



Review

Environmental and health effects of the herbicide glyphosate



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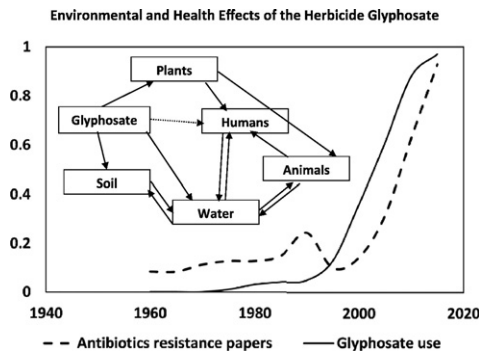
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HIGHLIGHTS

- Glyphosate and its degradation product AMPA have accumulated in the environment.
- Chronic low dose effects on animals and humans have been documented recently.
- Shifts in microbial community composition in soil, plants and animal guts resulted.
- Glyphosate and antibiotic resistance have arisen in fungi and bacteria in parallel.
- Glyphosate may serve as one of the drivers for antibiotic resistance.

GRAPHICAL ABSTRACT

Sources:
 Antibiotic resistance papers: Cantas et al., 2013
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ABSTRACT

The herbicide glyphosate, *N*-(phosphonomethyl) glycine, has been used extensively in the past 40 years, under the assumption that side effects were minimal. However, in recent years, concerns have increased worldwide about the potential wide ranging direct and indirect health effects of the large scale use of glyphosate. In 2015, the World Health Organization reclassified glyphosate as probably carcinogenic to humans. A detailed overview is given of the scientific literature on the movement and residues of glyphosate and its breakdown product aminomethyl phosphonic acid (AMPA) in soil and water, their toxicity to macro- and microorganisms, their effects on microbial compositions and potential indirect effects on plant, animal and human health. Although the acute toxic effects of glyphosate and AMPA on mammals are low, there are animal data raising the possibility of health effects associated with chronic, ultra-low doses related to accumulation of these compounds in the environment. Intensive glyphosate use has led to the selection of glyphosate-resistant weeds and microorganisms. Shifts in microbial compositions due to selective pressure by glyphosate may have contributed to the proliferation of plant and animal pathogens. Research on a link between glyphosate and antibiotic resistance is still scarce but we hypothesize that the selection pressure for glyphosate-resistance in bacteria could lead to shifts in microbiome composition and increases in antibiotic resistance to clinically important antimicrobial agents. We recommend interdisciplinary research on the associations between low level chronic glyphosate exposure, distortions in microbial communities, expansion of

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antibiotic resistance and the emergence of animal, human and plant diseases. Independent research is needed to revisit the tolerance thresholds for glyphosate residues in water, food and animal feed taking all possible health risks into account.

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1. Introduction

The herbicide glyphosate, *N*-(phosphonomethyl) glycine, is a biocide with a broad spectrum activity that was introduced for weed control in agricultural production fields in 1974 (Benbrook, 2016). Glyphosate is taken up by the foliage of plants and transported throughout the plant resulting in plant death after several days. Glyphosate is formulated with various adjuvants (Li et al., 2005), in particular surfactants such as polyoxyethylene amine (POEA), to enhance the uptake and translocation of the active ingredient in plants. The best known product formulated with POEA is Roundup® (Benbrook, 2016).

Glyphosate products are used primarily before planting of traditional agricultural crops and after planting of genetically modified glyphosate-resistant crops (Duke and Powles, 2009). Increasingly, they have been used for desiccation as a ‘harvest aid’ on traditional grain crops (Goffnett et al., 2016; Nelson et al., 2011; Zhang et al., 2017b). In addition, glyphosate has been widely used between trees in orchards and groves (Maqueda et al., 2017; Schrübbers et al., 2016; Singh et al., 2011; St. Laurent et al., 2008; Zhang et al., 2015b) and in urban areas for weed control along streets and in parks (Hanke et al., 2010; Kristoffersen et al., 2008). Finally, it has also been applied in waterways to eliminate invading aquatic plants (Clements et al., 2017; Monsanto, 2014).

As a result of the introduction of glyphosate-resistant soybean (*Glycine max*) and canola (*Brassica napus*) in 1996, cotton (*Gossypium hirsutum*) in 1997 and corn (*Zea mays*) in 1998 (Duke, 2015; Myers et al., 2016), as well as the expanding end of season glyphosate use to facilitate harvesting (Nelson et al., 2011), the total acreage treated with glyphosate has increased rapidly (see Graphical abstract). The annual glyphosate application rates per ha have increased too, for example on soybeans (Coupe and Capel, 2016), especially due to the development of glyphosate-resistant weeds (Benbrook, 2012). In 2012, about 127,000 tons of glyphosate were used in the USA and 700,000 tons worldwide (Swanson et al., 2014; US Geological Survey, 2012). Glyphosate use for agricultural production is now widespread, both in industrialized and developing countries (Benbrook, 2016).

The intensive use of glyphosate has resulted in increasing environmental and plant residues. Glyphosate is quite resistant to degradation due to the inert C-P linkage in the molecule (Chekan et al., 2016). Nevertheless, it is broken down in dead plant material and soil by various microorganisms (Mamy et al., 2016); the first decomposition product often is aminomethyl phosphonic acid, AMPA (Shushkova et al., 2009; Singh and Singh, 2016; Zhang et al., 2015b). However, decomposition of glyphosate takes place in living plants as well as in soils (Arregui et al., 2004), so that both glyphosate and AMPA residues can be found in plant products. In second generation glyphosate-resistant crop cultivars a gene that encodes for the enzyme glyphosate oxidase was inserted into the plant DNA, so that glyphosate is largely converted into AMPA and glyoxylate in those plants. As a result, glyphosate residues are negligible while AMPA residues may be considerable (Alves Corrêa et al., 2016; Monsanto, 2013). In some crop cultivars, a glyphosate-*N*-acetyl transferase or GAT gene was inserted to convert glyphosate to *N*-acetyl-glyphosate, which is broken down to *N*-acetyl-AMPA. In those cultivars all four residues (glyphosate, *N*-acetyl-glyphosate, *N*-acetyl-AMPA and AMPA) can be found and are often combined for dietary risk assessment (FAO, 2006). Total residues are mostly below 5 mg kg⁻¹ but occasionally up to 20 mg kg⁻¹ in harvested grain, fodder and oil crops when glyphosate is used as a ‘harvest aid’ before full crop maturity (Cessna et al., 1994, 2000; FAO, 2006; McNaughton et al., 2015; Zhang et al., 2017b). Total residue contents have been as high as 93 mg kg⁻¹ in forage (FAO, 2006).

Due to the large scale and intensive use of glyphosate and its accumulation in the environment and edible products, several major concerns have arisen in recent years about harmful side effects of glyphosate and AMPA for soil and water quality, and plant, animal and human health. Based on recent reports on potential chronic side effects of glyphosate (Battaglin et al., 2014; Séralini et al., 2014), the World Health Organization reclassified the herbicide glyphosate as probably carcinogenic to humans in 2015 (Bai and Ogbourne, 2016; EFSA, 2015; Guyton et al., 2015; IARC, 2015). Since then, many (about 1000) scientific research papers have been published on glyphosate, especially its potential side effects, in the last two years, but a comprehensive review is still missing.

The objectives of this review are to present a critical overview of the scientific literature on (1) glyphosate accumulation in the environment and plant products, (2) its mode of action and effects on plants and animals, (3) its effects on microbial communities in soil, water, plants, animals and humans and (4) potential effects of shifts in microbial community composition on plant, animal and human health. An additional objective is to formulate a hypothesis about a possible relationship between resistance to glyphosate and to antibiotics in microorganisms as a result of the very high glyphosate selection pressure in the environment.

2. Residues in soil, water and plant products

A brief overview of the accumulation of glyphosate and its main degradation product AMPA in the environment is presented to facilitate a full understanding of their potential side effects on plants, animals and microbial communities.

2.1. Residues in soil and water

Glyphosate containing herbicides may contaminate soils in and around treated areas. Glyphosate adsorbs to clay and organic matter, slowing its degradation by soil microorganisms and leading to accumulation in soils over time (Banks et al., 2014; Cassigneul et al., 2016; Okada et al., 2016; Sidoli et al., 2016; Simonsen et al., 2008; Sviridov et al., 2015; Travaglia et al., 2015). As a result, glyphosate and its degradation product AMPA may persist for more than a year in soils with high clay content but may quickly wash out of sandy soils (Bergström et al., 2011; Okada et al., 2016; Sidoli et al., 2016). Glyphosate and AMPA degradation is also strongly dependent on soil pH (Zhang et al., 2015b).

In the past, glyphosate was not considered a problem for ground water and surface water, because it has a relatively low potential to move through soil and contaminate water sources (Monsanto, 2002, 2014; Sihtmäe et al., 2013). However, despite its attachment to clay and organic matter, parts of the glyphosate and its metabolite AMPA end up in the dissolved phase in ground water after heavy rain (Maqueda et al., 2017; Rendón-von Osten and Dzul-Caamal, 2017). Rain and erosion can also transport soil particles with glyphosate and AMPA into surface water (Table 1), where it can remain in the particulate phase or be dissolved (Maqueda et al., 2017; Rendón-von Osten and Dzul-Caamal, 2017; Wang et al., 2016b; Yang et al., 2015). Dissolved glyphosate and AMPA in surface water can sorb to the bottom sediment. Contaminated particles can settle and become incorporated in the bottom sediment as well (Aparicio et al., 2013; Maqueda et al., 2017). Biodegradation of glyphosate is much slower in sediment than in dissolved in water (Wang et al., 2016b). Glyphosate and AMPA are now

widespread in a variety of natural waters and sediments (Aparicio et al., 2013; Maqueda et al., 2017; Grandcoin et al., 2017; Poiger et al., 2017).

In areas of the USA where genetically modified glyphosate-resistant crops are grown, glyphosate and AMPA occur widely in soil, surface water and ground water (Battaglin et al., 2014). Glyphosate has been measured in river water and stream water (Table 1) at levels from 2 to 430 $\mu\text{g l}^{-1}$ (Battaglin et al., 2005, 2009; Coupe et al., 2011; Mahler et al., 2017). It has also been detected in air and rain during the crop growing season and in water from spring snow melt (Battaglin et al., 2009, 2014; Chang et al., 2011). Ultimately glyphosate ends up in seawater, where it is highly persistent (Mercurio et al., 2014).

In Europe, where growing genetically modified crops is not allowed, glyphosate has been detected in various water sources (but at lower levels than in the USA). Very low concentrations of glyphosate (<0.1 to 2.5 $\mu\text{g l}^{-1}$) were detected in samples of surface water in Germany (Skark et al., 1998), Switzerland (Poiger et al., 2017), Hungary (Mörtl et al., 2013) and northeastern Spain (Sanchis et al., 2012). Higher levels (up to 165 $\mu\text{g l}^{-1}$) were sometimes found in France (Villeneuve et al., 2011) and Denmark (Rosenbom et al., 2010).

Very little is known about glyphosate residues in the environment in other continents (Table 1). In particular, hardly any information is publicly available about environmental residues in China (publications in Chinese checked by He Miaomiao), while most glyphosate is currently produced in China (http://www.cnchemicals.com/Newsletter/NewsletterDetail_14.html; Zhang et al., 2015a) and glyphosate is used intensively in that country (Zhang et al., 2015a).

Besides runoff from agricultural land, urban runoff is also a source of glyphosate to streams and rivers (Grandcoin et al., 2017; Hanke et al., 2010). Because runoff is enhanced from impervious and connected paved surfaces, glyphosate use on paved surfaces is banned in several countries in Northern Europe (Kristoffersen et al., 2008; Rosenbom et al., 2010). Nevertheless, glyphosate and AMPA were found in samples of sewage and stormwater overflows (Birch et al., 2011) as well as the outlets from wastewater treatments plants (Grandcoin et al., 2017) and even in bottled water (Rendón-von Osten and Dzul-Caamal, 2017). Glyphosate and AMPA are commonly found in drinking-water (WHO, 2005), but at very low concentrations below the acceptable daily intake as determined in 1997 (WHO, 2005).

2.2. Residues in plant products

Until recently, residue measurements in plant products were focused on the active ingredient glyphosate and less on its degradation product AMPA. However, since it became known that glyphosate is partially broken down to AMPA in living plants (Arregui et al., 2004) and AMPA is also toxic to various organisms (Gomes et al., 2016;

Table 1
Glyphosate occurrence and concentrations in surface or ground water samples in several countries in North America, South America, and Europe.

Country	Date	Glyphosate occurrence and concentrations	Authors
Canada	2002	22% of samples positive, up to 6.07 $\mu\text{g l}^{-1}$	Humphries et al., 2005
US (Midwest)	2002	36% of stream samples positive, up to 8.7 $\mu\text{g l}^{-1}$	Battaglin et al., 2005
US (Midwest)	2013	44% of stream samples positive, up to 27.8 $\mu\text{g l}^{-1}$	Mahler et al., 2017
US (Washington, Maryland, Iowa, Wyoming)	2005–2006	All streams positive, up to 328 $\mu\text{g l}^{-1}$	Battaglin et al., 2009
US (Iowa, Indiana, Mississippi)	2004–2008	Most rivers positive, up to 430 $\mu\text{g l}^{-1}$ after a storm	Coupe et al., 2011
Mexico	2015	All groundwater samples positive, up to 1.42 $\mu\text{g l}^{-1}$	Rendón-von Osten and Dzul-Caamal, 2017
Argentina	2012	35% of surface water samples positive, 0.1–7.6 $\mu\text{g l}^{-1}$	Aparicio et al., 2013
Germany	1998	Few positive samples in two tributaries to the Ruhr river, up to 0.59 $\mu\text{g l}^{-1}$	Skark et al., 1998
Switzerland	2016	Most stream water samples, up to 2.1 $\mu\text{g l}^{-1}$	Poiger et al., 2017
Spain	2007–2010	41% positive groundwater samples, up to 2.5 $\mu\text{g l}^{-1}$	Sanchis et al., 2012
Hungary	2010–2011	Most river and ground water samples positive, up to 0.001 $\mu\text{g l}^{-1}$	Mörtl et al., 2013
Denmark	1999–2009	25% of surface water samples positive, up to 31 $\mu\text{g l}^{-1}$; 4% of groundwater samples positive, up to 0.67 $\mu\text{g l}^{-1}$	Rosenbom et al., 2010
France	2003–2004	91% of stream samples positive, up to 165 $\mu\text{g l}^{-1}$	Villeneuve et al., 2011

Kwiatkowska et al., 2014a, 2014b), both glyphosate and AMPA are considered in residue analyses and regulations (Codex Alimentarius, 2013; EPA, 2013). The concentrations of glyphosate plus AMPA vary widely, ranging from 0.1–100 mg kg⁻¹ in legumes (including soybeans), 0.1–25 mg kg⁻¹ in cereals and rice, 0.1–28 mg kg⁻¹ in oil seeds and 1–344 mg kg⁻¹ in various types of fodder (Arregui et al., 2004; Bøhn et al., 2014; Çetin et al., 2017; Cuhra, 2015; FAO, 2006). The maximum residue limits of glyphosate plus AMPA in farm products vary widely too, ranging from 0.05 mg kg⁻¹ in milk, 0.1 mg kg⁻¹ in most plant products, 10–20 mg kg⁻¹ in seeds and up to 500 mg kg⁻¹ in fodder (Codex Alimentarius, 2013; Cuhra, 2015; EPA, 2013; FAO, 2006). The tolerable residue levels in seeds and fodder have increased over time to accommodate increasing concentrations detected in some farm products (Benbrook, 2016). Tolerable residue limits in China are similar to those elsewhere (Meador and Jie, 2014).

Residues of glyphosate and AMPA in water and plant products are taken up by animals and humans and excreted in their faeces and urine (Niemann et al., 2015; von Soosten et al., 2016). Glyphosate was detected in the urine of a high proportion (30–80%) of farm animals and humans (Krüger et al., 2014a, 2014b; Niemann et al., 2015). Residues were found not only in the urine of farmers but also in 60–80% of the general public, including children, in the USA and in 44% of the general public in Europe (Krüger et al., 2014a; Niemann et al., 2015). The concentrations in human urine samples were low, but higher among subjects in the USA (mean 2–3 µg l⁻¹ and maximum 233 µg l⁻¹) than in Europe (mean < 1 µg l⁻¹ and maximum 5 µg l⁻¹) (Niemann et al., 2015). Yet, exposure calculations have indicated that daily exposures to glyphosate are generally less than the tolerable reference dose as currently maintained by regulatory agencies (Solomon, 2016; WHO, 2005). However, these tolerance levels and safety standards are being challenged in view of the expanded human exposures (Vandenberg et al., 2017).

3. Effects of glyphosate on plants, animals and microorganisms

The biocidal activity of glyphosate is associated with the inhibition of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS). Glyphosate thus stops the sixth step in the shikimate pathway (conversion from shikimate-3-phosphate to EPSP), which is required for the production of aromatic amino acids and secondary compounds with defense functions in plants and many microorganisms (Funke et al., 2006; Krüger et al., 2013; Schrödl et al., 2014).

3.1. Effects on plants

Glyphosate is toxic to both monocotyledonous plants (such as grasses) and dicotyledonous plants (most broad leaf plants). Uptake and translocation of glyphosate in plants is enhanced by surfactants in the formulated product. Translocation takes place both acropetally and basipetally (upwards and downwards), so that glyphosate accumulates throughout the plant including in seeds and plant roots (Li et al., 2005; Walker and Oliver, 2008). Glyphosate and its breakdown product AMPA inhibit antioxidant enzyme activities and induce the accumulation of reactive oxygen species (ROS) that induce physiological dysfunction and cell damage (Gomes et al., 2016). Both glyphosate and AMPA decrease photosynthesis, but through different mechanisms: glyphosate increases chlorophyll degradation, while AMPA disturbs chlorophyll biosynthesis (Gomes et al., 2016). Both enhanced chlorophyll degradation and reduced biosynthesis result in yellowing and necrosis of foliage.

Plants treated with glyphosate do not produce secondary aromatic compounds, including antimicrobial phytoalexins that defend plants against pathogens. Consequently, glyphosate treated plants frequently die from infection by root pathogens that are universally present in soil (Babiker et al., 2011; Johal and Rahe, 1984; Lee et al., 2012; Meriles et al., 2008; Rashid et al., 2013; Rosenbaum et al., 2014). Even

sublethal glyphosate concentrations in plants, for example from residues in soil or water, diminish plant resistance to pathogens. Infection by *Fusarium* species is often more severe in fields where glyphosate was applied before planting of a crop compared with untreated control fields (Kremer et al., 2005; Kremer and Means, 2009; Sanogo et al., 2000; St. Laurent et al., 2008; van Bruggen et al., 2015). For example, soybean sudden death syndrome (caused by *Fusarium virguliforme*) was sometimes increased by glyphosate application in both glyphosate-tolerant and sensitive cultivars that were susceptible to the disease (Kremer and Means, 2009; Sanogo et al., 2000, 2001), but not always (Duke et al., 2012; Kandel et al., 2015). Infection of sugar beet (*Beta vulgaris*) by weakly pathogenic *Fusarium* and *Rhizoctonia* species was also enhanced after glyphosate application before planting sugar beet seeds (Larson et al., 2006). Yet, spore germination and mycelium growth of these and other pathogens are often reduced in vitro (Barnett et al., 2012; Larson et al., 2006; Mengistu et al., 2013; Sanogo et al., 2000; Sanyal and Shrestha, 2008). This supports the notion that increased root disease in glyphosate treated soil comes about through reduced plant resistance rather than enhanced pathogen growth or that glyphosate may suppress beneficial microorganisms more than plant pathogens like *Fusarium* species.

In addition to reduced plant resistance, indirect effects of glyphosate and AMPA on plant health are possible through changes in the endophytic and rhizosphere microbiome (Berg et al., 2014; Finckh et al., 2015; Kremer et al., 2005; Kuklinsky-Sobral et al., 2005; van Bruggen and Finckh, 2016; van Bruggen et al., 2016). The importance of the plant microbiome for plant health has been known for a long time (Kloepper et al., 1980; Pleban et al., 1995). The plant microbiome composition is largely determined by plant species and the soil where a plant is growing, including the soil microbiome as affected by pesticide use (Finckh et al., 2015; see also Section 3.3.1 of this review). Besides a reduction in plant resistance as a result of changes in microbial composition after glyphosate use, attraction of plant pathogens to the roots of glyphosate-resistant plants can be enhanced by increased exudation of carbohydrates and amino acids from roots of glyphosate treated plants (Kremer et al., 2005; Kremer and Means, 2009).

Another agricultural problem that has arisen in response to intensive glyphosate use is the widespread appearance of glyphosate-resistant weed species (Duke and Powles, 2009; Green and Owen, 2011; Schafer et al., 2014; Shaner et al., 2012). Glyphosate-resistance in plants can be conferred by several different mechanisms (Table 2) such as changes in translocation as a result of modified transporter genes, single point mutations of the target site making it insensitive, increased target expression or detoxification of the herbicide (Chekan et al., 2016; Pollegioni et al., 2011; Shaner et al., 2012; Tani et al., 2016; Zhang et al., 2015a). Recently, alternative glyphosate-resistance genes were found that could be incorporated into genetically modified crops in the near future (Staub et al., 2012; Tao et al., 2017; Tian et al., 2015), but different resistance mechanisms may evolve again in weeds exposed to glyphosate repeatedly.

In reaction to the glyphosate-resistance problem, farmers have increased the dosage and frequency of glyphosate use even further (Benbrook, 2012), and companies producing glyphosate-resistant crops added genes for resistance to other herbicides, 2,4-D and dicamba, in those crops (Duke and Powles, 2009; Leon et al., 2016; Ruen et al., 2017). However, weeds with multiple herbicide resistance at multiple sites of action will likely emerge soon after the widespread use of these herbicides (Bell et al., 2013). This may then lead to an additional increase in herbicide use and additional unintended side effects (Landrigan and Benbrook, 2015).

3.2. Effects on animals and humans

The absence of the shikimate pathway in animals is the basis for the lack of acute toxicity of glyphosate in animals such as mammals, amphibians and reptiles after a single exposure to relatively high dosages

Table 2

Mechanisms of resistance to glyphosate in plants and bacteria.

Mechanism	Examples in plants	References	Examples in bacteria	References
Mutation of the gene coding for the target site	Single point mutation of the target site (EPSPS) making it insensitive to glyphosate	Chekan et al., 2016; Pollegioni et al., 2011; Shaner et al., 2012	Amino acid substitution in EPSP synthase as found in <i>Staphylococcus aureus</i> and <i>Enterobacter</i> sp.	Priestman et al., 2005; Fei et al., 2013
Increased target expression	Increased target expression resulting in so many target molecules that glyphosate cannot block all targets	Chekan et al., 2016; Shaner et al., 2012; Zhang et al., 2015a		
Overexpression of membrane efflux transporter genes like ABC transporters	Modification of transporter genes resulting in reduced intra-plant translocation and possibly transfer into vacuoles	Chekan et al., 2016; Staub et al., 2012, Shaner et al., 2012; Tani et al., 2016	Increased efflux of glyphosate as found in <i>E. coli</i> and <i>Pseudomonas</i> sp. with glyphosate-tolerance	Staub et al., 2012
Horizontal gene transfer of <i>aroA</i> ^a CP4 resistance gene or other resistance genes	Transfer of the <i>aroA</i> CP4 gene or other resistance genes from bacteria or fungi into crop plants	Padgett et al., 1995; Tao et al., 2017; Tian et al., 2015	Transfer of the <i>aroA</i> CP4 gene from genetically modified plants back into plant-associated bacteria (<i>E. coli</i>) in the lab	Natarajan et al., 2007; Li et al., 2015
Degradation of glyphosate	Detoxification of glyphosate; cleavage of the C-P or C-N bond; this mechanism has not been found yet in naturally resistant plants	Pollegioni et al., 2011; Shaner et al., 2012	Glyphosate is degraded by various bacteria like <i>Azotobacter</i> sp., <i>Azospirillum</i> sp. and insensitive <i>Pseudomonas</i> sp.	Arunakumara et al., 2013; Singh and Singh, 2016; Sviridov et al., 2015; Travaglia et al., 2015; Zhao et al., 2015
Scavenging of free radicals providing stress resistance	Not found in glyphosate-resistant plants		Scavenging of free radicals by mycothiol ^b providing stress resistance and glyphosate-tolerance in Actinobacteria	Liu et al., 2013

^a *aroA* is the gene encoding the enzyme 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase.

^b Mycothiol is a specific thiol compound found in Actinobacteria.

(McComb et al., 2008; Weir et al., 2016). However, the median lethal doses vary considerably for different formulations, especially with respect to surfactants (Diamond and Durkin, 1997; Durkin, 2011). Formulations containing POEA are relatively toxic compared to other formulations. Lethal doses of the most toxic formulations are species specific varying from 175 to 540 mg glyphosate acid equivalent (a.e.) kg⁻¹ body weight for terrestrial animal species and from 1 to 52 mg a.e. l⁻¹ of water for aquatic species (Durkin, 2011). However, the glyphosate sensitivity of these two groups cannot be compared directly because the method of exposure is quite different for these groups.

3.2.1. Terrestrial animals and humans

Although the acute oral toxicity of technical grade glyphosate to mammals is low, with the LD₅₀ ranging from 800 to >5000 mg kg⁻¹ body weight for different animal species (McComb et al., 2008; WHO, 2009), there is increasing interest in potential chronic effects of formulated glyphosate and its degradation products as they accumulate in the environment (Bai and Ogbourne, 2016; Battaglin et al., 2014; Greim et al., 2015; Mesnage et al., 2015a; Séralini et al., 2014). Two research approaches have been taken to investigate chronic effects: correlative research and experimental studies that address possible causative relationships.

Correlations have been found between increased glyphosate use and a wide variety of human diseases, including various forms of cancer, kidney damage and mental conditions such as ADHD, autism, Alzheimer's and Parkinson's disease (Fluegge and Fluegge, 2016; Fortes et al., 2016; Jayasumana et al., 2014; Mesnage et al., 2015b; Swanson et al., 2014). Miscarriages and dermatological and respiratory illnesses were related to glyphosate exposure during aerial glyphosate spraying campaigns to eliminate coca plants in Colombia (Camacho and Mejía, 2017). Increases in infertility and malformation among pigs were correlated with glyphosate concentrations in the liver and kidneys and with residues in the feed (Krüger et al., 2014a, 2014b). Various confounding factors might have contributed to these correlations. Therefore, controlled experiments are essential to determine chronic toxic effects.

Under experimental conditions with cell cultures, glyphosate and its breakdown product AMPA increased the reactive oxygen species (ROS) in human erythrocyte cultures at moderately high concentrations (>42 mg l⁻¹ of either pure glyphosate or AMPA) for 24 h (Kwiatkowska et al., 2014a) (Table 3). AMPA is a glutamic acid receptor

in the central nervous system (Catarzi et al., 2006). Both glyphosate and AMPA decreased acetylcholinesterase activity in erythrocyte cultures (Kwiatkowska et al., 2014b). Acetylcholinesterase catalyzes the breakdown of acetylcholine that functions as a neurotransmitter. Decreased acetylcholinesterase activity by organophosphorus compounds hinders the termination of synaptic transmission. Neural cell development and axon growth of rats were impaired after exposure to a high dose of glyphosate (4000 mg l⁻¹) for 24 h (Coullery et al., 2016).

In other laboratory studies, exposure of human peripheral blood cells to glyphosate resulted in DNA damage in leucocytes at moderate to high concentrations (85 to 1690 mg l⁻¹) and decreased DNA methylation at 42 mg l⁻¹ glyphosate in vitro (Kwiatkowska et al., 2017). Changes in DNA methylation can disturb the balance between cancerous cell proliferation and programmed cell death (apoptosis) (Hervouet et al., 2013). DNA hypomethylation can lead to activation of oncogenes, while hypermethylation can silence tumor suppressor genes (Hervouet et al., 2013). Thus, glyphosate and AMPA can disturb normal neurotransmission and upset the delicate balance between cell proliferation and programmed cell death.

As predicted from correlation and cellular studies (Table 3), persistent low exposure to glyphosate (about 70 mg of glyphosate kg⁻¹ body weight day⁻¹) can affect the activity of the enzyme acetylcholinesterase at the organismal level (Cattani et al., 2017; Kwiatkowska et al., 2014b; Menéndez-Helman et al., 2012). If acetylcholinesterase is not working properly, nerve impulses are not switched off, causing serious neurological disorders (Čolović et al., 2013). For example, chronic exposure of pregnant rats (*Rattus norvegicus*) to glyphosate (Roundup®) in drinking water (0.36% or 3600 mg a.i. l⁻¹) led to oxidative stress and glutamate excitotoxicity in the rat hippocampus and decreased hippocampus acetylcholinesterase activity (Cattani et al., 2017). This resulted in depressive-like behavior in offspring rats exposed to glyphosate for 60 days (Cattani et al., 2017).

In another chronic exposure study (Table 3), daily treatments of live rats with a low dose (56 mg kg⁻¹) of Roundup® for 5 or 13 weeks resulted in biochemical and anatomical liver damage (Çağlar and Kolankaya, 2008). Chronic exposure (2 yr) to Roundup® at ultralow doses (50 ng l⁻¹; 4 ng kg⁻¹ bw d⁻¹) in drinking water caused liver and kidney damage and various tumors in laboratory rats (Mesnage et al., 2015a; Séralini et al., 2014), although conclusions regarding possible carcinogenicity have been disputed by researchers associated with the industry and others (EFSA, 2015; Greim et al., 2015). Recent

Table 3

Effects of chronic exposure of terrestrial cells and live animals and of aquatic animals to low dosages of Roundup®. See text for actual dosages used.

Terrestrial animals				Aquatic animals	
Effects on cell cultures	References	Effects on live animals	References	Effects on live animals	References
Increase in reactive oxygen species (ROS)	Kwiatkowska et al., 2014a	Impaired neural cell development and axon growth of rats	Coullery et al., 2016	Overproduction of ROS and oxidative stress in fish	Li et al., 2017
Decrease in acetylcholinesterase activity	Kwiatkowska et al., 2014b	Impaired acetyl cholinesterase activity; oxidative stress and glutamate excitotoxicity in the rat hippocampus; depressive-like behavior in offspring rats	Cattani et al., 2017; Kwiatkowska et al., 2014b; Menéndez-Helman et al., 2012	Suppression of acetylcholine-sterase activity in brown mussels and fish; damage of motoneurons in fish; developmental problems and brain damage	Menéndez-Helman et al., 2012; Sandrini et al., 2013; Zhang et al., 2017a; Roy et al., 2016
DNA damage in leucocytes and decreased DNA methylation	Kwiatkowska et al., 2017	Biochemical and anatomical liver damage; liver and kidney damage and tumors in rats	Çağlar and Kolankaya, 2008; Mesnage et al., 2015a; Mesnage et al., 2016; Séralini et al., 2014	Disturbed metabolism and renal injury in fish; DNA damage in blood, gills and liver of eel; changes in liver cells and mitochondria in carp	Li et al., 2017 Guilherme et al., 2009 Szarek et al., 2000
Deteriorated ovarian functions in cell cultures of cattle ovaries	Perego et al., 2017	Negative fertility effects in male rats	Abarikwu et al., 2015; Nardi et al., 2017		

work by Mesnage et al. (2016) further demonstrated that the chronic (2 year) exposure of rats to these ultralow dosage levels of Roundup® resulted in marked alterations of the liver proteome and metabolome, changes which overlap substantially with non-alcoholic fatty liver disease. In the experiments with Roundup®, no distinction was made between effects of glyphosate and of the adjuvant POEA, although the estimated acute oral toxicity of POEA is 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). However, these experiments were not carried out to estimate acute oral effects of glyphosate, but chronic effects of the formulated product as encountered in reality.

Finally, repeated application of glyphosate at relatively low doses (5 mg kg^{-1}) negatively affected fertility in male rats (Abarikwu et al., 2015), while a single application had a negative fertility effect at a high dose (500 mg kg^{-1}) only (Dai et al., 2016). Male rats that received soymilk with 100 mg l^{-1} glyphosate had a decrease in spermatids and increase in abnormal sperm morphology compared to the soymilk control (Nardi et al., 2017). Cell cultures of cattle ovaries showed deteriorated ovarian functions after exposure to low glyphosate concentrations (0.5 , 1.7 and 5 mg l^{-1}) but not at high concentrations (10 and 300 mg l^{-1}), which is typical of endocrine disruptor effects (Perego et al., 2017). Thus, at low concentrations, glyphosate could have hormonal effects and reduce fertility (Table 3), while at high doses various other organs may be affected, ultimately resulting in death.

3.2.2. Aquatic animals

Glyphosate and the surfactants POEA and MON 0818 (75% POEA) can have negative impacts on the health of a variety of animals in the aquatic food web, including protozoa, mussels, crustaceans, frogs and fish, similar to the effects on terrestrial animals (Bringolf et al., 2007; Durkin, 2011; Li et al., 2017; Moreno et al., 2014; Prosser et al., 2017; Rissoli et al., 2016; Sihtmäe et al., 2013; Tsui and Chu, 2003; Zhang et al., 2017a). Glyphosate formulations with POEA are generally more toxic than those without this surfactant (Bringolf et al., 2007; Prosser et al., 2017). Aquatic animals seem to be more sensitive to POEA than terrestrial animals. However, experimentation on health effects of adjuvants by independent entities has been quite limited due to the proprietary nature of these chemicals (Diamond and Durkin, 1997; Durkin, 2011). For example, formulations with POEA were more toxic to the microcrustacean *Artemia salina* and young zebrafish *Danio rerio* than formulations without POEA both at $360 \text{ g glyphosate a.e. l}^{-1}$ water (Rodriguez et al., 2017). Various species of freshwater mussels were more sensitive to glyphosate with MON 0818 ($EC_{50} = 1 \text{ mg a.e. l}^{-1}$)

and Roundup® ($EC_{50} = 4 \text{ mg a.e. l}^{-1}$) than to technical grade glyphosate ($EC_{50} > 200 \text{ mg a.e. l}^{-1}$) (Bringolf et al., 2007). At typical and maximum glyphosate application and runoff rates from soil, resulting in estimated concentrations of 0.21 to $0.99 \text{ mg POEA l}^{-1}$ surface water, 21–43% of a wide array of aquatic species were estimated to be impaired by these POEA concentrations (Rodriguez-Gil et al., 2017).

Similar to effects of glyphosate on terrestrial animals (Table 3), pure glyphosate suppressed the activity of acetylcholinesterase at low concentrations (1 – 676 mg l^{-1}) in brown mussels (*Perna perna*) (Sandrini et al., 2013) and several fish species (Menéndez-Helman et al., 2012; Sandrini et al., 2013). At an ultralow concentration of 0.01 mg l^{-1} glyphosate damaged the primary motoneurons in zebrafish resulting in abnormal movements at a young age (Zhang et al., 2017a). Exposure of zebrafish embryos to higher concentrations of Roundup® (50 mg l^{-1}) resulted in developmental problems including forebrain, midbrain and eye damage (Roy et al., 2016).

Again, similar to glyphosate effects on terrestrial animals, chronic exposure of gold fish (*Carassius auratus*) to moderately low levels of glyphosate (34 mg l^{-1}) disturbed the metabolism in various tissues, led to overproduction of ROS and oxidative stress (Li et al., 2017). The final result was severe renal injury (Li et al., 2017). Even lower concentrations of Roundup® (3.6 mg l^{-1} for 4 h) damaged the DNA in blood, gills and liver of the European eel (*Anguilla anguilla*) (Guilherme et al., 2009). Exposure of freshwater carp (*Cyprinus carpio*) to higher levels of Roundup® (205 mg or 410 mg of glyphosate l^{-1} ; still below the range of commercial applications) induced changes to liver cells and mitochondria (Szarek et al., 2000).

In addition to these direct effects on aquatic animals, glyphosate can affect the interactions between fish and their pathogens or parasites. Exposure of silver catfish (*Rhamdia quelen*) to sublethal concentrations of glyphosate (0.73 mg l^{-1} , 10% of the LC_{50} for 96 h) reduced the numbers of blood erythrocytes, thrombocytes, lymphocytes and total leukocytes, decreased immune cell phagocytosis and increased susceptibility to the pathogen *Aeromonas hydrophila*, resulting in a decrease in the survival rate (Kreutz et al., 2010, 2011). Similarly, environmentally relevant concentrations ($0.36 \text{ mg a.i. l}^{-1}$) of glyphosate enhanced infection of the freshwater fish *Galaxias anomalus* by the trematode flatworm parasite *Telogaster opisthorchis* (Kelly et al., 2010). However, horsehair worms (*Chordodes nobilii*) parasitic to mosquito larvae (*Aedes aegypti*) showed reduced infective ability and increased adult mortality following exposure to low concentrations (0.1 – 8 mg a.i. l^{-1}) of technical grade glyphosate and Roundup® (Achiorno et al., 2008). Thus, low levels of glyphosate in surface water could disturb the balance between hosts

and pathogens or parasites. This can result in unexpected shifts in aquatic communities.

3.3. Effects on microorganisms

The shikimate pathway is present not only in plants but also in fungi and bacteria, rendering many taxa of microorganisms sensitive to glyphosate. However, not all organisms with the shikimate pathway are sensitive to glyphosate, depending on the class of EPSPS they produce: class I EPSPS is glyphosate sensitive and class II EPSPS is glyphosate-tolerant (Funke et al., 2007; Priestman et al., 2005). For example, *Agrobacterium tumefaciens* strain CP4 has a gene coding for the class II version of EPSPS that is not inhibited by glyphosate (Padgett et al., 1995). Similar to plants, bacterial and fungal strains with low sensitivity to glyphosate have been selected, largely through the same mechanisms as the resistance mechanisms identified in plants (Li et al., 2015; Liu et al., 2013; Priestman et al., 2005; Staub et al., 2012). Consequently, differences in sensitivity among microorganisms have affected the microbial composition of various habitats harboring glyphosate, including soil, plant surfaces and animal intestinal tracts.

3.3.1. Microorganisms in soil, rhizosphere and plants

Glyphosate is taken up by the foliage of plants and transported throughout the plant and into the rhizosphere and soil (Yamada et al., 2009; Zobiolo et al., 2010). Because many microorganisms are sensitive to glyphosate, its application can affect the microbial composition and enzymatic activity in the plant endosphere, the rhizosphere and surrounding soil (Arango et al., 2014; Banks et al., 2014; Cherni et al., 2015; Druille et al., 2015; Schafer et al., 2014). For example, glyphosate treatments (applied at recommended or lower dosages) negatively affected microorganisms that promote plant growth, such as *Burkholderia* spp., *Pseudomonas* spp., arbuscular mycorrhizal fungi and nitrogen fixing *Rhizobium* spp. (Arango et al., 2014; Druille et al., 2015; Schafer et al., 2014; Zobiolo et al., 2010). These treatments resulted in reduced plant growth and/or changes in grassland vegetation cover and composition (Arango et al., 2014; Druille et al., 2015).

However, there is still much controversy about the effects of glyphosate on microbial communities and activities in the soil and rhizosphere (Allegrini et al., 2015; Hungria et al., 2014; Wolmarans and Swart, 2014). In studies comparing soil treated with glyphosate with untreated control soil, microbial communities seemed to recover from short term glyphosate treatment (Arango et al., 2014; Banks et al., 2014; Wolmarans and Swart, 2014) with only minor or no effect on global microbial structure, biomass or activity (Allegrini et al., 2015; Haney et al., 2000; Meriles et al., 2008; Nakatani et al., 2014; Wardle and Parkinson, 1990; Zabaloy et al., 2016), probably due to the great diversity and compensatory ability of microorganisms in soil. In addition, direct effects of glyphosate are confounded by increased availability of dead plant and microbial material, a food source for many microorganisms, including saprotrophic plant pathogenic fungi (Babiker et al., 2011; Meriles et al., 2008; Sharma-Poudyal et al., 2016).

Specific methods that can detect rare microorganisms, shifts in microbial composition, and changes in metabolic functions resulting from glyphosate applications, such as deep sequencing (sequencing of extracted DNA or RNA multiple times), have been used only by Schafer et al. (2014) and Newman et al. (2016). Schafer et al. (2014) investigated the taxonomic distribution of the microbial community, diversity and genera abundance within the rhizosphere of glyphosate susceptible and resistant giant ragweed (*Ambrosia trifida*) biotypes in response to a glyphosate application. DNA sequences of the pathogens *Verticillium* and *Xanthomonas* increased and of the beneficial bacterium *Burkholderia* decreased in glyphosate treated soil, but the differences in microbial community composition were small. Newman et al. (2016) showed that the phospholipid fatty acid composition in the rhizospheres of Roundup-ready® corn and soybeans changed as a result of long term (3 yr) glyphosate treatment at the recommended dose.

RNA-Seq analysis showed that carbohydrate and amino acid metabolism was downregulated in total extracted rhizosphere RNA (Newman et al., 2016), in agreement with a possible reduction in photosynthesis (Gomes et al., 2016). Iron acquisition and metabolism were also downregulated in the rhizosphere (Newman et al., 2016), in agreement with the reduced availability of iron in glyphosate treated soil (Cakmak et al., 2009). Protein metabolism and respiration sequences were upregulated (Newman et al., 2016), possibly due to increased amino acid exudation (Kremer et al., 2005).

Minor differences in sensitivity of soil and rhizosphere microorganisms to glyphosate may result in important shifts in plant or animal pathogens. For example, the root pathogen *Fusarium* sp. is comparatively insensitive to glyphosate. Thus, glyphosate application may shift the balance of pathogenic *Fusarium* spp. and antagonistic microorganisms such as *Pseudomonas fluorescens* in favor of the root pathogens (Kremer and Means, 2009; Yamada et al., 2009; Zobiolo et al., 2010). Increased root rot caused by pathogenic *Fusarium* spp. in glyphosate treated soil has been shown repeatedly as mentioned above (Fernandez et al., 2009; Johal and Huber, 2009; Rosenbaum et al., 2014; Yamada et al., 2009). Similarly, the human and animal pathogen *Staphylococcus aureus* is insensitive to glyphosate and may become more dominant in glyphosate treated soil (Funke et al., 2007; Priestman et al., 2005). Thus, the presence of glyphosate in soil could change the community compositions of bacteria and fungi, in turn altering soil ecosystem functions and plant and animal health (Kuklinsky-Sobral et al., 2005; Zobiolo et al., 2010).

3.3.2. Microorganisms in water

Negative effects of glyphosate and the surfactant POEA have been demonstrated for various species of microalgae, aquatic bacteria and protozoa (Rodriguez-Gil et al., 2017; Sihtmäe et al., 2013; Tsui and Chu, 2003). The modes of action in aquatic microorganisms are similar to those in terrestrial plants and microorganisms: glyphosate affects synthesis of aromatic amino acids, the production of chlorophyll, photosynthesis and respiration (Mensink and Janssen, 1994). The marine bacterial species *Vibrio fischeri* was sensitive to moderately low concentrations of glyphosate in water (EC_{50} values ranged from 5.4 to 7.6 mg a.e. l^{-1}), regardless of the formulation used (Sihtmäe et al., 2013). Microalgae are generally more sensitive to glyphosate and the formulated product Roundup® (1.2–7.8 mg l^{-1}) than are heterotrophic bacteria, although some species of microalgae are more tolerant than others (Mensink and Janssen, 1994; Tsui and Chu, 2003; Wang et al., 2016a).

Autotrophic microorganisms are vital to marine and freshwater ecosystems, because they form the base of food chains. Photosynthesis, cell densities and growth rates of three microalgae were diminished by exposure to a typical application rate of glyphosate (0.89 kg a.e. ha^{-1} , resulting in about 1.2 mg glyphosate l^{-1} and 0.21 mg POEA l^{-1} of surface water) (Rodriguez-Gil et al., 2017). Even a low glyphosate concentration (0.011 mg l^{-1}) inhibited the growth of the autotrophic community in river water for three weeks, although it did not cause chlorophyll reduction (Bricheux et al., 2013). Addition of Roundup® to pond water (6 and 12 mg a.i. l^{-1} , higher than the 3.5 mg a.i. l^{-1} recommended for weed control) decreased the abundance of total micro- and nanophytoplankton, but increased the abundance of picocyanobacteria and overall primary production (Pérez et al., 2007). This increase in picocyanobacteria was attributed to the direct toxicological effect of glyphosate on other microorganisms, resulting in release of nutrients from the dead bodies. In later studies, glyphosate formulated as Glifosato Atanor® at 3.5 mg a.i. l^{-1} as well as pure glyphosate and Glifosato Atanor® at 2.7–2.9 mg a.e. l^{-1} stimulated the abundance of bacterioplankton and planktonic picocyanobacteria, and the photosynthetic activity of periphytic algae (Vera et al., 2012, 2014; Wang et al., 2016a). This was attributed to increased phosphorous contents in glyphosate treated water (Vera et al., 2012, 2014; Wang et al., 2016a). Indeed, a single application of technical grade glyphosate (2.4 mg l^{-1})

to tap water in mesocosms that were left outside for 6 months increased the total phosphorous concentration seven fold (to 0.7 mg l^{-1}) and doubled the density of picocyanobacteria (to $2 \times 10^{-6} \text{ cells ml}^{-1}$ in turbid water) after 1–8 days (Pizarro et al., 2016).

Similar to the research results obtained for soil, global measures of microbial activity and diversity were negligibly affected by glyphosate treatments (0.01 – 0.37 mg l^{-1}) of surface water collected from various water bodies (Bricheux et al., 2013; Magbanua et al., 2013; Pesce et al., 2009). In situ measurements of microbial activity, diversity and composition in relation to glyphosate concentrations were confounded by the presence of other pesticides (Daouk et al., 2013). In controlled laboratory experiments, however, the growth and species composition of microbial populations (determined by Temporal Temperature Gradient Gel Electrophoresis with DNA from marine waters) were sometimes disturbed at levels of glyphosate (0.001 – 0.01 mg l^{-1}) typical of those caused by run off from land (Stachowski-Haberkorn et al., 2008). Thus, similar to the situation in soil, deep sequencing and metabolomics may be needed to detect subtle shifts in microbial communities in water (Beale et al., 2017; Muturi et al., 2017; Tromas et al., 2017). The results may be affected by many factors, including the glyphosate formulation and concentration, pH and sediment contents (Magbanua et al., 2013; Tsui and Chu, 2003; Wang et al., 2016b).

3.3.3. Microorganisms in animals

Relationships between microbiomes and human or animal health have received much attention in recent years (Berg et al., 2014; Hoffman et al., 2015; O'Doherty et al., 2014), but little research has been done on the potential influence of glyphosate on these relationships. Nevertheless, intestinal microbial communities can be affected by glyphosate in contaminated animal feed and water. Subsequently, the changes in these communities can be detrimental to animal health. For example, lactic acid producing bacteria generally are negatively affected by glyphosate (Clair et al., 2012; Krüger et al., 2013). These bacteria normally produce antibiotics and can suppress pathogenic bacteria such as *Clostridium botulinum* (Krüger et al., 2013; Rodloff and Krüger, 2012) and botulism has increasingly been found in cows (*Bos taurus*) that had high concentrations of glyphosate in their feed and urine (Gerlach et al., 2014; Krüger et al., 2013, 2014a). During in vitro fermentation in bovine rumen fluid, several species of bacteria and protozoa were suppressed after exposure to glyphosate at 1, 10 and 100 mg l^{-1} (Ackermann et al., 2015). However, botulinum neurotoxin concentration was enhanced at the highest level of glyphosate only (1000 mg l^{-1}). In poultry (*Gallus gallus domesticus*), *Bifidobacterium* and *Enterococcus* spp. were negatively affected by glyphosate at 0.08 – 0.15 mg g^{-1} , while pathogenic bacteria such as *Salmonella* and *Clostridium* spp. were less sensitive (Minimal Inhibitory Concentration, MIC = 1.2 – 5 mg g^{-1}) to this herbicide (Shehata et al., 2013). The tested concentrations were high, but the glyphosate concentration in the poultry feed was also high: 0.19 – 0.4 mg g^{-1} (Shehata et al., 2014).

Glyphosate in animal feed affects not only intestinal bacteria but also fungi, such as the *Mucorales*, fast growing fungi often forming spore balls on top of fungal threads and therefore sometimes called pin molds. They are common in soil and often cause food spoilage and sometimes mycoses in animals and humans (Morace and Borghi, 2012). A positive correlation was found between glyphosate concentrations in urine and the density of *Mucorales* in the rumen of dairy cows in Germany (Schrödl et al., 2014). This change in the fungal community could have come about through a disturbance of the intestinal microbiota in general, because members of the *Mucorales* were resistant to glyphosate in vitro (Schrödl et al., 2014). However, the observed reduction in antibodies against the *Mucorales* may indicate that glyphosate influenced the immune system of the cows, possibly through the toxic effects of glyphosate on the liver (Schrödl et al., 2014). Although *Mucorales* were resistant to glyphosate in vitro, it is possible that this change in prevalence was due to a disturbance of other intestinal microbiota.

4. Resistance to glyphosate and antibiotics

Little attention has been paid to potential indirect negative effects of glyphosate on human and animal health through a possible relationship between resistance to glyphosate and to antibiotics in bacteria (Fig. 1). In this section, we discuss glyphosate-resistance in bacteria and the potential mechanisms underlying this resistance, followed by observed associations between glyphosate-resistance and antibiotic resistance and a hypothesis about the selection pressure of intensive glyphosate use driving both forms of resistance.

Although many bacteria and fungi are sensitive to glyphosate, some are highly resistant (Fei et al., 2013; Kuklinsky-Sobral et al., 2005; Natarajan et al., 2007; Wolmarans and Swart, 2014). For example, strain CP4 of *Agrobacterium tumefaciens* was found in the wastewater of a glyphosate production plant and was highly resistant to glyphosate. This resistance is conferred by the gene coding for the enzyme CP4 EPSP synthase (EPSPS), which was inserted into crops to provide glyphosate-resistance (Padgett et al., 1995). A truncated form of the same enzyme was transferred experimentally from glyphosate-resistant plants to *Escherichia coli*, providing similar resistance as the original full length enzyme (Natarajan et al., 2007). Other functional genes of the glyphosate-resistant *E. coli* as well as its carbon utilization profile were only slightly affected by the inserted EPSP synthase gene, suggesting that this genetically modified *E. coli* could survive in the environment (Li et al., 2015). This implies that glyphosate-resistance could potentially return from plants to bacteria by horizontal gene transfer, and that the resulting glyphosate-resistant bacteria might successfully survive in the environment (Li et al., 2015). Although horizontal gene transfer by natural means has not been demonstrated conclusively, glyphosate-resistance has been identified in many genera of bacteria since the intensification of glyphosate use (Liu et al., 2013; Priestman et al., 2005; Staub et al., 2012). This resistance could have come about by various mechanisms other than horizontal gene transfer (Table 2). The mechanisms that provide resistance to glyphosate in bacteria are similar to those conveying resistance to glyphosate in plants. For example, mutations of the gene coding for the target site EPSP synthase and of efflux transporter genes have been found in plants and bacteria (Fei et al., 2013; Priestman et al., 2005; Staub et al., 2012). In addition, bacteria could be selected that produce glyphosate degradation enzymes (Arunakumara et al., 2013; Singh and Singh, 2016; Sviridov et al., 2015; Travaglia et al., 2015; Zhao et al., 2015). Or bacteria could circumvent some of the harmful effects of glyphosate by increasing the production of molecules that scavenge free radicals (Liu et al., 2013).

Some of the mechanisms conferring resistance to glyphosate in bacteria also confer resistance to clinically important antimicrobial agents (Kurenbach et al., 2015; Liu et al., 2013). For example, the reduction of

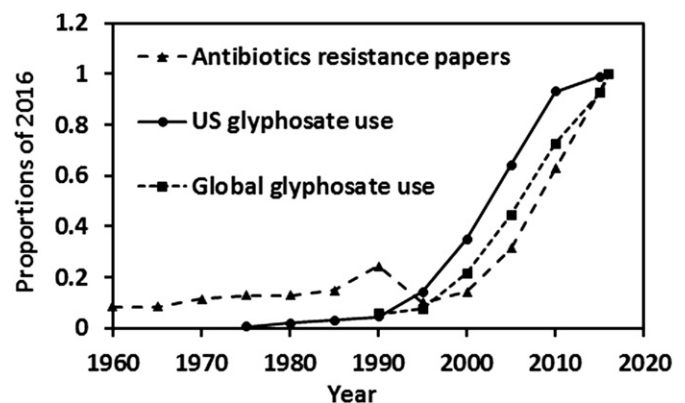


Fig. 1. Relative number of scientific publications (▲) on antibiotic resistance in soil, waste water and natural water (70 in 2016), relative total glyphosate use in the USA (●) and worldwide (■) (127 million and 900 million kg, respectively, in 2016) between 1960 and 2016 (Benbrook, 2016; Cantas et al., 2013; USDA NASS, 2014).

harmful radicals by mycothiol (a specific thiol compound found in Actinobacteria that scavenges free radicals) provides resistance not only to glyphosate but also to a wide range of antibiotics including the beta lactam antibiotic penicillin G (Liu et al., 2013). Another example is the modification of the AcrAB efflux pump in *E. coli* that had been exposed to glyphosate (1240 mg l^{-1}), which was associated with an increase in resistance from 0.03 to 0.09 mg l^{-1} of the fluoroquinolone antibiotic Ciprofloxacin (Cip) and from 5 to 20 mg l^{-1} of the aminoglycoside antibiotic Kanamycin (Kan) (Kurenbach et al., 2015). Similarly, *Salmonella enterica* serovar Typhimurium was more resistant to Cip at 0.08 mg l^{-1} and to Kan at $8\text{--}40 \text{ mg l}^{-1}$ after exposure to glyphosate, but potential changes in efflux pump were not investigated (Kurenbach et al., 2015). Cip and Kan are used as alternative antibiotics to control pathogens that are insensitive to beta lactam antibiotics such as penicillin, ampicillin and cephalosporin. Resistance to Cip and Kan would reduce the spectrum of clinically useful antibiotics even further.

Beta lactam resistant bacteria commonly produce Extended Spectrum Beta Lactamase (ESBL), an enzyme that breaks down beta lactam antibiotics and thus confers resistance to these antibiotics (Apostolakos et al., 2017; Brolund, 2014). ESBL production has been associated with field induced glyphosate-resistance, in particular in various species of Enterobacteriaceae (Krüger and Shehata, 2014). We isolated unidentified bacteria ($n = 101$) from citrus roots and rhizospheres (Shin et al., 2016; Shin and van Bruggen, 2017). In agreement with the findings by Krüger and Shehata (2014), the bacteria showed cross resistance (64% of the colonies) to Roundup® (7000 mg l^{-1} glyphosate) on penicillin-amended (20 mg l^{-1}) agar (Table 4). Penicillin is not used in citrus orchards and penicillin resistance is hard to explain, except via cross resistance with glyphosate, which is applied frequently in citrus groves (Shin et al., 2016). Of the bacterial isolates that had not been exposed to penicillin or glyphosate, 39% were able to grow on the glyphosate amended medium (Table 4). In a related experiment (Shin and van Bruggen, 2017), 95% of unidentified bacteria isolated on plates with glyphosate amended medium (7000 mg l^{-1}) from citrus groves were resistant to penicillin (20 mg l^{-1}), while only 15–20% of these bacteria were resistant to streptomycin (50 mg l^{-1}) or tetracycline (16 mg l^{-1}) (Table 5). A slightly lower proportion (88% compared to 95%) of bacteria that had not been exposed to glyphosate in the isolation medium grew on the penicillin amended medium, while a much higher proportion (48–63% compared to 15–20%) grew on media amended with streptomycin or tetracycline, which can be used in citrus groves to control citrus canker (caused by *Xanthomonas axonopodis* pathovar citri). Altogether, this suggests that cross resistance between glyphosate and penicillin may be more common in citrus groves than cross resistance between glyphosate and streptomycin or tetracycline. The mechanisms underlying the glyphosate and antibiotic resistance have not been elucidated.

Similar to the effects of glyphosate on microbial communities, the herbicides that will increasingly replace glyphosate, dicamba and 2,4-D, also have differential effects on microorganisms (Oleszczuk et al., 2014; Seghers et al., 2003). The mechanisms that convey resistance to herbicides in plants are largely similar to those conferring resistance

Table 4

Proportions (percentages) of bacteria that were isolated from soil on S medium plates amended with penicillin (20 mg l^{-1}) or on non-amended control plates and were able to grow on S medium plates amended with penicillin or glyphosate and on non-amended control plates.

Plates amended with	Concentration (mg l^{-1})	Colonies from penicillin amended S medium ^a	Colonies from non-amended S medium ^a
Penicillin	20	94/101 (93%)	17/84 (20%)
Glyphosate	7000	65/101 (64%)	33/84 (39%)
Control	0	101/101 (100%)	84/84 (100%)

^a Isolations made from soil with citrus trees injected with penicillin in a field experiment at Fort Meade or a greenhouse experiment with field soil in Gainesville, Florida (combined data) (Shin et al., 2016).

Table 5

Proportions (percentages) of bacteria that were isolated from soil on glyphosate amended (7000 mg l^{-1}) or non-amended S medium plates and were able to grow on plates with glyphosate, penicillin, streptomycin or tetracycline, and on non-amended control plates.

Plates amended with	Concentration (mg l^{-1})	Colonies from glyphosate amended S medium ^a	Colonies from non-amended S medium ^a
Glyphosate	7000	40/40 (100%)	10/40 (25%)
Penicillin	20	38/40 (95%)	35/40 (88%)
Streptomycin	50	6/40 (15%)	25/40 (63%)
Tetracycline	16	8/40 (20%)	19/40 (48%)
Control	0	40/40 (100%)	40/40 (100%)

^a Isolations made from soil from citrus groves at Clermont, Florida (Shin and van Bruggen, 2017).

to herbicides in microorganisms. Thus, insensitivity to dicamba and 2,4-D will likely increase in microbial communities after intensification of the use of these herbicides. Finally, similar to the association between glyphosate and antibiotic resistance in microorganisms, insensitivity to dicamba and 2,4-D is often accompanied by antibiotic resistance (Kurenbach et al., 2015). Ultimately, antibiotic-resistant bacteria will likely be transferred from agricultural fields to farm animals and human patients in the hospital environment (Smith et al., 2005; Stine et al., 2007).

5. Discussion and conclusions

Due to the almost exponential increase in glyphosate use and the slow decomposition of glyphosate and its breakdown product AMPA in soil, water and sediment, the accumulation of glyphosate in the environment, plant products and animal organs has become quite worrisome (Myers et al., 2016; Shehata et al., 2014). In particular, the high proportion of people and farm animals with glyphosate in their urine is concerning, even though the concentrations are still low (Niemann et al., 2015). Although the acute toxic effects of glyphosate on fish and mammals are low, the formulated products often are more toxic than glyphosate itself, and concerns have emerged about chronic effects of the formulated products on human and animal diseases, in particular various forms of cancer and mental disorders (Fortes et al., 2016; Mesnage et al., 2015a, 2015b; Swanson et al., 2014). Although conclusions regarding possible carcinogenicity and other health effects of glyphosate remain controversial, we feel that sufficient additional data has accumulated regarding the chronic toxic effects of the formulated products on aquatic and terrestrial animals and humans to warrant reconsideration of the tolerable residue levels of glyphosate and AMPA in plant and animal products and the environment. The recent reclassification of glyphosate as probably carcinogenic by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) was based primarily on research with the main formulated product Roundup® (IARC, 2015; Séralini et al., 2014). Additional research is needed to come to a definitive conclusion on the chronic health effects of the various formulated products containing glyphosate.

In addition to the possible chronic direct health effects of glyphosate on a variety of aquatic and terrestrial animals and humans, we documented shifts in microbial communities in soil, plants, water and intestinal tracts and the association with specific plant and animal pathogens (Ackermann et al., 2015; Priestman et al., 2005; Sanogo et al., 2000, 2001). The shifts in microbiomes resulting from intensive glyphosate use can affect resistance mechanisms and have severe impacts on plant, animal and human health (Hoffman et al., 2015). These complex, indirect effects of glyphosate need to be taken into account by regulatory agencies.

Other indirect health effects can come about through the recently documented cross resistance to glyphosate and clinically important antibiotics (Kurenbach et al., 2015). The surge in antibiotic resistance has been attributed primarily to the increased use of antibiotics by human patients and farm animals (Smith et al., 2005; Stine et al., 2007), but

antibiotic resistance is also widespread in agricultural soils that were not exposed to high antibiotic concentrations (Udikovic-Kolic et al., 2014). Considering that subsets of the microbiomes in soil transfer to plants, fresh plant products, animal and human intestinal tracts (Berg et al., 2014), and then to excrements that return to soil and water, we suggest that there are microbial cycles that are characteristic for particular management systems. Management of weeds with multiple glyphosate applications could result in microbiomes that are relatively glyphosate and antibiotic resistant. This leads us to the hypothesis that the selection pressure for glyphosate-resistance and the associated resistance to antibiotics in the soil microbiome result in transfer of antibiotic resistant bacteria from soil to plants, animals and humans through the food web, even in urban and hospital environments.

The sequence of events outlined here for glyphosate, namely introduction of glyphosate resistant crops, intensification of glyphosate use, emergence of glyphosate-resistant weeds and microorganisms, changes in microbiomes and disease resistance, deteriorated plant and animal health, and increased antibiotic resistance, could serve as a harbinger for events to follow the introduction of genes conferring resistance to other herbicides. The recent addition of genes for resistance to the herbicides dicamba and 2,4-D to glyphosate resistant crops (Ruen et al., 2017) will likely result in additional increases in herbicide use and unintended side effects (Leon et al., 2016). Weeds with multiple herbicide resistance at multiple sites of action have been detected already (Bell et al., 2013). Similar to glyphosate, dicamba and 2,4-D have differential effects on microorganisms, and shifts in plant and animal microbiomes can be expected as a result of intensification of the use of dicamba and 2,4-D (Oleszczuk et al., 2014; Seghers et al., 2003). The mechanisms that convey resistance to herbicides in plants are largely similar to those conferring resistance to herbicides in microorganisms, and thus, insensitivity to herbicides other than glyphosate will likely also increase in microbial communities, possibly followed by increased antibiotic resistance. These wide-ranging consequences of intensive herbicide use have not been pointed out previously.

In conclusion, we suggest that the problems associated with the large scale and intensive use of glyphosate (and other herbicides in the future) are much more encompassing than originally anticipated by the regulatory agencies (EPA, 2013). We recommend additional interdisciplinary research on the associations between low level chronic herbicide exposure, distortions in microbial communities, expansion of antibiotic resistance and the emergence of animal, human and plant diseases. Independent research is needed to revisit the tolerance thresholds for glyphosate residues in water, food and animal feed taking all possible health risks into account. A global effort will be needed to collect appropriate high quality residue and health data across the range of settings in which glyphosate and other herbicides are used; only as such data become available will we be able to design, develop and implement strategies to counter further escalation of the problems associated with the use of glyphosate and other herbicides.

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