaranthaceae	<i>Amaranthus tuberculatus</i> L.	Common water hemp	GR soybean, cotton	Argentina, USA	Owen and Zelaya (2005); Nandula et al. (2014)
	<i>Amaranthus palmeri</i> L.	Palmer pigweed			
	<i>Amaranthus palmeri</i> L.	Water hemp			
	<i>Amaranthus rudis</i> L.	Spiny pigweed			
	<i>Amaranthus spinosus</i> L.	Ataco			
	<i>Amaranthus quinensis</i> L.				
Asteraceae	<i>Ambrosia artemisiifolia</i> L.	Common ragweed	GR soybean, orchard and vineyard, GR cotton, unknown farmland, roadsides, wheat, etc.	Australia, South Africa, Brazil, Colombia, Spain, France, Portugal, Poland, Israel, Italy, South China, Czech Republic, Canada, Greece, Mexico, USA	VanGessel (2001); Mueller et al. (2003); Koger et al. (2004); Nandula et al. (2005); Powles (2008a, b); Heap (2014a)
	<i>Ambrosia trifida</i> L.	Giant ragweed			
	<i>Bidens pilosa</i>	Spanish needle			
	<i>Conyza canadensis</i> L.	Horseweed			
	<i>Conyza bonariensis</i> L.	Hairy fleabane			
	<i>Conyza sumatrensis</i> L.	White horseweed			
	<i>Parthenium hysterophorus</i> L.	Whitetop weed			
Brassicaceae	<i>Raphanus raphanistrum</i> L.	Wild radish	Unknown	Australia	Heap (2014b)
Chenopodiaceae	<i>Chenopodium album</i> L.	Common lambsquarters	GR soybean, canola, wheat, corn, sorghum, sugar beet, alfalfa, pastures, rangeland, waste areas, ditch banks, and roadsides	USA, Canada	Owen and Zelaya (2005); Wiersma et al. (2015)
	<i>Kochia scoparia</i> L.	Burningbush			
Commelinaceae	<i>Commelina communis</i> L.	Asiatic dayflower	Cotton, peanut, soybean, GR cotton	USA	Culpepper et al. (2004)
	<i>Commelina benghalensis</i> L.	Tropical spiderwort			
Convolvulaceae	<i>Convolvulus arvensis</i> L.	Field bindweed	Unknown	Unknown	De Gennaro and Weller (1984); Duke and Powles (2008)
Euphorbiaceae	<i>Euphorbia heterophylla</i> L.	Milkweed	Unknown	Brazil	Duke and Powles (2009)
Fabaceae	<i>Lotus corniculatus</i> L.	Birdsfoot trefoil	Regenerated from callus	Unknown	Boerboom et al. (1990); Nandula et al. (2005)
Malvaceae	<i>Abutilon theophrasti</i> L.	Velvet leaf	GR soybean, corn	Asia, USA, Canada	Owen and Zelaya (2005)
Plantaginaceae	<i>Plantago lanceolata</i> L.	Buckhorn plantain	Orchard and vineyard	South Africa	Powles (2008b)
Poaceae	<i>Cynodon dactylon</i> L.	Bermuda grass	GR soybean, orchard, cotton, summer and winter crops	Australia, Argentina, Brazil, Bolivia, Canada, China, Chile, Colombia, Costa Rica, France, Israel, Italy, Japan, Malaysia, Mexico, New Zealand, Portugal, Paraguay, Spain, South Africa, Taiwan, USA	Bryson and Wills (1985); Powles et al. (1998); Pratley et al. (1999); Lee and Ngim (2000); Perez and Kogan (2003); Simarmata et al. (2003); Powles (2008a, b); Duke and Powles (2009); de Carvalho et al. (2012); Ge et al. (2012); Vila-Aiub et al. (2012); Alarcón-Reverte et al. (2013); Heap (2014b)
	<i>Chloris elata</i>	Tall windmill grass			
	<i>Chloris truncata</i>				
	<i>Digitaria insularis</i> L.	Fingergrass			
	<i>Echinochloa colona</i>	Sourgrass			
	<i>Eleusine indica</i>	Junglerice			
	<i>Leptochloa virginica</i>	Goosegrass			
	<i>Lolium rigidum</i>	Sprangletops			
	<i>Lolium multiflorum</i>	Rigid ryegrass			
	<i>Lolium perenne</i>	Italian ryegrass			
	<i>Urochloa panicoides</i>	English ryegrass			
	<i>Sorghum halepense</i> L.	Liverseed grass			
	<i>Poa annua</i>	Johnsongrass			
		Annual meadow grass			
Rubiaceae	<i>Hedyotis verticillata</i>	Woody boreria	Unknown	Malaysia	Heap (2014b)

adapted annual ryegrass was due to the evolution of GR populations on a large scale (Peterson et al., 2018). Annual ryegrass is the world's most recognized weed that developed resistance by the evolving site(s) of actions (SOAs) to 11 herbicides including glyphosate (Heap and Duke, 2018). In Australia, a total of 48 HR weed species were identified with multiple SOAs which include wild radish (five SOAs) (Ashworth et al., 2014; Owen et al., 2015), wild oat (three SOAs) (Owen and Powles, 2016), barley grass (*Hordeum leporinum*) (three SOAs) (Owen et al., 2012), annual bluegrass (*Poa annua*) (five SOAs) (Heap, 2017), and tall fleabane (*Conyza sumatrensis*) (Asaduzzaman et al., 2019). Such an extent in the occurrence of GR weed populations in Australia indicates that many herbicides that were effective earlier are no longer useful now.

5.3. Glyphosate-resistant pathogens

Nowadays, the evolution of pathogens resistant to glyphosate (Table 5) is another growing concern to the scientific community worldwide. The application of glyphosate provides stress to living microorganisms due to modifications in the environment. It has been reported that the pathogenic bacteria like *Salmonella enteritidis*, *Salmonella typhimurium*, *Salmonella gallinarum*, *Clostridium botulinum* and *Clostridium perfringens* are highly resistant to glyphosate (Shehata et al., 2013). Among them, *Salmonella* infections raise public health concerns all over the world, as they are widely distributed in the environment, causing an array of diseases in humans and animals (Shehata et al., 2013). Poultry eggs and meat are one of the main sources of human foodborne infections caused by species of *Salmonella* like *S. enteritidis*, *S. typhimurium* and *S. gallinarum* which are highly resistant to glyphosate (Authority, 2009; Shehata et al., 2013). Moreover, Bifidobacteria which play a beneficial role by creating unfavourable conditions for the growth of pathogens are highly sensitive to glyphosate (Isolauri et al., 2001). In fact, chicken gastrointestinal tract's microbiota received serious attention since the focus was to prevent foodborne illness in humans, to improve animal nutrition, and to reduce dependence on non-therapeutic antibiotics in poultry (Isolauri et al., 2001; Gong et al., 2002). It has also been reported that glyphosate suppresses the antagonistic effect of *Enterococcus* spp. and *C. botulinum* (Krüger et al., 2013a). In cattle, *Clostridium botulinum*-associated diseases are in two forms, an acute form of botulism that occurs after the uptake of botulinum neurotoxin performed in feeds causing flaccid paralysis and death by respiratory failure, and a chronic form characterized by weakness, local paralysis, emaciation, muscular stiffness and varying degrees of recumbency (Krüger et al., 2013b). In addition, several beneficial bacteria such as *Campylobacter* spp., *Enterococcus faecalis*, *Enterococcus faecium*, *Bifidobacterium adolescentis*, *Bacillus badius* and *Lactobacillus* spp. were found to be moderate to highly susceptible to glyphosate (Shehata et al., 2013). Since the predictions about the environmental consequences of pesticide applications in agriculture are challenging (Ramakrishnan et al., 2019), better insights into the development of antimicrobial resistance in soil bacteria are greatly needed. Because glyphosate has been shown to induce multiple antibiotic resistance in bacteria (Kurenbach et al., 2015), a large number of studies involving several bacterial strains must be carried out to understand the global spread of antimicrobial resistance due to the extensive use of glyphosate.

6. Future of glyphosate in agriculture: either restricted use or a ban?

Glyphosate, being a cheaper herbicide with a typical half-life of 47 days in soil, is highly effective compared to other weed killers

like atrazine whose residues are detected in the water supply at unsafe levels after their applications (<https://www.panna.org/sites/default/files/AtrazineReportBig2010.pdf>). By considering glyphosate as 'almost as fundamental to farming as tractors', millions of farmers use it safely every year. After the introduction of GR crops, the extensive and repeated applications of glyphosate over the last 45 years continuously resulted in developing resistance by some weed species, possibly due to improper use of glyphosate for such a long time. A perusal of the literature reveals that glyphosate is basically non-toxic or extremely less toxic to higher animals. In fact, the minimum concentrations of glyphosate that might cause health effects in humans are 1000 times higher than the recommended field doses. It seems that the benefit-risk ratio for glyphosate is one of the highest of all the established herbicides. If not ingested in very large quantities intentionally, glyphosate is not even as toxic as the common chemicals like aspirin (Virginia Tech, 2018). Although IARC re-evaluated and classified glyphosate as 'probably carcinogenic to humans' based on the alleged evidence of glyphosate being associated with non-Hodgkin's lymphoma, other regulatory authorities in Canada, Australia, Germany, New Zealand, and Japan, as well as the European Food Safety Authority and European Chemicals Agency indicated that judicious application of glyphosate and its formulations does not pose a genotoxic or carcinogenic threat to the humans.

Following a study involving 45,000 people who handled the herbicide in the 1990s, FAO reported that Roundup does not cause cancer or affect human genetics (Tarazona et al., 2017). The findings that the commercial formulations like Roundup are more toxic than glyphosate have been very well supported by the fact that POEA and MON 0818 contained in the formulations are primarily responsible for the greater toxicity. As of now, there is no clear substitute for glyphosate in controlling a wide range of weeds in crop fields. Hence, without any ambiguity and restrictions, glyphosate can be widely used in modern agriculture. According to Brookes et al. (2017), restricting the use of glyphosate might incur an annual loss of US\$ 6.76 billion globally besides resulting in 12.4% net negative environmental impact, as measured by the environmental impact factor. Instead of making any attempts to ban the commercial formulations like Roundup, the toxic surfactants currently in use could be replaced by safe, effective and economical alternatives in future commercial formulations. By simultaneously protecting pollinators like bees, glyphosate must be appropriately used against the targeted weeds. Necessary regulatory strategies need to be developed for safer use of glyphosate while cultivating the genetically modified crops for increased yield of food materials.

7. Conclusions

The formulations of glyphosate have been extensively used to control a wide array of weeds in the modern agricultural and non-agricultural settings worldwide. A perusal of the literature on toxicity of glyphosate particularly to humans indicates contrasting observations thereby drawing the attention of researchers to the growing concern in public health. On one hand, several reports suggest that glyphosate-based formulations are linked to the increased risk of cancer, endocrine disruption, celiac disease, autism, effect on erythrocytes, leaky gut syndrome and other disorders. Though IARC reclassified in 2015 glyphosate as 'probably carcinogenic' under Group 2A, this decision was not confirmed by the EU evaluation or the recent joint FAO/WHO assessment. But, the decision of IARC has been broadly circulated by anti-chemical and environmental advocacy groups and proclaimed for restriction or ban of glyphosate. On the other hand, several other regulatory authorities and scientific bodies reported no significant relationship of glyphosate with any kind of cancer. Very recently, USEPA

Table 5

Effect of glyphosate-based herbicide formulations on potentially beneficial, pathogenic, soil rhizosphere bacteria and other organisms.

Source	Ecological type	Bacterial species	Toxicity status	Glyphosate concentration	References
Poultry	Pathogenic	<i>Clostridium botulinum</i>	Highly resistant	5 mg mL ⁻¹	Shehata et al. (2013)
		<i>Clostridium perfringens</i>	Highly resistant		
		<i>Escherichia coli</i>	Highly resistant	1.2 mg mL ⁻¹	
		<i>Salmonella enteritidis</i>	Highly resistant	5 mg mL ⁻¹	
		<i>Salmonella gallinarum</i>	Highly resistant		
	Beneficial	<i>Salmonella typhimurium</i>	Highly resistant		
		<i>Staphylococcus</i> sp.	Moderate	0.3 mg mL ⁻¹	
		<i>Bacillus badius</i>	Moderate to highly susceptible	0.15 mg mL ⁻¹	
		<i>Bifidobacterium adolescentis</i>	Moderate to highly susceptible	0.075 mg mL ⁻¹	
		<i>Enterococcus faecalis</i>	Moderate to highly susceptible	0.15 mg mL ⁻¹	
Cattle	Pathogenic	<i>Enterococcus faecium</i>	Moderate to highly susceptible	0.15 mg mL ⁻¹	Ackermann et al. (2015) Krüger et al. (2013b)
		<i>Lactobacillus</i> spp.	Moderate to highly susceptible	0.6 mg mL ⁻¹	
	Ruminant fermenter	<i>Campylobacter</i> spp.	Susceptible	0.15–5.0 mg mL ⁻¹	
		<i>C. botulinum</i>	Resistant	>1 mg mL ⁻¹	
NA	Ruminococcus sp.		Susceptible - Strong inhibitory effect	0.01 mg mL ⁻¹	Schulz et al. (1985)
	Beneficial	<i>Enterococcus</i> sp.	Toxicity	0.1 mg mL ⁻¹	
Rhizosphere	Pathogenic	<i>Pseudomonas aeruginosa</i>	Resistant	>1 mg mL ⁻¹	Fischer et al. (1986); Zobiole et al. (2011) Newman et al. (2016) Moorman et al. (1992); Hernandez et al. (1999) Moorman (1986)
	Beneficial	<i>Bacillus subtilis</i>	50% inhibition	174 µM	
		<i>E. coli</i>	50% inhibition	75 µM	
		<i>Fusarium</i> spp.	Increased profusion	NA	
		<i>P. aeruginosa</i>	50% inhibition	1100 µM	
	Pathogenic	<i>Acidobacteria</i> spp.	Decreased profusion	NA	
		<i>Bradyrhizobium japonicum</i>	Inhibitory and lethal	0.5–1 mM and 5 mM, respectively	
		<i>B. japonicum</i>	Sensitive (>50% inhibition) and insensitive (~50% inhibition)	30 µM and >1000 µM, respectively	
			Growth inhibition	≥1000 to ≥5000 ppm and some above 10 ppm	
Soil	Mycorrhizal fungi/ Mushrooms	<i>Cenococcum geophilum</i> , <i>Hebeloma longicaudum</i> , <i>Hebeloma crustuliniforme</i> , <i>Laccaria laccata</i> , <i>Pisolithus tinctorius</i> , <i>Suillus tomentosus</i> , <i>Thelephora americana</i> , <i>Thelephora terrestris</i>			Chakravarty and Sidhu (1987); Estok et al. (1989)
		<i>Euglena gracilis</i>	21–69% reduction in chlorophyll content, and 20% reduction in photosynthesis and respiration at levels below 1.2 × 10 ⁻⁴ M	3 × 10 ⁻³ M	
		<i>Selenastrum capricornutum</i>	Sensitive	24.7 mg L ⁻¹ (glyphosate) and 41.0 mg L ⁻¹ (isopropyl salt of glyphosate)	
		<i>Scenedesmus acutus</i>	Reduced chlorophyll a content	50 mg L ⁻¹	
		<i>Scenedesmus quadricauda</i>	No harmful chronic effects		
	Algae	<i>Gayralia oxysperma</i> , <i>Myriophyllum aquaticum</i> , <i>Pterocladiella capillacea</i> , <i>Rhizoclonium riparium</i> , <i>Ruppia maritima</i> , <i>Ulva intestinalis</i>	Reduced chlorophyll content	0.45 g L ⁻¹	Tsui and Chu (2003) Kittle and McDermid (2016)
		<i>Nitella microcarpa</i> var. <i>wrightii</i>	Photosynthesis hampered	0.28–6 mg L ⁻¹	
		<i>Skeletonema costatum</i>	More sensitive		
	Diatom			2.27 mg L ⁻¹ (glyphosate) and 5.89 mg L ⁻¹ (isopropyl salt of glyphosate)	Oliveira et al. (2016)

NA = Not available.

also endorsed that glyphosate use as per the manufacturer's instructions does not pose any human health risks. Also, many researchers considered that glyphosate was non-toxic or less toxic to non-target organisms, and the toxic effects were observed with its prolonged exposure only at higher doses. The main controversial issue is about the differential toxicity of glyphosate and the surfactants in formulations like POEA to humans and ecological health. Moreover, due to the significant increase in the use of glyphosate for over 45 years after the development of GM-GR crops, about 38 weed species developed resistance to glyphosate. Although glyphosate formulations have potential detrimental effects on beneficial terrestrial and aquatic microorganisms, several pathogenic microorganisms developed resistance to these commercial formulations. Consequent to the controversial scenario on the toxicity of glyphosate, its use in the recent years has been either restricted or banned in about 20 countries. Based on the state-of-the-art situation, it appears that glyphosate is a lesser toxic herbicide compared to several other weed killers if proper guidelines are followed during its application at judicious concentrations. However, the potential health risk of glyphosate in the soil ecosystem, in terms of *GUS*, *LIX* and *HI*, needs to be clearly established. In order to avoid the controversies over the toxicity of glyphosate-based formulations to human health and other organisms of ecological importance, surfactants/adjuvants alternative to POEA should be developed.

Declaration of competing interest

None.

Acknowledgment

MMI acknowledges the University of Newcastle for providing UNIPRS and UNRSC scholarship, and Sher-e-Bangla Agricultural University, Bangladesh for granting study leave for PhD program.

References

- Ackermann, W., Coenen, M., Schrödl, W., Shehata, A.A., Krüger, M., 2015. The influence of glyphosate on the microbiota and production of botulinum neurotoxin during ruminal fermentation. *Curr. Microbiol.* 70, 374–382.
- Al-Rajab, A.J., Hakami, O.M., 2014. Behavior of the non-selective herbicide glyphosate in agricultural soil. *Am. J. Environ. Sci.* 10, 94–101.
- Al-Rajab, A.J., Schiavon, M., 2010. Degradation of ¹⁴C-glyphosate and aminomethylphosphonic acid (AMPA) in three agricultural soils. *J. Environ. Sci.* 22, 1374–1380.
- Alarcón-Reverte, R., García, A., Urzúa, J., Fischer, A.J., 2013. Resistance to glyphosate in jungle rice (*Echinochloa colona*) from California. *Weed Sci.* 61, 48–54.
- Alberdi, J.L., Saenz, M.E., Di Marzio, W.D., Tortorelli, M.C., 1996. Comparative acute toxicity of two herbicides, paraquat and glyphosate, to *Daphnia magna* and *D. spinulata*. *Bull. Environ. Contam. Toxicol.* 57, 229–235.
- Alexa, E., Bragea, M., Sumalan, R., Lăzureanu, A., Negrea, M., Iancu, S., 2009. Dynamic of glyphosate mineralization in different soil types. *Rom. Agric. Res.* 26, 57–60.
- Alimentarius, C., 2013. Pesticide Residues in Food and Feed: 158 Glyphosate. Food and Agriculture Organization and World Health Organization. <http://www.codexalimentarius.net/pestres/data/pesticides/details.html?id=158>. (Accessed 29 September 2015).
- Annett, R., Habibi, H.R., Hontela, A., 2014. Impact of glyphosate and glyphosate-based herbicides on the freshwater environment. *J. Appl. Toxicol.* 34, 458–479.
- Aparicio, V.C., De Gerónimo, E., Marino, D., Primost, J., Carriquiriborde, P., Costa, J.L., 2013. Environmental fate of glyphosate and aminomethylphosphonic acid in surface waters and soil of agricultural basins. *Chemosphere* 93, 1866–1873.
- Araújo, A.d., Monteiro, R.T.R., Abarkeli, R., 2003. Effect of glyphosate on the microbial activity of two Brazilian soils. *Chemosphere* 52, 799–804.
- Asaduzzaman, M., An, M., Pratley, J.E., Luckett, D.J., Lemerle, D., 2014a. Canola (*Brassica napus*) germplasm shows variable allelopathic effects against annual ryegrass (*Lolium rigidum*). *Plant Soil* 380, 47–56.
- Asaduzzaman, M., Pratley, J.E., An, M., Luckett, D.J., Lemerle, D., 2014b. Canola Interference for Weed Control, vol. 2. Springer Sci. Rev., pp. 63–74.
- Asaduzzaman, M., Pratley, J.E., Luckett, D., Lemerle, D., Wu, H., 2019. Weed management in canola (*Brassica napus* L): a review of current constraints and future strategies for Australia. *Arch. Agron. Soil Sci.* <https://doi.org/10.1080/03601500.2019.1624726>.
- Ascolani, Yael, J., Fuhr, J., Bocan, G., Daza Millone, A., Tognalli, N., dos Santos Afonso, M., Martiarena, M., 2014. Abiotic degradation of glyphosate into aminomethylphosphonic acid in the presence of metals. *J. Agric. Food Chem.* 62, 9651–9656.
- Ashworth, M.B., Walsh, M.J., Flower, K.C., Powles, S.B., 2014. Identification of the first glyphosate-resistant wild radish (*Raphanus raphanistrum* L.) populations. *Pest Manag. Sci.* 70, 1432–1436.
- Authority, E.F.S., 2009. The community summary report on trends and sources of zoonoses and zoonotic agents in the European Union in 2007. *EFSA J.* 7, 223r.
- Authority, E.F.S., 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. *EFSA J.* 13, 4302.
- Bai, S.H., Ogbourne, S.M., 2016. Glyphosate: environmental contamination, toxicity and potential risks to human health via food contamination. *Environ. Sci. Pollut. Res.* 23, 18988–19001.
- Bain, C., Selfa, T., Dandachi, T., Velardi, S., 2017. 'Superweeds' or 'survivors'? Framing the problem of glyphosate resistant weeds and genetically engineered crops. *J. Rural Stud.* 51, 211–221.
- Balbuena, M.S., Tison, L., Hahn, M.-L., Greggers, U., Menzel, R., Farina, W.M., 2015. Effects of sublethal doses of glyphosate on honeybee navigation. *J. Exp. Biol.* 218, 2799–2805.
- Barja, B., dos Santos Afonso, M., 2005. Aminomethylphosphonic acid and glyphosate adsorption onto goethite: a comparative study. *Environ. Sci. Technol.* 39, 585–592.
- Barrett, K., McBride, M., 2005. Oxidative degradation of glyphosate and aminomethylphosphonate by manganese oxide. *Environ. Sci. Technol.* 39, 9223–9228.
- Battaglin, W.A., Rice, K.C., Focazio, M.J., Salmons, S., Barry, R.X., 2009. The occurrence of glyphosate, atrazine, and other pesticides in vernal pools and adjacent streams in Washington, DC, Maryland, Iowa, and Wyoming, 2005–2006. *Environ. Monit. Assess.* 155, 281–307.
- Battaglin, W.A., Meyer, M., Kuivila, K., Dietze, J., 2014. Glyphosate and its degradation product AMPA occur frequently and widely in US soils, surface water, groundwater, and precipitation. *J. Am. Water Resour. Assoc.* 50, 275–290.
- Beckie, H.J., Harker, K.N., Legere, A., Morrison, M.J., Seguin-Swartz, G., Falk, K.C., 2011. GM canola: the Canadian experience. *Farm Policy J.* 8 (I), 43–49.
- Benachour, N., Séralini, G.E., 2008. Glyphosate formulations induce apoptosis and necrosis in human umbilical, embryonic, and placental cells. *Chem. Res. Toxicol.* 22, 97–105.
- Benbrook, C.M., 2016. Trends in glyphosate herbicide use in the United States and globally. *Environ. Sci. Eur.* 28, 3.
- Bento, C.P., Yang, X., Gort, G., Xue, S., van Dam, R., Zomer, P., Mol, H.G., Ritsema, C.J., Geissen, V., 2016. Persistence of glyphosate and aminomethylphosphonic acid in loess soil under different combinations of temperature, soil moisture and light/darkness. *Sci. Total Environ.* 572, 301–311.
- Berendsen, R.L., Pieters, C.M., Bakker, P.A., 2012. The rhizosphere microbiome and plant health. *Trends Plant Sci.* 17, 478–486.
- Bergström, L., Börjesson, E., Stenström, J., 2011. Laboratory and lysimeter studies of glyphosate and aminomethylphosphonic acid in a sand and a clay soil. *J. Environ. Qual.* 40, 98–108.
- Boerboom, C.M., Wyse, D.L., Somers, D.A., 1990. Mechanism of glyphosate tolerance in bird'sfoot trefoil (*Lotus corniculatus*). *Weed Sci.* 38, 463–467.
- Bøhn, T., Cuhra, M., Traavik, T., Sanden, M., Fagan, J., Primicerio, R., 2014. Compositional differences in soybeans on the market: glyphosate accumulates in Roundup Ready GM soybeans. *Food Chem.* 153, 207–215.
- Boily, M., Sarrasin, B., DeBlois, C., Aras, P., Chagnon, M., 2013. Acetylcholinesterase in honey bees (*Apis mellifera*) exposed to neonicotinoids, atrazine and glyphosate: laboratory and field experiments. *Environ. Sci. Pollut. Res.* 20, 5603–5614.
- Bonnet, L., Bonnemoy, F., Dusser, M., Bohatier, J., 2007. Assessment of the potential toxicity of herbicides and their degradation products to non-target cells using two microorganisms, the bacteria *Vibrio fischeri* and the ciliate *Tetrahymena pyriformis*. *Environ. Toxicol.* 22, 78–91.
- Borggaard, O.K., Gimsing, A.L., 2008. Fate of glyphosate in soil and the possibility of leaching to ground and surface waters: a review. *Pest Manag. Sci.* 64, 441–456.
- Botero-Coy, A.M., Ibáñez, M., Sancho, J., Hernández, F., 2013. Improvements in the analytical methodology for the residue determination of the herbicide glyphosate in soils by liquid chromatography coupled to mass spectrometry. *J. Chromatogr. A* 1292, 132–141.
- Brausch, J.M., Smith, P.N., 2007. Toxicity of three polyethoxylated tallowamine surfactant formulations to laboratory and field collected fairy shrimp, *Thamnocephalus platyurus*. *Arch. Environ. Contam. Toxicol.* 52, 217–221.
- Bringolf, R.B., Cope, W.G., Mosher, S., Barnhart, M.C., Shea, D., 2007. Acute and chronic toxicity of glyphosate compounds to *Glochidia* and juveniles of *Lampsilis siliquoidea* (Unionidae). *Environ. Chem.* 26, 2094–2100.
- Brookes, G., Taheripour, F., Tyner, W.E., 2017. The contribution of glyphosate to agriculture and potential impact of restrictions on use at the global level. *GM Crops Food* 8, 216–228.
- Broster, J., Koetz, E., Wu, H., 2013. Herbicide resistance levels in annual ryegrass (*Lolium rigidum* Gaud.) and wild oat (*Avena* spp.) in southwestern New South Wales. *Plant Protect. Q.* 28, 126–132.
- Bryson, C.T., Wills, G.D., 1985. Susceptibility of bermudagrass (*Cynodon dactylon*) biotypes to several herbicides. *Weed Sci.* 33, 848–852.
- Bueno, A.D.F., Bueno, R.C.O.D.F., Parra, J.R.P., Vieira, S.S., 2008. Effects of pesticides used in soybean crops to the egg parasitoid *Trichogramma pretiosum*. *Ciencia Rural* 38, 1495–1503.
- Busse, M.D., Ratcliff, A.W., Shestak, C.J., Powers, R.F., 2001. Glyphosate toxicity and

- the effects of long-term vegetation control on soil microbial communities. *Soil Biol. Biochem.* 33, 1777–1789.
- Canada, H., 2015. Proposed Re-evaluation Decision PDRV2015-01, Glyphosate. Ottawa (ON): Health Canada, Pest Management Regulatory Agency (PMRA). http://www.hc-sc.gc.ca/cps-spc/pest/part/consultations/_prvd2015-01/prvd2015-01eng. (Accessed 17 August 2019).
- Carpenter, J.K., Monks, J.M., Nelson, N., 2016. The effect of two glyphosate formulations on a small, diurnal lizard (*Oligosoma polychroma*). *Ecotoxicology* 25, 548–554.
- Cassigneul, A., Benoit, P., Bergheaud, V., Dumeny, V., Etievant, V., Goubard, Y., Maylin, A., Justes, E., Allitto, L., 2016. Fate of glyphosate and degradates in cover crop residues and underlying soil: a laboratory study. *Sci. Total Environ.* 545, 582–590.
- Çağlar, S., Kolankaya, D., 2008. The effect of sub-acute and sub-chronic exposure of rats to the glyphosate-based herbicide Roundup. *Environ. Toxicol. Pharmacol.* 25, 57–62.
- Cerdeira, A.L., Gazziero, D.L., Duke, S.O., Matallo, M.B., Spadotto, C.A., 2007. Review of potential environmental impacts of transgenic glyphosate-resistant soybean in Brazil. *J. Environ. Sci. Health B* 42, 539–549.
- Çetin, E., Şahan, S., Ülgen, A., Şahin, U., 2017. DLLME-spectrophotometric determination of glyphosate residue in legumes. *Food Chem.* 230, 567–571.
- Chakravarty, P., Sidhu, S.S., 1987. Effect of glyphosate, hexazinone and triclopyr on in vitro growth of five species of ectomycorrhizal fungi. *Eur. J. For. Pathol.* 17, 204–210.
- Chang, F.C., Simcik, M.F., Capel, P.D., 2011. Occurrence and fate of the herbicide glyphosate and its degradate aminomethylphosphonic acid in the atmosphere. *Environ. Toxicol. Chem.* 30, 548–555.
- Chauhan, G., Coalova, I., de Molina, M.C.R., 2014. Glyphosate commercial formulation causes cytotoxicity, oxidative effects, and apoptosis on human cells: differences with its active ingredient. *Int. J. Toxicol.* 33, 29–38.
- Chèvre, A.-M., Eber, F., Baranger, A., Renard, M., 1997. Gene flow from transgenic crops. *Nature* 389, 924–924.
- Clive, J., 2009. Global Status of Commercialized Biotech/GM Crops: 2009. ISAAA Brief No. 41. ISAAA, Ithaca, NY.
- Čolović, M.B., Krstić, D.Z., Lazarević-Pasti, T.D., Bondžić, A.M., Vasić, V.M., 2013. Acetylcholinesterase inhibitors: pharmacology and toxicology. *Curr. Neuropharmacol.* 11, 315–335.
- Contaminants, C., 2003. Health Effects Technical Support Document, Six-Year Review. United States Environmental Protection Agency, Washington, DC, p. 32.
- Correia, F.V., Moreira, J.C., 2010. Effects of glyphosate and 2, 4-D on earthworms (*Eisenia foetida*) in laboratory tests. *Bull. Environ. Contam. Toxicol.* 85, 264–268.
- Coullier, R.P., Ferrari, M.E., Rosso, S.B., 2016. Neuronal development and axon growth are altered by glyphosate through a WNT non-canonical signaling pathway. *Neurotoxicology* 52, 150–161.
- Coupe, R.H., Kalkhoff, S.J., Capel, P.D., Gregoire, C., 2012. Fate and transport of glyphosate and aminomethylphosphonic acid in surface waters of agricultural basins. *Pest Manag. Sci.* 68, 16–30.
- Cuhra, M., 2015. Review of GMO safety assessment studies: glyphosate residues in Roundup Ready crops is an ignored issue. *Environ. Sci. Eur.* 27, 1–14.
- Cuhra, M., Traavik, T., Bohn, T., 2013. Clone-and age-dependent toxicity of a glyphosate commercial formulation and its active ingredient in *Daphnia magna*. *Ecotoxicology* 22, 251–262.
- Culpepper, A.S., Flanders, J., York, A.C., Webster, T.M., 2004. Tropical spiderwort (*Commelinopsis benghalensis*) control in glyphosate-resistant cotton. *Weed Technol.* 18, 432–436.
- Culpepper, A.S., Grey, T.L., Vencill, W.K., Kichler, J.M., Webster, T.M., Brown, S.M., York, A.C., Davis, J.W., Hanna, W.W., 2006. Glyphosate-resistant Palmer amaranth (*Amaranthus palmeri*) confirmed in Georgia. *Weed Sci.* 54, 620–626.
- Daouk, S., Copin, P.-J., Rossi, L., Chèvre, N., Pfeifer, H.-R., 2013. Dynamics and environmental risk assessment of the herbicide glyphosate and its metabolite AMPA in a small vineyard river of the Lake Geneva catchment. *Environ. Toxicol. Chem.* 32, 2035–2044.
- de Carvalho, L.B., Alves, P.L.d.C.A., González-Torralva, F., Cruz-Hipolito, H.E., Rojano-Delgado, A.M., De Prado, R., Gil-Humanes, J., Barro, F., Luque de Castro, M.D., 2012. Pool of resistance mechanisms to glyphosate in *Digitaria insularis*. *J. Agric. Food Chem.* 60, 615–622.
- De Gennaro, F.P., Weller, S.C., 1984. Differential susceptibility of field bind weed (*Convolvulus arvensis*) biotypes to glyphosate. *Weed Sci.* 32, 472–476.
- Diamond, G.L., Durkin, P.R., 1997. Effects of Surfactants on the Toxicity of Glyphosate, With Specific Reference to RODEO. Animal and Plant Health Inspection Service (APHIS), Biotechnology, Biologics and Environmental Protection, Environmental Analysis and Documentation, United States Department of Agriculture, Riverdale, MD 20737, USA, p. 28. <https://www.fs.fed.us/foresthealth/pesticide/pdfs/Surfactants.pdf>. (Accessed 17 September 2019).
- Domínguez, A., Brown, G.G., Sautter, K.D., De Oliveira, C.M.R., De Vasconcelos, E.C., Niva, C.C., Bartz, M.L.C., Bedano, J.C., 2016. Toxicity of AMPA to the earthworm *Eisenia andrei* Bouché, 1972 in tropical artificial soil. *Sci. Rep.* 6, 19731.
- Dornelles, M.F., Oliveira, G.T., 2016. Toxicity of atrazine, glyphosate, and quinclorac in bullfrog tadpoles exposed to concentrations below legal limits. *Environ. Sci. Pollut. Res.* 23, 1610–1620.
- Druart, C., Millet, M., Scheifler, R., Delhomme, O., De Vauflrey, A., 2011. Glyphosate and glufosinate-based herbicides: fate in soil, transfer to, and effects on land snails. *J. Soils Sediments* 11, 1373–1384.
- Duke, S.O., 2005. Taking stock of herbicide-resistant crops ten years after introduction. *Pest Manag. Sci.* 61, 211–218.
- Duke, S.O., 2010. Glyphosate degradation in glyphosate-resistant and-susceptible crops and weeds. *J. Agric. Food Chem.* 59, 5835–5841.
- Duke, S.O., 2018. The history and current status of glyphosate. *Pest Manag. Sci.* 74, 1027–1034.
- Duke, S.O., Powles, S.B., 2008. Glyphosate: a once-in-a-century herbicide. *Pest Manag. Sci.* 64, 319–325.
- Duke, S.O., Powles, S.B., 2009. Glyphosate-resistant crops and weeds: now and in the future. *AgBioforum* 12, 346–357.
- Durkin, P.R., 2011. Glyphosate: Human Health and Ecological Risk Assessment. Syracuse Environmental Research Associates, Inc., Manlius, New York, USA. Final Report Submitted to the USDA Forest Service, SERA TR-052-22-03b. https://www.fs.fed.us/foresthealth/pesticide/pdfs/Glyphosate_SERA_TR-052-2203b.pdf. (Accessed 22 September 2019).
- Erickson, B.E., 2020. Glyphosate Is Not Carcinogenic, USEPA Says. *C & En News*, 5 February 2020. American Chemical Society.
- Erickson, G., Robbins, N., Simon, J., Berger, L., Klopfenstein, T., Stanisiewski, E., Hartnell, G., 2003. Effect of feeding glyphosate-tolerant (Roundup-Ready events GA21 or nk603) corn compared with reference hybrids on feedlot steer performance and carcass characteristics. *J. Anim. Sci.* 81, 2600–2608.
- Estok, D., Freedman, B., Boyle, D., 1989. Effects of the herbicides 2,4-D, glyphosate, hexazinone, and triclopyr on the growth of three species of ectomycorrhizal fungi. *Bull. Environ. Contam. Toxicol.* 42, 835–839.
- Fagin, D., 2012. Toxicology: the learning curve. *Nature* 490, 462–465.
- Fan, J., Geng, J., Ren, H., Wang, X., 2013. Time-effect relationship of toxicity induced by Roundup® and its main constituents in liver of *Carassius auratus*. *Comput. Water Energy Environ. Eng.* 2, 20–25.
- Fan, L., Feng, Y., Weaver, D.B., Delaney, D.P., Wehtje, G.R., Wang, G., 2017. Glyphosate effects on symbiotic nitrogen fixation in glyphosate-resistant soybean. *Appl. Soil Ecol.* 121, 11–19.
- Fenner, K., Canonica, S., Wackett, L.P., Elsner, M., 2013. Evaluating pesticide degradation in the environment: blind spots and emerging opportunities. *Science* 341, 752–758.
- Figueiredo, M.D.V.B., Seldin, L., de Araujo, F.F., Mariano, R.L.R., 2011. Plant Growth Promoting Rhizobacteria: Fundamentals and Applications. Plant Growth and Health Promoting Bacteria. Springer, pp. 21–43.
- Fischer, R.S., Berry, A., Gaines, C.G., Jensen, R., 1986. Comparative action of glyphosate as a trigger of energy drain in eubacteria. *J. Bacteriol.* 168, 1147–1154.
- Fishel, F., 2017. This Document Is PI254, One of a Series of the Agronomy Department, UF/IFAS Extension. Original publication date December 2014. Reviewed September 2017. <http://edis.ifas.ufl.edu>. (Accessed 18 October 2019).
- Fluegge, K., Fluegge, K., 2016. Glyphosate use predicts healthcare utilization for ADHD in the healthcare cost and utilization project net (HCUPnet): a two-way fixed-effects analysis. *Pol. J. Environ. Stud.* 25, 1489–1503.
- Fortes, C., Mastroeni, S., Segatto, M.M., Hohmann, C., Miligi, L., Bakos, L., Bonamigo, R., 2016. Occupational exposure to pesticides with occupational sun exposure increases the risk for cutaneous melanoma. *J. Occup. Environ. Med.* 58, 370–375.
- Gaines, T.A., Shaner, D.L., Ward, S.M., Leach, J.E., Preston, C., Westra, P., 2011. Mechanism of resistance of evolved glyphosate-resistant Palmer amaranth (*Amaranthus palmeri*). *J. Agric. Food Chem.* 59, 5886–5889.
- Gasnier, C., Dumont, C., Benachour, N., Clair, E., Chagnon, M.-C., Séralini, G.-E., 2009. Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines. *Toxicology* 262, 184–191.
- Ge, X., d'Avignon, D.A., Ackerman, J.J., Collavo, A., Sattin, M., Ostrander, E.L., Hall, E.L., Sammons, R.D., Preston, C., 2012. Vacuolar glyphosate-sequestration correlates with glyphosate resistance in ryegrass (*Lolium spp.*) from Australia, South America, and Europe: a 31P NMR investigation. *J. Agric. Food Chem.* 60, 1243–1250.
- Giesy, J.P., Dobson, S., Solomon, K.R., 2000. Eco-toxicological risk assessment for Roundup herbicide. *Rev. Environ. Contam. Toxicol.* 167, 35–120.
- Gimsing, A., Borggaard, O., Bang, M., 2004a. Influence of soil composition on adsorption of glyphosate and phosphate by contrasting Danish surface soils. *Eur. J. Soil Sci.* 55, 183–191.
- Gimsing, A.L., Borggaard, O.K., Jacobsen, O.S., Aamand, J., Sørensen, J., 2004b. Chemical and microbiological soil characteristics controlling glyphosate mineralisation in Danish surface soils. *Appl. Soil Ecol.* 27, 233–242.
- Gimsing, A.L., Szilas, C., Borggaard, O.K., 2007. Sorption of glyphosate and phosphate by variable-charge tropical soils from Tanzania. *Geoderma* 138, 127–132.
- Gomes, M.P., Smedbol, E., Chalifour, A., Hénault-Ethier, L., Labrecque, M., Lepage, L., Lucotte, M., Juneau, P., 2014. Alteration of plant physiology by glyphosate and its by-product aminomethylphosphonic acid: an overview. *J. Exp. Bot.* 65, 4691–4703.
- Gomes, M.P., Le Manac'h, S.G., Maccario, S., Labrecque, M., Lucotte, M., Juneau, P., 2016. Differential effects of glyphosate and aminomethylphosphonic acid (AMPA) on photosynthesis and chlorophyll metabolism in willow plants. *Pestic. Biochem. Physiol.* 130, 65–70.
- Gong, J., Forster, R.J., Yu, H., Chambers, J.R., Sabour, P.M., Wheatcroft, R., Chen, S., 2002. Diversity and phylogenetic analysis of bacteria in the mucosa of chicken ceca and comparison with bacteria in the cecal lumen. *FEMS Microbiol. Lett.* 208, 1–7.
- Grandcoin, A., Piel, S., Baures, E., 2017. Aminomethylphosphonic acid (AMPA) in natural waters: its sources, behavior and environmental fate. *Water Res.* 117, 187–197.
- Green, J.M., 2009. Evolution of glyphosate-resistant crop technology. *Weed Sci.* 57, 108–117.

- Gressel, P.D., Roehrs, R.E., 1991. Ophthalmic Carboxy Vinyl Polymer Gel for Dry Eye Syndrome. Google Patents.
- Grundmann, S., Dorfler, U., Ruth, B., Loos, C., Wagner, T., Karl, H., Munch, J.C., Schroll, R., 2008. Mineralization and transfer processes of ¹⁴C-labeled pesticides in outdoor lysimeters. *Water Air Soil Pollut. Focus* 8, 177–185.
- Guilherme, S., Gaivao, I., Santos, M., Pacheco, M., 2010. European eel (*Anguilla anguilla*) genotoxic and pro-oxidant responses following short-term exposure to Roundup® – a glyphosate-based herbicide. *Mutagenesis* 25, 523–530.
- Guilherme, S., Santos, M., Barroso, C., Gaivão, I., Pacheco, M., 2012. Differential genotoxicity of Roundup® formulation and its constituents in blood cells of fish (*Anguilla anguilla*): considerations on chemical interactions and DNA damaging mechanisms. *Ecotoxicology* 21, 1381–1390.
- Guilherme, S., Santos, M.A., Gaivão, I., Pacheco, M., 2014. DNA and chromosomal damage induced in fish (*Anguilla anguilla* L.) by aminomethylphosphonic acid (AMPA) – the major environmental breakdown product of glyphosate. *Environ. Sci. Pollut. Res.* 21, 8730–8739.
- Hall, L., Topinka, K., Huffman, J., Davis, L., Good, A., 2000. Pollen flow between herbicide-resistant *Brassica napus* is the cause of multiple-resistant *Brassica napus* volunteers. *Weed Sci.* 48, 688–694.
- Haney, R., Senseman, S., Hons, F., Zuberer, D., 2000. Effect of glyphosate on soil microbial activity and biomass. *Weed Sci.* 48, 89–93.
- Hanke, I., Wittmer, I., Bischofberger, S., Stamm, C., Singer, H., 2010. Relevance of urban glyphosate use for surface water quality. *Chemosphere* 81, 422–429.
- Harrison, J., 2008. Abandoned bodies and spaces of sacrifice: pesticide drift activism and the contestation of neoliberal environmental politics in California. *Geoforum* 39, 1197–1214.
- Hart, M.R., Brookes, P.C., 1996. Soil microbial biomass and mineralization of soil organic matter after 19 years of cumulative field applications of pesticides. *Soil Biol. Biochem.* 28, 1641–1649.
- Heap, I., 2006. International survey of herbicide resistant weeds. *West. Soc. Weed Sci.* 5 (0091–4487), 27–29.
- Heap, I., 2011. International Survey of Herbicide Resistant Weeds. <http://www.weedscience.org>. (Accessed 28 June 2019).
- Heap, I., 2014a. *Herbicide Resistant Weeds, Integrated Pest Management*. Springer, pp. 281–301.
- Heap, I., 2014b. International Survey of Herbicide Resistant Weeds. <http://www.weedscience.org>. (Accessed 14 October 2019).
- Heap, I., 2017. International Survey of Herbicide Resistant Weeds. Wiley Publications, pp. 217–287. <http://www.weedscience.com>.
- Heap, I., Duke, S.O., 2018. Overview of glyphosate-resistant weeds worldwide. *Pest Manag. Sci.* 74, 1040–1049.
- Herbert, L.T., Vázquez, D.E., Arenas, A., Farina, W.M., 2014. Effects of field-realistic doses of glyphosate on honeybee appetitive behaviour. *J. Exp. Biol.* 217, 3457–3464.
- Hernandez, A., Garcia-Plazaola, J.I., Becerril, J.M., 1999. Glyphosate effects on phenolic metabolism of nodulated soybean (*Glycine max* L. Merr.). *J. Agric. Food Chem.* 47, 2920–2925.
- Horth, H., Blackmore, K., 2009. Survey of Glyphosate and AMPA in Groundwaters and Surface Waters in Europe. Report by WRc Plc. Swindon, Swindon, Wiltshire, United Kingdom. No. UC8073, 2.
- Howe, C.M., Berrill, M., Pauli, B.D., Helbing, C.C., Werry, K., Veldhoen, N., 2004. Toxicity of glyphosate-based pesticides to four North American frog species. *Environ. Toxicol. Chem.* 23, 1928–1938.
- Hudson, D., Richards, R., 2014. Evaluation of the Agronomic, Environmental, Economic, and Coexistence Impacts Following the Introduction of GM Canola to Australia, 2008–2010.
- Hued, A.C., Oberhofer, S., de los Ángeles Bistoni, M., 2012. Exposure to a commercial glyphosate formulation (Roundup®) alters normal gill and liver histology and affects male sexual activity of *Jenynsia multidentata* (Anablepidae, Cyprinodontiformes). *Arch. Environ. Contam. Toxicol.* 62, 107–117.
- IARC, 2015. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlорvinphos. <http://monographs.iarc.fr/ENG/Monographs/vol112/index.php>. (Accessed 19 August 2019).
- IARC, 2016. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlорvinphos. <https://www.iarc.fr/featured-news/media-centre-iarc-news-glyphosate/>. (Accessed 10 August 2019).
- Isolauri, E., Sütas, Y., Kankaanpää, P., Arvilommi, H., Salminen, S., 2001. Probiotics: effects on immunity. *Am. J. Clin. Nutr.* 73, 444S–450S.
- James, C., 2016. Global status of commercialized biotech/GM crops. *ISAAA Brief* 52. ISBN: 978-1-892456-66-4.
- Jasieniuk, M., Brûlé-Babel, A.L., Morrison, I.N., 1996. The evolution and genetics of herbicide resistance in weeds. *Weed Sci.* 44, 176–193.
- Jin, J., Kurobe, T., Ramírez-Duarte, W.F., Bolotaolo, M.B., Lam, C.H., Pandey, P.K., Hung, T.-C., Stillway, M.E., Zweig, L., Caudill, J., 2018. Sub-lethal effects of herbicides penoxsulam, imazamox, fluridone and glyphosate on Delta Smelt (*Hypomesus transpacificus*). *Aquat. Toxicol.* 197, 79–88.
- Jofré, D.M., Germanó García, M.J., Salcedo, R.E., Morales, M., Alvarez, M., Enriz, R.D., Gianinni, F., 2013. Fish toxicity of commercial herbicides formulated with glyphosate. *J. Environ. Anal. Toxicol.* 4, 1–3.
- Keshtkar, S., Azarpira, N., Ghahremani, M.H., 2018. Mesenchymal stem cell-derived extracellular vesicles: novel frontiers in regenerative medicine. *Stem Cell Res. Ther.* 9, 1–9.
- Kier, L.D., Kirkland, D.J., 2013. Review of genotoxicity studies of glyphosate and glyphosate-based formulations. *Crit. Rev. Toxicol.* 43, 283–315.
- Kittle, R.P., McDermid, K.J., 2016. Glyphosate herbicide toxicity to native Hawaiian macroalgal and seagrass species. *J. Appl. Phycol.* 28, 2597–2604.
- Klümper, W., Qaim, M., 2014. A meta-analysis of the impacts of genetically modified crops. *PLoS One* 9, e111629.
- Koger, C.H., Poston, D.H., Hayes, R.M., Montgomery, R.F., 2004. Glyphosate-resistant horseweed (*Conyza canadensis*) in Mississippi. *Weed Technol.* 18, 820–825.
- Koller, V.J., Fürhacker, M., Nersesyan, A., Mišik, M., Eisenbauer, M., Knasmüller, S., 2012. Cytotoxic and DNA damaging properties of glyphosate and Roundup in human derived buccal epithelial cells. *Arch. Toxicol.* 86, 805–813.
- Kolpin, D.W., Thurman, E.M., Lee, E.A., Meyer, M.T., Furlong, E.T., Glassmeyer, S.T., 2006. Urban contributions of glyphosate and its degradate AMPA to streams in the United States. *Sci. Total Environ.* 354, 191–197.
- Krüger, M., Schrödl, W., Neuhaus, J., Shehata, A., 2013a. Field investigations of glyphosate in urine of Danish dairy cows. *J. Environ. Anal. Toxicol.* 3 (5), 186. <https://doi.org/10.4172/2161-0525.1000186>.
- Krüger, M., Shehata, A.A., Schrödl, W., Rodloff, A., 2013b. Glyphosate suppresses the antagonistic effect of *Enterococcus* spp. on *Clostridium botulinum*. *Anaerobe* 20, 74–78.
- Krüger, M., Schledorn, P., Schrödl, W., Hoppe, H.-W., Lutz, W., Shehata, A.A., 2014. Detection of glyphosate residues in animals and humans. *J. Environ. Anal. Toxicol.* 4 (2), 210. <https://doi.org/10.4172/2161-0525.1000210>.
- Kurenbach, B., Marjoshi, D., Amabile-Cuevas, C.F., Ferguson, G.C., Godsoe, W., Gibson, P., Heinemann, J.A., 2015. Sublethal exposure to commercial formulations of the herbicides dicamba, 2,4-dichlorophenoxyacetic acid, and glyphosate cause changes in antibiotic susceptibility in *Escherichia coli* and *Salmonella enterica* serovar Typhimurium. *mBio* 6 e00009–15.
- Kwiatkowska, M., Huras, B., Bukowska, B., 2014a. The effect of metabolites and impurities of glyphosate on human erythrocytes (in vitro). *Pestic. Biochem. Physiol.* 109, 34–43.
- Kwiatkowska, M., Nowacka-Krukowska, H., Bukowska, B., 2014b. The effect of glyphosate, its metabolites and impurities on erythrocyte acetylcholinesterase activity. *Environ. Toxicol. Pharmacol.* 37, 1101–1108.
- Kwiatkowska, M., Reszka, E., Woźniak, K., Jabłońska, E., Michałowicz, J., Bukowska, B., 2017. DNA damage and methylation induced by glyphosate in human peripheral blood mononuclear cells (in vitro study). *Food Toxicol.* 105, 93–98.
- Laitinen, P., 2009. Fate of the Organophosphate Herbicide Glyphosate in Arable Soils and its Relationship to Soil Phosphorus Status. MTT Agrifood Research Finland. <http://www.mtt.fi/mttiede/pdf/mttiede3.pdf>. (Accessed 25 October 2019).
- Laitinen, P., Siimes, K., Eronen, L., Rämö, S., Welling, L., Oinonen, S., Mattsoff, L., Ruohonen-Lehto, M., 2006. Fate of the herbicides glyphosate, glufosinate-ammonium, phenmedipham, ethofumesate and metamitron in two Finnish arable soils. *Pest Manag. Sci.* 62, 473–491.
- Lajmanovich, R.C., Attademo, A.M., Simoniello, M.F., Poletta, G.L., Junges, C.M., Peltzer, P.M., Cabagna-Zenklausen, M.C., 2015. Harmful effects of the dermal intake of commercial formulations containing chlorpyrifos, 2,4-D and glyphosate on the common toad *Rhinella arenarum* (Anura: bufonidae). *Water Air Soil Pollut.* 226, 427.
- Lane, M., Lorenz, N., Saxena, J., Ramsier, C., Dick, R.P., 2012. The effect of glyphosate on soil microbial activity, microbial community structure, and soil potassium. *Pedobiologia* 55, 335–342.
- Lee, L.J., Ngim, J., 2000. A first report of glyphosate-resistant goosegrass (*Eleusis indica* L. Gaertn) in Malaysia. *Pest Manag. Sci.* 56, 336–339.
- Lee, H.L., Kan, D., Tsai, C.L., Liou, M.J., Guo, H.R., 2009. Comparative effects of the formulation of glyphosate-surfactant herbicides on hemodynamics in swine. *Clin. Toxicol.* 47, 651–658.
- Li, M.H., Ruan, L.Y., Zhou, J.W., Fu, Y.H., Jiang, L., Zhao, H., Wang, J.S., 2017. Metabolic profiling of goldfish (*Carassius auratus*) after long-term glyphosate based herbicide exposure. *Aquat. Toxicol.* 188, 159–169.
- Linz, G.M., Blixt, D.C., Bergman, D.L., Bleier, W.J., 1996. Responses of redwinged blackbirds, yellow-headed blackbirds and marsh wrens to glyphosate-induced alterations in cattail density. *J. Field Ornithol.* 67, 167–176.
- Liu, Y., Wei, W., Ma, K., Li, J., Liang, Y., Darmency, H., 2013. Consequences of gene flow between oilseed rape (*Brassica napus*) and its relatives. *Plant Sci.* 211, 42–51.
- Locke, M., Zablotowicz, R., 2004. Pesticides in soil: benefits and limitations to soil health. In: Schjonning, P., Elmholz, S., Christensen, B.T. (Eds.), *Managing Soil Quality: Challenges in Modern Agriculture*, pp. 239–260.
- Lugowska, K., 2018. The effects of Roundup on gametes and early development of common carp (*Cyprinus carpio* L.). *Fish Physiol. Biochem.* 44, 1109–1117.
- Mahler, B.J., Van Metre, P.C., Burley, T.E., Loftin, K.A., Meyer, M.T., Nowell, L.H., 2017. Similarities and differences in occurrence and temporal fluctuations in glyphosate and atrazine in small Midwestern streams (USA) during the 2013 growing season. *Sci. Total Environ.* 579, 149–158.
- Manas, F., Peralta, L., Raviola, J., Ovando, H.G., Weyers, A., Ugnia, L., Gorla, N., 2009. Genotoxicity of glyphosate assessed by the comet assay and cytogenetic tests. *Environ. Toxicol. Pharmacol.* 28, 37–41.
- Maqueda, C., Undabeytia, T., Villaverde, J., Morillo, E., 2017. Behaviour of glyphosate in a reservoir and the surrounding agricultural soils. *Sci. Total Environ.* 593, 787–795.
- Marshall, M.W., Al-Khatib, K., Maddux, L., 2000. Weed Community Shifts Associated with Continuous Glyphosate Applications in Corn and Soybean Rotation. Western Society of Weed Science, Kansas, pp. 22–25.
- Martini, C.N., Gabrielli, M., Codesido, M.M., Del Vilà, M.C., 2016. Glyphosate-based herbicides with different adjuvants are more potent inhibitors of 3T3-L1

- fibroblast proliferation and differentiation to adipocytes than glyphosate alone. *Comp. Clin. Pathol.* 25, 607–613.
- MDH, 2017. Glyphosate and Drinking Water. Minnesota Department of Health. <https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/glyphosateinfo.pdf>. (Accessed 12 August 2019).
- Meftaul, I.M., Venkateswarlu, K., Dharmarajan, R., Annamalai, P., Megharaj, M., 2020. Pesticides in the urban environment: a potential threat that knocks at the door. *Sci. Total Environ.* 711, 134612. <https://doi.org/10.1016/j.scitotenv.2019.134612>.
- Menéndez-Helman, R.J., Ferreyroa, G.V., dos Santos Afonso, M., Salibián, A., 2012. Glyphosate as an acetylcholinesterase inhibitor in *Cnesterodon decemmaculatus*. *Bull. Environ. Contam. Toxicol.* 88, 6–9.
- Mesnage, R., Bernay, B., Séralini, G.-E., 2013. Ethoxylated adjuvants of glyphosate-based herbicides are active principles of human cell toxicity. *Toxicology* 313, 122–128.
- Mesnage, R., Arno, M., Costanzo, M., Malatesta, M., Séralini, G.E., Antoniou, M.N., 2015a. Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure. *Environ. Health* 14, 70–84.
- Mesnage, R., Defarge, N., De Vendomois, J.S., Séralini, G., 2015b. Potential toxic effects of glyphosate and its commercial formulations below regulatory limits. *Food Chem. Toxicol.* 84, 133–153.
- Mink, P.J., Mandel, J.S., Lundin, J.I., Sceurman, B.K., 2011. Epidemiologic studies of glyphosate and non-cancer health outcomes: a review. *Regul. Toxicol. Pharmacol.* 61, 172–184.
- Mink, P.J., Mandel, J.S., Sceurman, B.K., Lundin, J.I., 2012. Epidemiologic studies of glyphosate and cancer: a review. *Regul. Toxicol. Pharmacol.* 63, 440–452.
- Monheit, S., 2007. Glyphosate-based Aquatic Herbicides. An Overview of Risk. <http://teamarundo.org/controlmanage/docs/glyphosateaquarisk.pdf>. (Accessed 13 October 2019).
- Monheit, S., Leavitt, J., Trumbo, J., 2004. The ecotoxicology of surfactants: glyphosate based herbicides. *Noxious Times* 6, 6–12.
- Monsanto, 2005. Backgrounder: History of Monsanto's Glyphosate Herbicides. http://www.monsanto.com/products/documents/glyphosatebackgroundmaterials/back_history.pdf. (Accessed 22 September 2019).
- Monsanto, 2009. Backgrounder: History of Monsanto's Glyphosate Herbicides. http://www.monsanto.com/monsanto/content/products/productivity/roundup/back_histroy.pdf. (Accessed 22 September 2019).
- Monsanto, 2014. Backgrounder: Glyphosate and Water Quality. <https://monsanto.com/app/uploads/2017/06/glyphosate-and-water-quality.pdf>. (Accessed 22 September 2019).
- Moore, L.J., Fuentes, L., Rodgers Jr., J.H., Bowerman, W.W., Yarrow, G.K., Chao, W.Y., Bridges Jr., W.C., 2012. Relative toxicity of the components of the original formulation of Roundup® to five North American anurans. *Ecotoxicol. Environ. Saf.* 78, 128–133.
- Moorman, T.B., 1986. Effects of herbicides on the survival of *Rhizobium japonicum* strains. *Weed Sci.* 34, 628–633.
- Moorman, T.B., Becerril, J.M., Lydon, J., Duke, S.O., 1992. Production of hydroxybenzoic acids by *Bradyrhizobium japonicum* strains after treatment with glyphosate. *J. Agric. Food Chem.* 40, 289–293.
- Moreno, N.C., Sofía, S.H., Martínez, C.B.R., 2014. Genotoxic effects of the herbicide Roundup Transorb® and its active ingredient glyphosate on the fish *Prochilodus lineatus*. *Environ. Toxicol. Pharm.* 37, 448–454.
- Morini, R., Frank, D.J., Fenner-Crisp, P., 2018. Glyphosate: Health Controversy, Benefits and Continuing Debate. https://www.pubs.ext.vt.edu/content/dam/pubs_ext_vt_edu/spes/spes-63/SPES-63.pdf. (Accessed 19 September 2019).
- Mörtl, M., Németh, G., Jurácsik, J., Darvas, B., Kamp, L., Rubio, F., Székács, A., 2013. Determination of glyphosate residues in Hungarian water samples by immunoassay. *Microchem. J.* 107, 143–151.
- Mueller, T.C., Massey, J.H., Hayes, R.M., Main, C.L., Stewart, C.N., 2003. Shikimate accumulates in both glyphosate-sensitive and glyphosate-resistant horseweed (*Conyza canadensis* L. Cronq.). *J. Agric. Food Chem.* 51, 680–684.
- Murussi, C.R., Costa, M.D., Leitemperger, J.W., Guerra, L., Rodrigues, C.C., Menezes, C.C., Severo, E.S., Flores-Lopes, F., Salbego, J., Loro, V.L., 2016. Exposure to different glyphosate formulations on the oxidative and histological status of *Rhamdia quelen*. *Fish Physiol. Biochem.* 42, 445–455.
- Myers, J.P., Antoniou, M.N., Blumberg, B., Carroll, L., Colborn, T., Everett, L.G., Hansen, M., Landrigan, P.J., Lanphear, B.P., Mesnage, R., 2016. Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. *Environ. Health* 15, 1–13.
- Nandula, V.K., Reddy, K.N., Duke, S.O., Poston, D.H., 2005. Glyphosate-resistant weeds: current status and future outlook. *Outlooks Pest Manag.* 16, 183.
- Nandula, V.K., Wright, A.A., Bond, J.A., Ray, J.D., Eubank, T.W., Molin, W.T., 2014. EPSPS amplification in glyphosate resistant spiny amaranth (*Amaranthus spinosus*): a case of gene transfer via interspecific hybridization from glyphosate-resistant Palmer amaranth (*Amaranthus palmeri*). *Pest Manag. Sci.* 70, 1902–1909.
- Neve, P., 2007. Challenges for herbicide resistance evolution and management: 50 years after Harper. *Weed Res.* 47, 365–369.
- Newman, M.M., Hoilett, N., Lorenz, N., Dick, R.P., Liles, M.R., Ramsier, C., Kloepper, J.W., 2016. Glyphosate effects on soil rhizosphere-associated bacterial communities. *Sci. Total Environ.* 543, 155–160.
- Nguyen, N.K., Dörfler, U., Welzl, G., Munch, J.C., Schroll, R., Suhadolc, M., 2018. Large variation in glyphosate mineralization in 21 different agricultural soils explained by soil properties. *Sci. Total Environ.* 627, 544–552.
- Niemann, L., Sieke, C., Pfeil, R., Solecki, R., 2015. A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers. *J. Verbr. Lebensm.* 10, 3–12.
- Norgaard, T., Moldrup, P., Ferré, T., Olsen, P., Rosenbom, A.E., de Jonge, L.W., 2014. Leaching of glyphosate and aminomethylphosphonic acid from an agricultural field over a twelve-year period. *Vadose Zone J.* 13, 1–18. <https://doi.org/10.2136/vzj2014.05.0054>.
- NTP, 2007. National Toxicology Program, CAS Registry Number 1071-83-6, Glyphosate, Roundup. <http://ntp.niehs.nih.gov/index.cfm?objectid=E87C011C-BDB5-82F8-F662151416F8EC9>. (Accessed 15 September 2019).
- Nufarm, 2014. Press Release. Dual Salts Increase Effectiveness and Compatibility. http://www.nufarm.com/Assets/25820/1/NUF0007WeedmasterDST_Specnote_V7.pdf. (Accessed 22 September 2019).
- Nwani, C., Ibiam, U., Ibiam, O., Nworie, O., Onyishi, G., Atama, C., 2013. Investigation on Acute toxicity and behavioral changes in *Tilapia zillii* due to glyphosate-based herbicide, forceup. *J. Anim. Plant Sci.* 23, 888–892.
- Okada, E., Costa, J.L., Bedmar, F., 2017. Glyphosate dissipation in different soils under no-till and conventional tillage. *Pedosphere*. [https://doi.org/10.1016/S1002-0160\(17\)60430-2](https://doi.org/10.1016/S1002-0160(17)60430-2).
- Oliveira, A.G., Telles, L.F., Hess, R.A., Mahecha, G.A., Oliveira, C.A., 2007. Effects of the herbicide Roundup on the epididymal region of drakes *Anas platyrhynchos*. *Reprod. Toxicol.* 23, 182–191.
- Oliveira, R.D., Boas, L.K., Branco, C.C., 2016. Assessment of the potential toxicity of glyphosate-based herbicides on the photosynthesis of *Nitella microcarpa* var. *wrightii* (Charophyceae). *Phycologia* 55, 577–584.
- Olson, B.M., Lindwall, C.W., 1991. Soil microbial activity under chemical fallow conditions: effects of 2,4-D and glyphosate. *Soil Biol. Biochem.* 23, 1071–1075.
- Ortiz, A.M.G., Okada, E., Bedmar, F., Costa, J.L., 2017. Sorption and desorption of glyphosate in Mollisols and Ultisols soils of Argentina. *Environ. Toxicol. Chem.* 36, 2587–2592.
- Owen, M.J., Powles, S.B., 2016. The frequency of herbicide-resistant wild oat (*Avena spp.*) populations remains stable in Western Australian cropping fields. *Crop Pasture Sci.* 67, 520–527.
- Owen, M.D., Zelaya, I.A., 2005. Herbicide resistant crops and weed resistance to herbicides. *Pest Manag. Sci.* 61, 301–311.
- Owen, M.J., Goggin, D.E., Powles, S.B., 2012. Identification of resistance to either paraquat or ALS-inhibiting herbicides in two Western Australian *Hordeum leporinum* biotypes. *Pest Manag. Sci.* 68, 757–763.
- Owen, M.J., Martinez, N., Powles, S.B., 2014. Multiple herbicide-resistant *Lolium rigidum* (annual ryegrass) now dominates across the Western Australian grain belt. *Weed Res.* 54, 314–324.
- Owen, M.J., Martinez, N.J., Powles, S.B., 2015. Multiple herbicide-resistant wild radish (*Raphanus raphanistrum*) populations dominate Western Australian cropping fields. *Crop Pasture Sci.* 66, 1079–1085.
- Padilla, J.T., Selim, H.M., 2019. Interactions among glyphosate and phosphate in soils: laboratory retention and transport studies. *J. Environ. Qual.* 48, 156–163.
- Perez, A., Kogan, M., 2003. Glyphosate resistant *Lolium multiflorum* in Chilean orchards. *Weed Res.* 43, 12–19.
- Pérez-Iglesias, J.M., Franco-Belussi, L., Moreno, L., Tripole, S., de Oliveira, C., Natale, G.S., 2016. Effects of glyphosate on hepatic tissue evaluating melanoma macrophages and erythrocytes responses in neotropical anuran *Leptodactylus latinasus*. *Environ. Sci. Pollut. Res.* 23, 9852–9861.
- Pernak, J., Niemczak, M., Giszter, R., Shamshina, J.L., Gurau, G., Cojocaru, O.A., Pracyk, T., Marcinkowska, K., Rogers, R.D., 2014. Glyphosate based herbicidal ionic liquids with increased efficacy. *ACS Sustain. Chem. Eng.* 2, 2845–2851.
- Peterson, M.A., Collavo, A., Ovejero, R., Shivrain, V., Walsh, M.J., 2018. The challenge of herbicide resistance around the world: a current summary. *Pest Manag. Sci.* 74, 2246–2259.
- Piccolo, A., Celano, G., Arienza, M., Mirabella, A., 1994. Adsorption and desorption of glyphosate in some European soils. *J. Environ. Sci. Health B29*, 1105–1115.
- Piccolo, A., Celano, G., Conte, P., 1996. Adsorption of glyphosate by humic substances. *J. Agric. Food Chem.* 44, 2442–2446.
- Poiger, T., Buerge, I.J., Bächli, A., Müller, M.D., Balmer, M.E., 2017. Occurrence of the herbicide glyphosate and its metabolite AMPA in surface waters in Switzerland determined with on-line solid phase extraction LC-MS/MS. *Environ. Sci. Pollut. Res.* 24, 1588–1596.
- Powles, S.B., 2008a. Evolution in action: glyphosate-resistant weeds threaten world crops. *Outlooks Pest Manag.* 19, 256–259.
- Powles, S.B., 2008b. Evolved glyphosate resistant weeds around the world: lessons to be learnt. *Pest Manag. Sci.* 64, 360–365.
- Powles, S.B., Gaines, T.A., 2016. Exploring the potential for a regulatory change to encourage diversity in herbicide use. *Weed Sci.* 64, 649–654.
- Powles, S.B., Yu, Q., 2010. Evolution in action: plants resistant to herbicides. *Annu. Rev. Plant Biol.* 61, 317–347.
- Powles, S.B., Lorraine-Colwill, D.F., Dellow, J.J., Preston, C., 1998. Evolved Resistance to Glyphosate in Rigid Ryegrass (*Lolium rigidum*) in Australia. *Weed Sci.*, pp. 604–607.
- Prashar, P., Kapoor, N., Sachdeva, S., 2014. Rhizosphere: its structure, bacterial diversity and significance. *Rev. Environ. Sci. Biotechnol.* 13, 63–77.
- Pratley, J., Baines, P., Eberbach, P., Incerti, M., Broster, J., 1996. Glyphosate resistance in annual ryegrass. In: Proceedings of the 11th Annual Conference of the Grassland Society of NSW; Jul 10–11; Wagga Wagga. The Grassland Society of NSW, p. 122.
- Pratley, J., Urwin, N., Stanton, R., Baines, P., Broster, J., Cullis, K., Schafer, D., Bohn, J., Krueger, R., 1999. Resistance to glyphosate in *Lolium rigidum*. I. Bioevaluation.

- Weed Sci. 47, 405–411.
- Preston, C., Baker, J., 2009. Genetically Modified Canola in Australian Farming Systems: Opportunities, Challenges and Segregation. School of Agriculture, Food and Wine, University of South Australia, pp. 1–9.
- Primost, J.E., Marino, D.J., Aparicio, V.C., Costa, J.L., Carriquiriborde, P., 2017. Glyphosate and AMPA, "pseudo-persistent" pollutants under real-world agricultural management practices in the Mesopotamic Pampas agroecosystem, Argentina. Environ. Pollut. 229, 771–779.
- Prosser, R.S., Rodriguez-Gil, J.L., Solomon, K.R., Sibley, P.K., Poirier, D.G., 2017. Effects of the herbicide surfactant Mon0818 on oviposition and viability of eggs of the Ramshorn snail (*Planorbella pilosbyri*). Environ. Toxicol. Chem. 36, 522–531.
- Piatkowski, M., Telesiński, A., 2016. Response of soil phosphatases to glyphosate and its formulations – roundup (laboratory conditions). Plant Soil Environ. 62, 286–292.
- Rajabilarjani, H.R., Aghaalkhani, M., 2011. In: Non-chemical Weed Control in Winter Canola (*Brassica Napus L.*). Thomson, I.S.I. IACSIT, Maldives.
- Ramakrishnan, B., Venkateswarlu, K., Sethuraman, N., Megharaj, M., 2019. Local applications but global implications: can pesticides drive microorganisms to develop antimicrobial resistance? Sci. Total Environ. 654, 177–189.
- Rampazzo, N., Todorovic, G.R., Mentler, A., Blum, W.E., 2013. Adsorption of glyphosate and aminomethylphosphonic acid in soils. Int. Agrophys. 27, 203–209.
- Ratcliff, A.W., Busse, M.D., Shestak, C.J., 2006. Changes in microbial community structure following herbicide (glyphosate) additions to forest soils. Appl. Soil Ecol. 34, 114–124.
- Relyea, R.A., 2005a. The lethal impact of Roundup on aquatic and terrestrial amphibians. Ecol. Appl. 15, 1118–1124.
- Relyea, R.A., 2005b. The lethal impacts of Roundup and predatory stress on six species of North American tadpoles. Arch. Environ. Contam. Toxicol. 48, 351–357.
- Ren, Z., Dong, Y., Liu, Y., 2014. Enhanced glyphosate removal by montmorillonite in the presence of Fe (III). Ind. Eng. Chem. Res. 53, 14485–14492.
- Rendón-von Osten, J., Dzul-Caamal, R., 2017. Glyphosate residues in groundwater, drinking water and urine of subsistence farmers from intensive agriculture localities: a survey in Hopelchén, Campeche, Mexico. Int. J. Environ. Res. Publ. Health 14, 595.
- Richard, S., Moslemi, S., Sipahutar, H., Benachour, N., Seralini, G.-E., 2005. Differential effects of glyphosate and roundup on human placental cells and aromatase. Environ. Health Perspect. 113, 716–720.
- Richardson, J.T., Frans, R.E., Talbert, R.E., 1979. Reactions of *Euglena gracilis* to fluometuron, MSMA, metribuzin, and glyphosate. Weed Sci. 27, 619–624.
- Rissoli, R.Z., Camargo Abdalla, F., Jones Costa, M., Tadeu Rantin, F., McKenzie, D.J., Kalinin, A.L., 2016. Effects of glyphosate and the glyphosate based herbicides Roundup Original® and Roundup Transorb® on respiratory morphophysiology of bullfrog tadpoles. Chemosphere 156, 37–44.
- Rosenbom, A.E., Brüsch, W.M., Juhrer, R.K., Ernstsen, V., Gudmundsson, L., Kjær, J., Plauborg, F., Grant, R., Nyegaard, P., Olsen, P., 2010. The Danish Pesticide Leaching Assessment Programme: Monitoring Results May 1999–June 2009, Danmarks Og Grønlands Geologiske Undersøgelse.
- Rosenbom, A.E., Olsen, P., Plauborg, F., Grant, R., Juhrer, R.K., Brüsch, W., Kjær, J., 2015. Pesticide leaching through sandy and loamy fields Long term lessons learnt from the Danish Pesticide Leaching Assessment Programme. Environ. Pollut. 201, 75–90.
- Ruiz-Toledo, J., Castro, R., Rivero-Pérez, N., Bello-Mendoza, R., Sánchez, D., 2014. Occurrence of glyphosate in water bodies derived from intensive agriculture in a tropical region of southern Mexico. Bull. Environ. Contam. Toxicol. 93, 289–293.
- Saenz, M.E., Di Marzio, W.D., Alberdi, J.L., del Carmen Tortorelli, M., 1997. Effects of technical grade and a commercial formulation of glyphosate on algal population growth. Bull. Environ. Contam. Toxicol. 59, 638–644.
- Samsel, A., Seneff, S., 2013a. Glyphosate, pathways to modern diseases II: celiac sprue and gluten intolerance. Interdiscipl. Toxicol. 6, 159–184.
- Samsel, A., Seneff, S., 2013b. Glyphosate's suppression of cytochrome P450 enzymes and amino acid biosynthesis by the gut microbiome: pathways to modern diseases. Entropy 15, 1416–1463.
- Sanchís, J., Kantiani, L., Llorca, M., Rubio, F., Ginebreda, A., Fraile, J., Garrido, T., Farré, M., 2012. Determination of glyphosate in groundwater samples using an ultrasensitive immunoassay and confirmation by online solid phase extraction followed by liquid chromatography coupled to tandem mass spectrometry. Anal. Bioanal. Chem. 402, 2335–2345.
- Santillo, D.J., Brown, P.W., Leslie Jr., D.M., 1989. Response of songbirds to glyphosate-induced habitat changes on clearcuts. J. Wildl. Manag. 64–71.
- Saunders, L., Pezeshki, R., 2015. Glyphosate in runoff waters and in the root-zone: a review. Toxics 3, 462–480.
- Schaumburg, L.G., Siroski, P.A., Poletta, G.L., Mudry, M.D., 2016. Genotoxicity induced by Roundup® (Glyphosate) in tegu lizard (*Salvator merianae*) embryos. Pestic. Biochem. Physiol. 130, 71–78.
- Schroll, R., Becher, H.H., Dörfler, U., Gayler, S., Grundmann, S., Hartmann, H.P., Ruoss, J., 2006. Quantifying the effect of soil moisture on the aerobic microbial mineralization of selected pesticides in different soils. Environ. Sci. Technol. 40, 3305–3312.
- Schuette, J., 1998. Environmental fate of glyphosate. Environ. Monit. Pest Manag. 1, 1–13.
- Schulz, A., Krüper, A., Amrhein, N., 1985. Differential sensitivity of bacterial 5-enolpyruylshikimate-3-phosphate synthases to the herbicide glyphosate. FEMS Microbiol. Lett. 28, 297–301.
- Scribner, E.A., Battaglin, W.A., Gilliom, R.J., Meyer, M.T., 2007. Concentrations of glyphosate, its degradation product, aminomethylphosphonic acid, and glufoinate in ground- and surface-water, rainfall, and soil samples collected in the United States, 2001–06, Scientific Investigations Report 2007e5122. US Geological Survey.
- Seralini, G.E., Clair, E., Mesnage, R., Gress, S., Defarge, N., Malatesta, M., Hennequin, D., Spirou de Vendôme, J., 2014. Republished study: long term toxicity of a roundup herbicide and a Roundup-tolerant genetically modified maize. Environ. Sci. Eur. 26, 14.
- Sheals, J., Persson, P., Hedman, B., 2001. IR and EXAFS spectroscopic studies of glyphosate protonation and copper (II) complexes of glyphosate in aqueous solution. Inorg. Chem. 40, 4302–4309.
- Shehata, A.A., Schrödl, W., Aldin, A.A., Hafez, H.M., Krüger, M., 2013. The effect of glyphosate on potential pathogens and beneficial members of poultry microbiota in vitro. Curr. Microbiol. 66, 350–358.
- Si, Y.-B., Xiang, Y., Tian, C., Si, X.-Y., Zhou, J., Zhou, D.-M., 2013. Complex interaction and adsorption of glyphosate and lead in soil. Soil Sediment Contam. 22, 72–84.
- Sidoli, P., Baran, N., Angulo-Jaramillo, R., 2016. Glyphosate and AMPA adsorption in soils: laboratory experiments and pedotransfer rules. Environ. Sci. Pollut. Res. 23, 5733–5742.
- Sihtmäe, M., Blinova, I., Künnis-Beres, K., Kanarbik, L., Heinlaan, M., Kahru, A., 2013. Ecotoxicological effects of different glyphosate formulations. Appl. Soil Ecol. 72, 215–224.
- Simard, M.-J., Léger, A., Warwick, S.I., 2006. Transgenic *Brassica napus* fields and *Brassica rapa* weeds in Quebec: sympatry and weed-crop in situ hybridization. Botany 84, 1842–1851.
- Simarmata, M., Kaufmann, J.E., Penner, D., 2003. Potential basis of glyphosate resistance in California rigid ryegrass (*Lolium rigidum*). Weed Sci. 51, 678–682.
- Siroski, P.A., Poletta, G.L., Latorre, M.A., Merchant, M.E., Ortega, H.H., Mudry, M.D., 2016. Immunotoxicity of commercial-mixed glyphosate in broad snouted caiman (*Caiman latirostris*). Chem. Biol. Interact. 244, 64–70.
- Skeff, W., Neumann, C., Schulz-Bull, D.E., 2015. Glyphosate and AMPA in the estuaries of the Baltic Sea method optimization and field study. Mar. Pollut. Bull. 100, 577–585.
- Skeff, W., Recknagel, C., Düwel, Y., Schulz-Bull, D.E., 2018. Adsorption behaviors of glyphosate, glufoinate, aminomethylphosphonic acid, and 2-aminoethylphosphonic acid on three typical Baltic Sea sediments. Mar. Chem. 198, 1–9.
- Solomon, K., Thompson, D., 2003. Ecological risk assessment for aquatic organisms from over water uses of glyphosate. J. Toxicol. Environ. Health B6 289–324.
- Soloneski, S., de Arcuate, C.R., Laramandy, M.L., 2016. Genotoxic effect of a binary mixture of dicamba-and glyphosate-based commercial herbicide formulations on *Rhinella arenarum* (Hensel, 1867) (Anura, Bufonidae) late-stage larvae. Environ. Sci. Pollut. Res. 23, 17811–17821.
- Springett, J., Gray, R., 1992. Effect of repeated low doses of biocides on the earthworm *Aporrectodea caliginosa* in laboratory culture. Soil Biol. Biochem. 24, 1739–1744.
- Stadnik, J., Karwowska, M., Dolatowski, Z.J., Świątkiewicz, S., Kwiatek, K., 2011. Effect of genetically modified, insect resistant corn (Mon 810) and glyphosate tolerant soybean meal (Roundup ready) on physico-chemical properties of broilers' breast and thigh muscles. Bull. Vet. Inst. Pulawy 55, 541–546.
- Susana, H., Silvia, C.L., 2015. 14C-Glyphosate mineralization in soils enriched with glucose and phosphate. Int. J. Plant Soil Sci. 6, 310–318.
- Sustainable Pulse, 2019. Glyphosate Herbicides Now Banned or Restricted in 20 Countries Worldwide-Sustainable Pulse Research. <https://sustainablepulse.com/2019/05/28/glyphosate-herbicides-now-banned-or-restricted-in-17-countries-worldwide-sustainable-pulse-research/#.XfLW7UeDBUW>. (Accessed 15 December 2019).
- Sviridov, A., Shushkova, T., Ermakova, I., Ivanova, E., Epiktetov, D., Leontievsky, A., 2015. Microbial degradation of glyphosate herbicides. Appl. Biochem. Microbiol. 51, 188–195.
- Swanson, N.L., Leu, A., Abrahamson, J., Wallet, B., 2014. Genetically engineered crops, glyphosate and the deterioration of health in the United States of America. J. Org. Syst. 9, 6–37.
- Tapkir, S.D., Kharat, S.S., Kumkar, P., Gosavi, S.M., 2019. Impact, recovery and carryover effect of Roundup® on predator recognition in common spiny loach, *Lepidocephalichthys thermalis*. Ecotoxicology 28, 189–200.
- Tarazona, J.V., Tiramani, M., Reich, H., Pfeil, R., Istace, F., Crivellente, F., 2017. Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC. Arch. Toxicol. 91, 2723–2743.
- Tate, T., Spurlock, J., Christian, F., 1997. Effect of glyphosate on the development of *Pseudosuccinea columella* snails. Arch. Environ. Contam. Toxicol. 33, 286–289.
- Thongprakaisang, S., Thiantanawat, A., Rangkadilok, N., Suriyo, T., Satayavivad, J., 2013. Glyphosate induces human breast cancer cells growth via estrogen receptors. Food Chem. Toxicol. 59, 129–136.
- Tizhe, E.V., Ibrahim, N.D.G., Fatihu, M.Y., Igbokwe, I.O., George, B.D.J., Ambali, S.F., Shallangwa, J.M., 2014a. Serum biochemical assessment of hepatic and renal functions of rats during oral exposure to glyphosate with zinc. Comp. Clin. Pathol. 23, 1043–1050.
- Tizhe, E.V., Ibrahim, N.D.G., Fatihu, M.Y., Onyebuchi, I.I., George, B.D.J., Ambali, S.F., Shallangwa, J.M., 2014b. Influence of zinc supplementation on histopathological changes in the stomach, liver, kidney, brain, pancreas and spleen during sub-chronic exposure of Wistar rats to glyphosate. Comp. Clin. Pathol. 23, 1535–1543.

- Tomlin, C.D., 2009. The Pesticide Manual: A World Compendium. British Crop Production Council.
- Topp, E., 2003. Bacteria in agricultural soils: diversity, role and future perspectives. *Can. J. Soil Sci.* 83, 303–309.
- Tsui, M.T., Chu, L.M., 2003. Aquatic toxicity of glyphosate-based formulations: comparison between different organisms and the effects of environmental factors. *Chemosphere* 52, 1189–1197.
- Uren Webster, T.M., Laing, L.V., Florance, H., Santos, E.M., 2014. Effects of glyphosate and its formulation, roundup, on reproduction in zebrafish (*Danio rerio*). *Environ. Sci. Technol.* 48, 1271–1279.
- USEPA, 2013. Environmental Protection Agency. Electronic Code of Federal Regulations, Title 40: Protection of Environment. PART 180-Tolerances and Exemptions for Pesticide Chemical Residues in Food. Subpart C-specific Tolerances. Environmental Protection Agency, Washington, DC. http://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title40/40cfr180_main_02.tpl. (Accessed 29 September 2019).
- Valavanidis, A., 2018. Glyphosate, the Most Widely Used Herbicide. Health and safety issues. Why scientists differ in their evaluation of its adverse health effects. *Sci. Rev.* 1–40. www.chem-tox-ecotox.org/ScientificReviews.
- Van Bruggen, A., He, M., Shin, K., Mai, V., Jeong, K., Finckh, M., Morris Jr., J., 2018. Environmental and health effects of the herbicide glyphosate. *Sci. Total Environ.* 616, 255–268.
- VanGessel, M.J., 2001. Glyphosate-resistant horseweed from Delaware. *Weed Sci.* 49, 703–705.
- Velasques, R.R., Sandrini, J.Z., da Rosa, C.E., 2016. Roundup® in zebrafish: effects on oxidative status and gene expression. *Zebrafish* 13, 432–441.
- Vencill, W.K., Nichols, R.L., Webster, T.M., Soteres, J.K., Mallory-Smith, C., Burgos, N.R., Johnson, W.G., McClelland, M.R., 2012. Herbicide resistance: toward an understanding of resistance development and the impact of herbicide-resistant crops. *Weed Sci.* 60, 2–30.
- Vila-Aiub, M.M., Goh, S.S., Gaines, T.A., Han, H., Busi, R., Yu, Q., Powles, S.B., 2014. No fitness cost of glyphosate resistance endowed by massive EPSPS gene amplification in *Amaranthus palmeri*. *Planta* 239, 793–801.
- Vila-Aiub, M.M., Balbi, M.C., Distefano, A.J., Fernández, L., Hopp, E., Yu, Q., Powles, S.B., 2012. Glyphosate resistance in perennial *Sorghum halepense* (Johnsongrass), endowed by reduced glyphosate translocation and leaf uptake. *Pest Manag. Sci.* 68, 430–436.
- Villeneuve, A., Larroudé, S., Humbert, J.-F., 2011. Herbicide Contamination of Freshwater Ecosystems: Impact on Microbial Communities. *Pesticides Formulations, Effects, Fate*. InTech (Open Access Publisher), Reyeka (Croatia), pp. 285–312.
- Virginia Tech, 2018. Glyphosate: Health Controversy, Benefits and Continuing Debate. https://www.pubs.ext.vt.edu/content/dam/pubs_ext_vt_edu/spes/spes-63/SPES-63.pdf. (Accessed 20 December 2019).
- Von Soosten, D., Meyer, U., Hüther, L., Dänicke, S., Lahrssen-Wiederholz, M., Schafft, H., Spolders, M., Breves, G., 2016. Excretion pathways and ruminal disappearance of glyphosate and its degradation product amino-methylphosphonic acid in dairy cows. *J. Dairy Sci.* 99, 5318–5324.
- Wang, S., Seiwert, B., Kästner, M., Miltner, A., Schäffer, A., Reemtsma, T., Yang, Q., Nowak, K.M., 2016. (Bio)degradation of glyphosate in water-sediment microcosms-A stable isotope co-labeling approach. *Water Res.* 99, 91–100.
- Wardle, D.A., Parkinson, D., 1990. Effects of three herbicides on soil microbial biomass and activity. *Plant Soil* 122, 21–28.
- Wardle, D.A., Parkinson, D., 1992. Influence of the herbicides 2,4-D and glyphosate on soil microbial biomass and activity: a field experiment. *Soil Biol. Biochem.* 24, 185–186.
- Weber, J.B., Best, J.A., Gonese, J.U., 1993. Bioavailability and bioactivity of sorbed organic chemicals. In: Linn, D.M., et al. (Eds.), *Sorption and Degradation of Pesticides and Organic Chemicals in Soil*. American Society of Agronomy and Soil Science Society of America, Madison, WI, pp. 153–196.
- Webster, T.M.U., Santos, E.M., 2015. Global transcriptomic profiling demonstrates induction of oxidative stress and of compensatory cellular stress responses in brown trout exposed to glyphosate and Roundup. *BMC Genom.* 16, 32. <https://doi.org/10.1186/s12864-015-1254-5>.
- Weir, S.M., Yu, S., Knox, A., Talent, L.G., Monks, J.M., Salice, C.J., 2016. Acute toxicity and risk to lizards of rodenticides and herbicides commonly used in New Zealand. *N. Z. J. Ecol.* 40, 342–350.
- WHO, 1994. Glyphosate. Geneva: World Health Organization (WHO)/International Programme on Chemical Safety (IPCS)/United Nations Environment Program (UNEP). Environmental Health Criteria, p. 159. <http://www.inchem.org/documents/ehc/ehc159.htm>. (Accessed 15 September 2019).
- Wiersma, A.T., Gaines, T.A., Preston, C., Hamilton, J.P., Giacomini, D., Buell, C.R., Leach, J.E., Westra, P., 2015. Gene amplification of 5-enol-pyruvylshikimate-3-phosphate synthase in glyphosate-resistant *Kochia scoparia*. *Planta* 241, 463–474.
- Williams, G.M., Kroes, R., Munro, I.C., 2000. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. *Regul. Toxicol. Pharmacol.* 31, 117–165.
- Williams, G.M., Aardema, M., Acquavella, J., Berry, S.C., Brusick, D., Burns, M.M., de Camargo, J.L.V., Garabrant, D., Greim, H.A., Kier, L.D., 2016. A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment. *Crit. Rev. Toxicol.* 46, 3–20.
- Yadav, S.S., Giri, S., Singha, U., Boro, F., Giri, A., 2013. Toxic and genotoxic effects of Roundup on tadpoles of the Indian skittering frog (*Euphlyctis cyanophlyctis*) in the presence and absence of predator stress. *Aquat. Toxicol.* 132, 1–8.
- Yang, X., Wang, F., Bento, C.P., Meng, L., van Dam, R., Mol, H., Liu, C., Ritsema, C.J., Geissen, V., 2015a. Decay characteristics and erosion-related transport of glyphosate in Chinese loess soil under field conditions. *Sci. Total Environ.* 530, 87–95.
- Yang, X., Wang, F., Bento, C.P., Xue, S., Gai, L., van Dam, R., Mol, H., Ritsema, C.J., Geissen, V., 2015b. Short-term transport of glyphosate with erosion in Chinese loess soil a flume experiment. *Sci. Total Environ.* 512, 406–414.
- Yuan, C.-L., Chaing, M.-Y., Chen, Y.-M., 2002. Triple mechanisms of glyphosate-resistance in a naturally occurring glyphosate-resistant plant *Dicliptera chinensis*. *Plant Sci.* 163, 543–554.
- Zhang, C., Hu, X., Luo, J., Wu, Z., Wang, L., Li, B., Wang, Y., Sun, G., 2015. Degradation dynamics of glyphosate in different types of citrus orchard soils in China. *Molecules* 20, 1161–1175.
- Zhang, S., Xu, J., Kuang, X., Li, S., Li, X., Chen, D., Zhao, X., Feng, X., 2017. Biological impacts of glyphosate on morphology, embryo biomechanics and larval behavior in zebrafish (*Danio rerio*). *Chemosphere* 181, 270–280.
- Zhao, J., Pacenza, S., Wu, J., Richards, B.K., Steenhuis, T., Simpson, K., Hay, A.G., 2018. Detection of glyphosate residues in companion animal feeds. *Environ. Pollut.* 243, 1113–1118.
- Zobiole, L.H.S., de Oliveira, R.S., Huber, D.M., Constantin, J., de Castro, C., de Oliveira, F.A., de Oliveira, A., 2010. Glyphosate reduces shoot concentrations of mineral nutrients in glyphosate-resistant soybeans. *Plant Soil* 328, 57–69.
- Zobiole, L., Kremer, R., Oliveira, R., Constantin, J., 2011. Glyphosate affects microorganisms in rhizospheres of glyphosate-resistant soybeans. *J. Appl. Microbiol.* 110, 118–127.
- Zoller, O., Rhyn, P., Rupp, H., Zarn, J.A., Geiser, C., 2018. Glyphosate residues in Swiss market foods: monitoring and risk evaluation. *Food Addit. Contam.* B11, 83–91.