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Review

Environmental and health effects of the herbicide glyphosate

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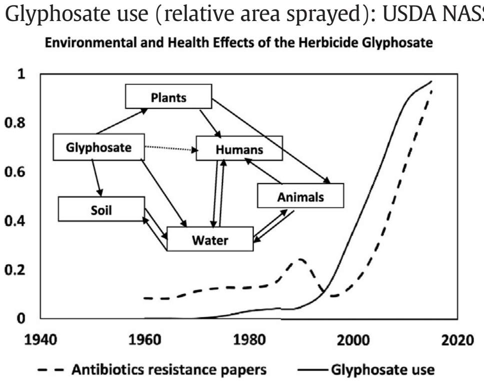
HIGHLIGHTS

- 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
Glyphosate use (relative area sprayed): USDA NASS, 2014.



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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.

Contents

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.