Glifosato no Brasil: uso, contaminação aquática, efeitos ambientais e perigos para a saúde humana

Glyphosate in Brazil: use, aquatic contamination, environmental effects, and health hazards

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Resumo
Os herbicidas à base de glifosato têm amplo espectro de ação e estão associados a uma série de impactos ambientais. O glifosato é amplamente utilizado em áreas agrícolas e urbanas e é frequentemente encontrado em águas superficiais e no solo. Apresenta efeitos nocivos para o funcionamento ecossistêmico, devido à sua toxicidade para organismos de todos os níveis tróficos, além de casos de bioacumulação relatados. Além disso, a contaminação de recursos hídricos com glifosato põe em perigo a saúde humana. Medidas de mitigação são necessárias para reduzir os impactos do glifosato na saúde ecossistêmica e humana, com controles mais rígidos necessários para prevenir a sua crescente contaminação em águas superficiais e subterrâneas no território brasileiro.

Palavras–chave: pesticidas, herbicidas, ecossistemas aquáticos, toxicidade.

Abstract
Glyphosate-based herbicides have a broad spectrum of action and are associated with a series of environmental impacts. Glyphosate is widely used in agricultural and urban areas and is frequently found in surface water and soil. It has harmful effects on ecosystem functioning because of its toxicity to organisms of all trophic levels, and bioaccumulation has been reported. Further, glyphosate contamination of water resources endangers human health. Mitigation measures are needed to reduce the impacts on the ecosystem and human health, and stricter controls are necessary to prevent the increasing contamination of surface and ground waters with glyphosate in the Brazilian territory.

Keywords: pesticides, herbicides, aquatic ecosystems, toxicity.

1. INTRODUCTION

Herbicide use is a common practice worldwide both in intensive agriculture and urban areas and gardens. When used without proper control, herbicides can leach into water bodies susceptible to chemical contamination (DONG *et al.*, 2020; HE and LI, 2020; MEHMOOD *et al.*, 2020), which are, e.g., nurseries for various species and, therefore, crucial for the conservation of biodiversity and ecosystem services (THOMPSON *et al.*, 2004). In rural areas, agricultural activities are mainly responsible for pesticide contamination of surface waters, in which pesticides may remain in solution, in suspension associated with particles, be deposited in sediments, or be absorbed by organisms. Besides constituting a risk to environmental health, public health can also be affected by the contamination of water resources (GAVRILESCU, 2005). Moreover, the application of herbicides in urban gardens is the main source of these contaminants for nearby aquatic systems (MOURA, 2009).

Glyphosate-based herbicides are widely used worldwide. Until September 2000, Monsanto™ held a patent for the use of glyphosate as a herbicide, which was commercialized as Roundup Original®. Since this date, formulations of several brands became available on the market, which led Monsanto™ to launch new presentations of the product such as Roundup WG®, Roundup ULTRA®, Roundup Transorb R®, and Roundup Original Mais® (LOUWAARS and MINDERHOUD, 2001). Glyphosate is a broad-spectrum defensive indicated for controlling terrestrial and aquatic weeds and, after being absorbed by plant leaves, acts on various enzyme complexes and blocks the synthesis of aromatic amino acids (AMARANTE JUNIOR *et al.*, 2002). The manufacturer indicates the direct application in aquatic environments at a concentration of 3.7 $mg.L^{-1}$ for aquatic weed control, aggravating the problem of aquatic contamination (GIESY *et al.*, 2000).

Although widely used in pest control and agricultural management, the harmful effects of glyphosate and its formulations on the structure and functioning of aquatic ecosystems have still not been completely understood (SOLOMON and THOMPSON, 2003; VERA *et al.*, 2010). Similarly, the transport mechanisms of this contaminant in river basins remain uncertain, and exports to aquatic systems located downstream of application sites are difficult to estimate. Its transport depends on a multitude of uncertain variables, such as the quantity applied at the source, local rainfall, and runoff direction (COUPE *et al.*, 2012). In cases of considerable downstream transport, glyphosate and other components added to commercial formulations may impact aquatic ecosystems due to their toxicity to non-target organisms (THANOMSIT *et al.*, 2020) affecting aquatic community structure, ecosystem functioning, and finally the provision of ecosystem services to human society, e.g., water and food supply (MAS *et al.*, 2020; MOURA, 2009). Therefore, it is necessary to assess the extent of the impact of glyphosate-based herbicides, to associate it with the anthropogenic activities causing it, and to devise best management techniques (ARAUJO *et al.*, 2005). Here, we review the literature on the occurrence and behavior of glyphosate in the environment and its effects on organisms exposed to it, highlighting its harmful effects on the structure and functioning of aquatic ecosystems and human health caused by the consumption of contaminated water and food. In this review, we focus on the contamination of surface waters in Brazil and therefore discuss several issues such as legislation and water resources in the Brazilian context.

2. LITERATURE REVIEW

2.1. Water resource use

The first human civilizations developed in proximity to rivers, due to the need for constant water supply and fertile soils, both necessary for socioeconomic development (KOBIYAMA *et al.*, 2008). With the development and intensification of agricultural and industrial production, as well as urban settlement, the demand for water resources increased. However, poor management creates conflicts among the economic sectors that depend on this resource (TUNDISI, 2003). Among economic sectors, agriculture consumes most of the available water resources, accounting for approximately 85% of total consumption worldwide (FOLEY *et al.*, 2005). In Brazil, 2,083 $m^3.s^{-1}$ of water were collected in 2017, of which 60% was used for agricultural activities, 25.5% for urban and rural supply, and 14.5% by the industry and mining operations, as well as for thermoelectric power generation (Figure 1).

For a long time, water resources were believed to be inexhaustible, and their conservation was therefore neglected. Urban centers were, then, developed without adequate management, which resulted in poor water quality and availability (MCDONALD *et al.*, 2014). Nowadays, water scarcity has become a global issue, and the lack of adequate treatment, as well as intensive pesticide and fertilizer use, coupled with reductions in rainfall in many parts of the world, such as Brazil, have aggravated the problem (KOBIYAMA *et al.*, 2008).

2.2. History of pesticide use in Brazil

An expansion of pesticide use occurred in Brazil during World War II. With the release of dichlorodiphenyltrichloroethane (DDT) to the market, profound changes in pest management and control occurred. DDT was a high-efficiency, low-cost product, and therefore became popular quickly, long before its potential harm to human health and the environment were elucidated. The success of DDT triggered the agrochemical industry's rapid expansion. The massive use of chemical additives, such as fertilizers and pesticides, in agriculture, coupled with new cultivation techniques and genetic improvement of crop strains, characterized the period that has become known as the “Green Revolution” (BULL and HOTHAWAY, 1986).

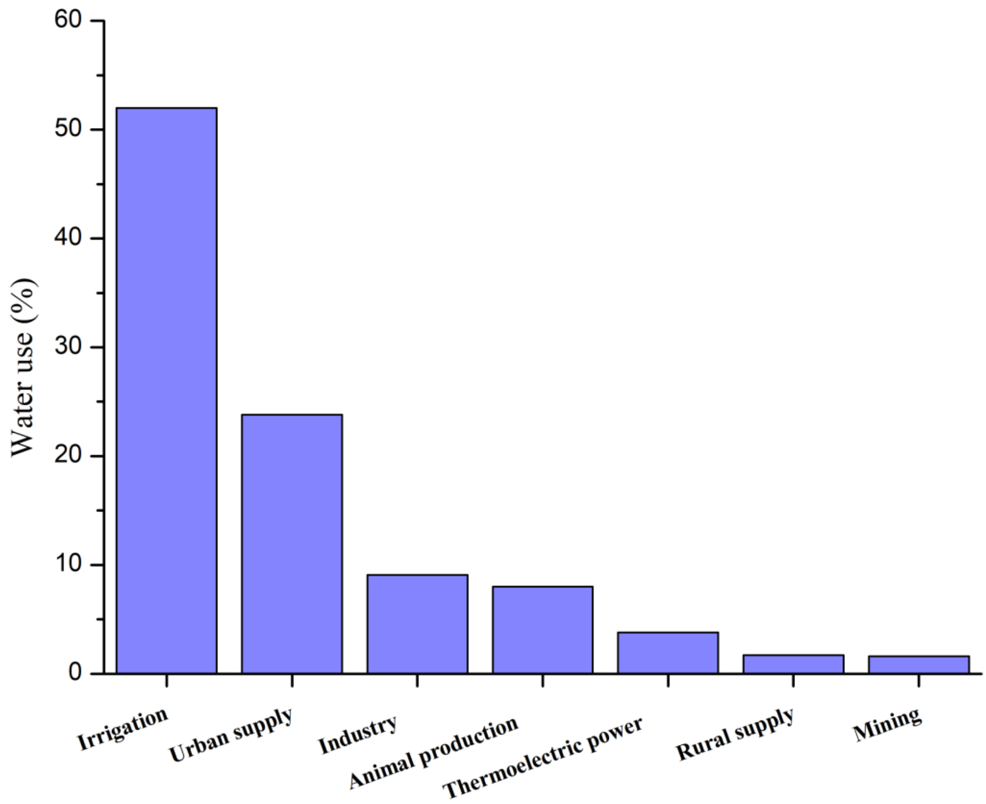

Figure 1 - Water use in Brazil in 2017 by sector. Total volume collected: 2,083 $m^3.s^{-1}$.
Source: National Water Agency (RIGODANZO *et al.*, 2019).

In the 1940s and 50s, fertilizer and pesticide use increased in Brazilian agriculture due to fiscal incentives, increases in farmers' incomes, and rural credits from the federal government. Government incentives and marketing strategies contributed to the indiscriminate use of pesticides and fertilizers by both large producers and family farmers (TEIXEIRA, 2005). The expansion of agricultural frontiers was another crucial factor for the increase of pesticide consumption in the country (SCORZA JÚNIOR, 2006). From the 1990s on, there was a reduction in incentives provided by the government. Despite this, pesticide use further increased due to greater economic stability of the country that provided increases in farmers' income, making them more independent of state support (Figure 2). This increase in agricultural pesticide use led to a high intake of pesticides by the population (IBAMA, 2018; MARTINS, 2000).

Between 2014 and 2017, 27 pesticides were detected in the Brazilian public water supply according to the NGOs Repórter Brasil and the Public Eye. These NGOs obtained data from the Sistema de Informação de Vigilância da Qualidade da Água para Consumo Humano (Sisagua) database of the Brazilian Health Ministry and compiled them in an interactive map (ARANHA and ROCHA, 2019). According to the survey, 1 in 4 cities had at least one pesticide detected, and some larger cities had all of the 27 detected pesticides present in their public water supply. The percentage of water samples with detected pesticides increased during the survey period, from 75% in 2014 to 92% in 2017, suggesting a pattern of increasing pesticide use. This report also expressed concerns regarding the general lack of monitoring. Of the 5,570 Brazilian municipalities, 2,931 did not carry out any monitoring of pesticides in potable water between 2014 and 2017. Of the 27 pesticides detected, 21 are currently forbidden in the European Union, for causing environmental and health hazards. In 23% of the investigated water samples, glyphosate concentrations surpassed the security limit adopted by the European Union (0.1 $\mu g.L^{-1}$; BOMBARDI, 2019). However, only 0.02% of the tested samples exceeded the 5,000-fold higher Brazilian security limit for glyphosate in potable water (500 $\mu g.L^{-1}$, BOMBARDI, 2019).

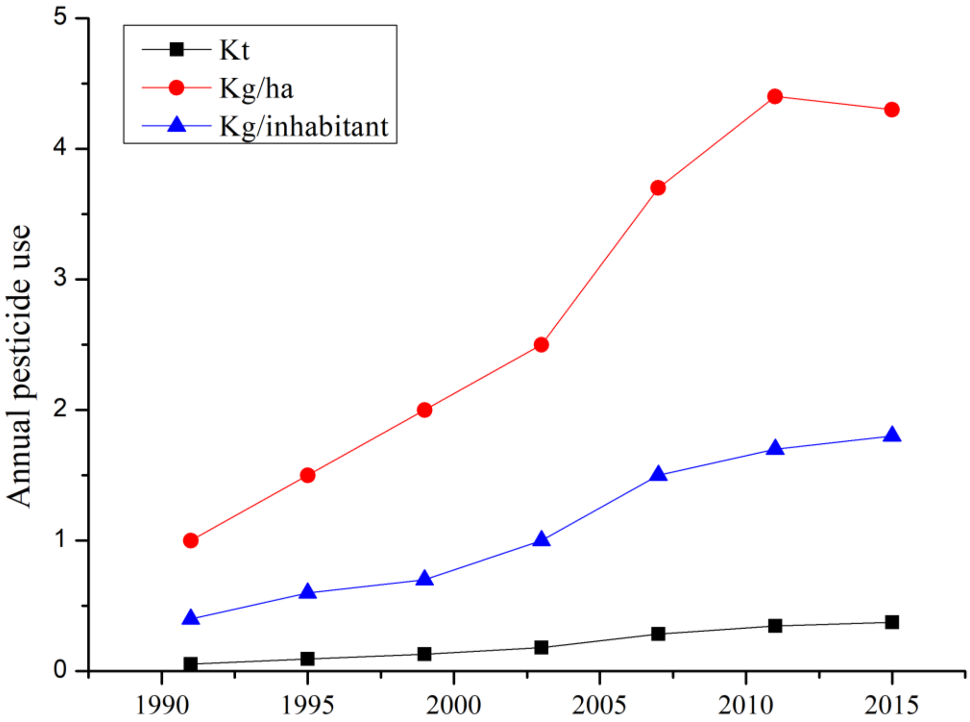

Figure 2 - Pesticide use in Brazil between 1991 and 2015 as mass marketed per year in kt, mass per inhabitant, and mass per hectare cultivated.
Source: Brazilian Institute of the Environment and Renewable Natural Resources (IBAMA, 2018).

2.3. Physicochemical properties of glyphosate and its behavior in the soil

Glyphosate [$C_3H_8NO_5P$] is absorbed by plant leaves and acts on several enzyme complexes, blocking the synthesis of some amino acids (AMRHEIN *et al.*, 1980). Commercial formulations such as Roundup Original®, which is diluted to 44.5% before use, have a recommended application of 5 $l.ha^{-1}$ (MONSANTO, 2010) They contain the glyphosate molecule as its isopropyl ammonium salt, which is a polar solid with a high water solubility (12 $g.L^{-1}$ at 25 °C), has a melting point of 200 °C and low solubility in organic solvents. It has a density of 0.5 $g.cm^{-3}$ and does not degrade in the presence of visible light, even at temperatures above 60 °C (AMARANTE JUNIOR *et al.*, 2002). In contact with soil, it interacts with metals and humic acids, adhering to soil particles, and staying there for periods ranging from 4 to 835 days (Table 1).

Table 1: Glyphosate half-lives measured under different physical, chemical, and environmental conditions.

Half-life (days)	Medium	Experimental condition	Reference
8.4–9.1	Laboratory incubation	Microbial degradation of pure glyphosate	SINGH *et al.*, 2019
10.0–11.2	Laboratory incubation	Microbial degradation of pure glyphosate; Fe(III) and Cu(II) presence	SINGH *et al.*, 2019
12.5–13.1	Laboratory incubation	Microbial degradation of pure glyphosate; presence of humic acids	SINGH *et al.*, 2019
11.0–17.0	Sediment from a reservoir	Application of glyphosate by landowners around a reservoir	GRUNEWALD *et al.*, 2001
14.5–31.0	Laboratory incubation	Silt/clay/loam soil incubated at 20°C	AL-RAJAB *et al.*, 2008
110–151	Laboratory incubation	Clay soil in different depths	BERGSTRÖM *et al.*, 2011
16.9–36.5	Laboratory incubation	Sandy soil in different depths	BERGSTRÖM *et al.*, 2011
5.0–23.0	Soil samples	Area with heavy metal contamination	KOOLS *et al.*, 2005
6.0–9.0	Soil samples	Labile phase of sample	EBERBACH, 1998
222–835	Soil samples	Non-labile phase of sample	EBERBACH, 1998
10.0–12.6	Soil samples	Clay soil in different depths (0–90 cm)	ZHANG *et al.*, 2015
4.0	Laboratory incubation	Glyphosate in aqueous medium in presence of UV light	LUND-HØIE and FRIESTAD, 1986
1.5–53.5	Laboratory incubation	Glyphosate applied to soils with different water contents	BENTO *et al.*, 2016
21.0–47.0	Soil samples	Glyphosate applied to soil samples with different crop cover *(Vicia sativa*, *Sinapis alba*, *Lolium hybridum, Vicia sativa and Avena sativa together)*	CASSIGNEUL *et al.*, 2016

Once in the environment, microbial degradation is the predominant pathway of glyphosate mineralization. Microorganisms from different taxonomic groups can metabolize glyphosate using the enzyme glyphosate oxidoreductase. Glyphosate metabolism by this enzymatic pathway generates (aminomethyl)phosphonic acid (AMPA) and glyoxylate as the main degradation products (Figure 3) (JACOB e*t al.*, 1988). Some bacteria of the genus Pseudomonas can use AMPA as a source of phosphorus, but in most cases, AMPA is not metabolized and is secreted to the environment, leading to secondary contamination (QUINN e*t al.*, 1989). AMPA may be absorbed by other organisms or undergo degradation through the C-P lyase (Figure 3). This pathway generates inorganic phosphorus (P_i), which can contribute to eutrophication, and volatile methylamine (SVIRIDOV *et al.*, 2015).

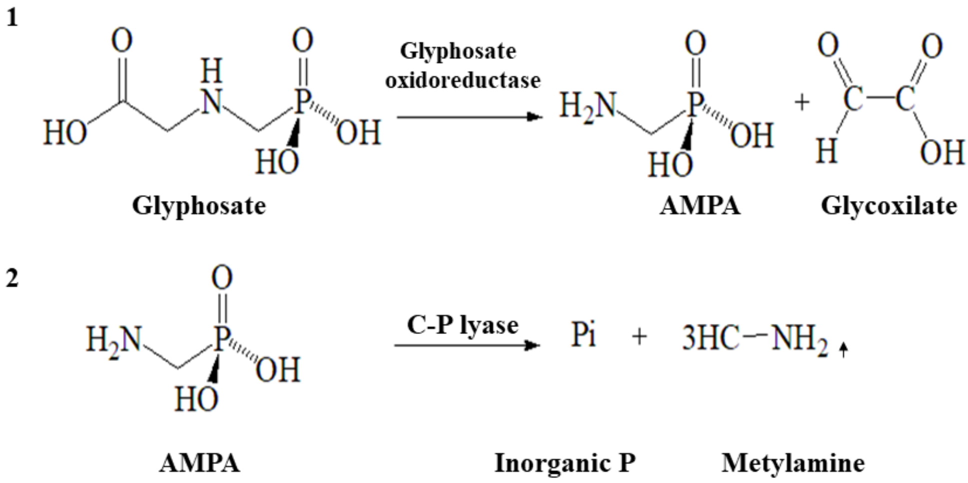

Figure 3 - Microbiological degradation of glyphosate and AMPA in the environment. Metabolic pathway of glyphosate oxidoreductase producing AMPA and glyoxylate (1), mineralization of AMPA through C-P lyase generating inorganic phosphorus, and volatile methylamine (2).

The degradation of glyphosate present in contaminated water and soil depends on microbiological activity. Thus, microorganisms capable of degrading glyphosate could potentially be used to transform this pesticide and its residues into less toxic molecules. However, *in situ* and *in vitro* tests have not yet been able to achieve a satisfactory degradation efficiency (ZHAN *et al.*, 2018).

In general, pesticides are the most commonly encountered contaminants in soil, where their permanence and degradation depend on many chemical, physical, biological, and climate variables (SARKAR *et al.*, 2020). Pesticides may remain sorbed or absorbed on soil, be leached, degraded, or volatilized, depending on their chemical properties and interactions with environmental factors (ENFIELD and YATES, 2018). Sorption is a physicochemical phenomenon in which absorption (when a substance in one physical state is absorbed by a substance in another physical state) and adsorption (chemical binding of molecules or ions to the surface of a substance) co-occur. Organic molecules, such as glyphosate, may be sorbed on the soil (MUNIRA *et al.*, 2016). In this case, pesticides that are carried by surface water are first absorbed into the soil and then adsorbed to the soil, forming a residue-bound complex. In the residue-bound phase, pesticides adsorbed to soil particles have no chemical equilibrium with the soil solution, forming a stable complex. Some of these molecules can detach from the bound-residue and re-enter solution, being absorbed by the soil matrix. This process is called desorption and makes pesticides available again for leaching and runoff (AL-RAJAB *et al.*, 2008).

Molecules that have high water solubility and low volatility are transported in the soil mainly through leaching processes. Water flow directs the transport of these molecules, which can occur through the soil profile and reach the water table or be carried by surface runoff and directly reach surface waters (BOUCHARD *et al.*, 2015). Temporal dynamics and concentrations of glyphosate vary greatly from one waterbody to another. Glyphosate contamination depends on factors such as the amount and frequency of its application to crops, precipitation events that cause runoff, and the direction of water flow (Figure 4) (GERECKE *et al.*, 2002).

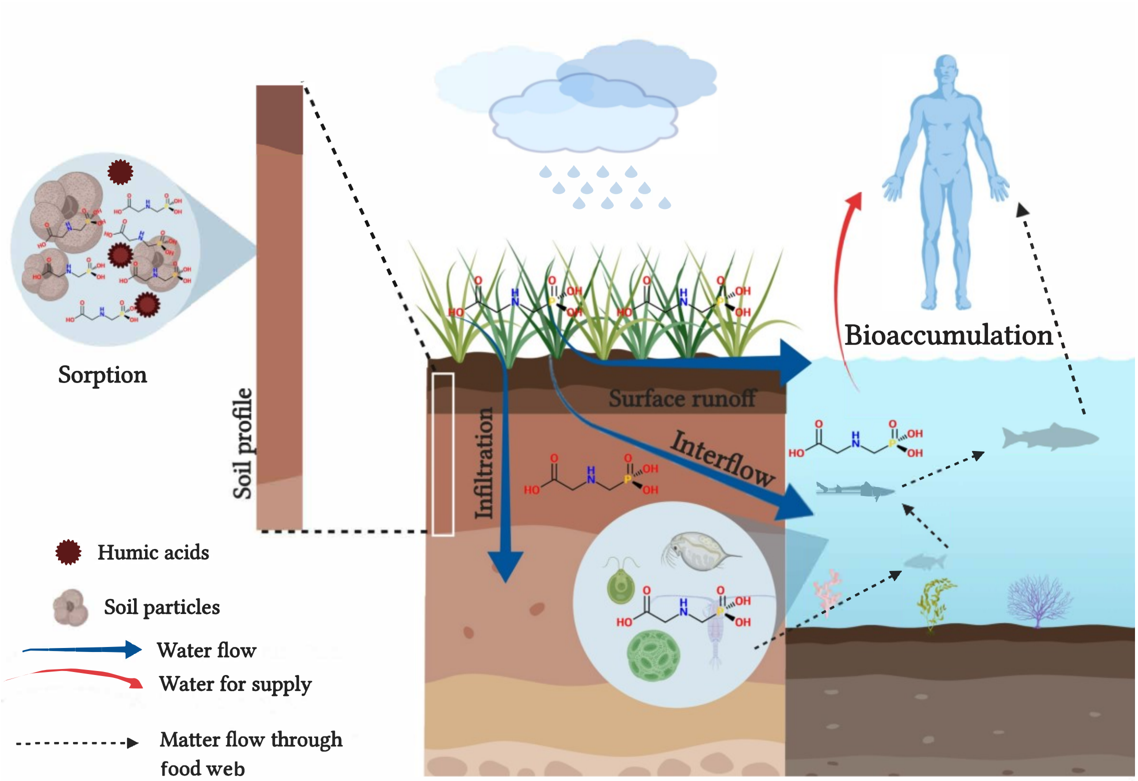

Figure 4 - Soil contamination by glyphosate, transport processes, and flow through aquatic food webs.

As glyphosate is a molecule that shows sorption with soil colloids (HERMANSEN *et al.*, 2020), it can be found in surface soil even after more than four months after glyphosate application and in concentrations of up to 10.6 $\mu g.kg^{-1}$ (9.48% recovery of the applied dose), with even higher concentrations of AMPA (CASTRO, 2012). Its permanence in the soil for prolonged periods becomes a potential source of contamination due to leaching during rain events leading to high concentrations in rivers (DE JONGE, 2001). Moreover, the glyphosate molecule is also leached when residue-bound (COUPE *et al.*, 2012). Additionally, inadequate herbicide management by farmers and rural workers, who often discard packaging improperly and wash spray equipment in water bodies adjacent to application sites, causes variable point-source contamination in agricultural areas (GLOZIER *et al.*, 2012).

2.4. Contamination in urban areas

Urban areas are also relevant sources of glyphosate to surface waters. Glyphosate is widely used for weed control on highways, streets, in backyards, and urban gardens (OKADA *et al.*, 2020). Although the total amount of glyphosate applied in urban areas is considerably lower than that used in agriculture, urban surface runoff is usually higher due to the impermeable surface areas that have reduced retention capacities compared to natural soil (GERECKE *et al.*, 2002). Moreover, more intense runoff peaks typically occur after rainfall events in urban areas (HANKE *et al.*, 2010; COUPE *et al.*, 2012; GLOZIER *et al.*, 2012).

However, there are only a few studies reporting surface water contamination with glyphosate due to urban land use in Brazil. In the municipality of Marau (Rio Grande do Sul state), glyphosate showed seasonal ranges between 50 and 305 $\mu g.kg^{-1}$ in river epilithic biofilms in an agricultural catchment. However, concentrations reached 670 $\mu g.kg^{-1}$ in river biofilms of urban areas, suggesting the indiscriminate application of glyphosate in these areas (FERNANDES *et al.*, 2019). The Brazilian National Health Surveillance Agency (ANVISA) issued a technical note on January 15, 2010, in which it repudiates the use of pesticides in urban areas in Brazil. The use of agrochemicals is linked to a series of preventive measures, such as the use of personal protective equipment (PPE) and the isolation of the area for a minimum of 24 hours, to avoid intoxication of humans and domestic animals. The isolation of urban areas for this purpose is impracticable, and therefore passers-by who do not use PPE run the risk of contamination. Given these facts, the ANVISA has not authorized the use of any herbicide for chemical weeding in urban areas, emphasizing the absence of products registered for this purpose (ANVISA, 2010). Since then, several state courts have ruled against chemical weeding in urban areas (e.g., decisions AC 10155130021217001 MG and AC 70050514843 RS). Nonetheless, the practice of chemical weeding in urban areas has not yet found its way into federal law in the positivistic Brazilian legal system and is still recurrent in many municipalities. Increases in the occurrence of this practice have been observed (BRITO, 2012), causing high concentrations in urban runoff and potentially high exports during rainfall events (DUKE and POWLES, 2008).

Glyphosate contamination of water resources becomes even more worrying considering the overall scenario of wastewater treatment, water pollution, and public water supply in Brazil. Indirect drinking reuse (IDR) is a recurring practice in most Brazilian municipalities (HESPANHOL, 2015). In IDR, water for consumption is taken from a water treatment plant located at a river section upstream of a municipality. After the distribution and consumption of this water, it will or will not pass through a sewage treatment plant and be returned to the river downstream of the municipality. In a municipality located further downstream at the same river, the same process occurs. With each step of reuse, the treatment process becomes more costly and difficult. The problem of IRD is aggravated with the advent of emerging pollutants (drugs, hormones, etc.), because water treatment in Brazil uses conventional potabilization technology, often without complementary techniques, such as adsorption with activated carbon, and therefore not being able to eliminate these molecules efficiently (IBGE, 2011). Given the dominance of IRD in Brazil, glyphosate contamination of rivers is a public health concern.

2.5. Ecophysiological and ecological disturbances due to glyphosate

Initially, glyphosate application was restricted to shortly before or after the sowing of crops, to avoid contact with plants of commercial interest. The creation and patenting of glyphosate-resistant plant lines (Roundup Ready PLUS™) by Monsanto® (now Bayer®) has allowed it to be applied at any time and increased its indiscriminate use. USA, Canada, Argentina, and Brazil are the countries that have the largest area under glyphosate-resistant genetically modified plants (POWLES, 2008). In 2015, the Brazilian ANVISA classified glyphosate as a potentially carcinogenic substance, based on information presented by the International Agency for Research on Cancer (ANVISA, 2017). However, in February 2019, ANVISA published a technical note reiterating the safety of glyphosate use (ANVISA, 2019), contradicting its previous statement.

Despite the existence of numerous scientific studies highlighting the potential carcinogenic, teratogenic, and endocrine-disrupting effects of glyphosate (GASNIER *et al.*, 2009; GEORGE *et al.*, 2010; ZHANG *et al.*, 2019; GASTIAZORO *et al.*, 2020; GORGA *et al.*, 2020; LANZARIN *et al.*, 2020; LIMA *et al.*, 2020; PORTIER, 2020; TRASANDE *et al.*, 2020; TURHAN *et al.*, 2020), the agency claims that there is no scientific evidence to classify glyphosate as a hazardous substance for the environment and human health (ANVISA, 2019).

The contamination of aquatic ecosystems by pesticides and herbicides is a public problem of great concern today (BOMBARDI, 2019), but detailed scientific studies testing the effects of glyphosate on different biotic communities and ecosystem processes are still rare. According to laboratory tests, the presence of pesticides and herbicides in water bodies may adversely affect the structure and composition of communities, thereby potentially also changing trophic structure and ecosystem processes (such as primary and secondary production) of aquatic ecosystems (VERA *et al.*, 2012; GOMES and JUNEAU, 2016; GUTIERREZ *et al.*, 2017; SMEDBOL *et al.*, 2018). High concentrations of pesticides in surface and ground waters may compromise ecosystem services, such as drinking water supply to human populations (JÖNSSON *et al.*, 2013; MAS *et al.*, 2020). However, groundwater contamination may take longer times to occur and be detected because transport through soil profiles and aquifer circulation occur slowly compared to surface runoff, which rapidly carries pesticide molecules, often adsorbed to soil particles, to streams, lakes, and reservoirs (FEITOSA and FILHO, 2008).

Glyphosate is one of the most consumed herbicide active ingredients in the world, representing approximately 60% of total herbicide use. An average of 185,000 tons of active ingredient is marketed in Brazil per year (ANVISA, 2019). The Brazilian Ministry of Health established, through Ordinance No. 2914, of December 12, 2011, that the maximum glyphosate concentration in water for human consumption should not exceed 500 $\mu g.L^{-1}$ (MINISTÉRIO DA SAÚDE, 2011), which differs from concentrations allowed by the United States Environmental Protection Agency (700 $\mu g.L^{-1}$) (AMARANTE JUNIOR *et al.*, 2002) and the European Union (0.1 $\mu g.L^{-1}$) (BOMBARDI, 2019). In a stream located in Pelotas, o town in the Brazilian State of Rio Grande do Sul, glyphosate concentrations were higher than 100 $\mu g.L^{-1}$ (DA SILVA *et al.*, 2009). In rice plantations in South Brazil, glyphosate concentrations between 13 and 144 $\mu g.L^{-1}$ were found (MATTOS and PERALBA, 2002).

The effects of glyphosate on aquatic communities are mostly unclear. Its mechanism of action is based on blocking the activity of the 5-enolpyruvylchiquimate-3-phosphate synthase, a key enzyme for the metabolism of aromatic amino acids in plants and some microorganisms, such as chlorophytes (AMRHEIN *et al.*, 1980). Glyphosate is not considered toxic by the manufacturer since this metabolic pathway does not occur in animals (WHO, 2005). However, both pure glyphosate and its commercial formulations are capable of causing toxic effects in organisms from different taxonomic groups such as rats, fish, tegu lizards, amphibians, benthic macroinvertebrates, honeybees, and even humans (BERNAL-REY *et al.*, 2020; MESTRE *et al.*, 2020; TURHAN *et al.*, 2020; TURKMEN and DOGAN, 2020; VÁZQUEZ *et al.*, 2020; XIANG *et al.*, 2020; YANG, 2020). Under acute exposure to pure glyphosate and one commercial formulation, bacteria and protozoa suffered from toxicity at concentrations of 23.5 $mg.L^{-1}$, while algae and crustaceans were four to five times more sensitive (TSUI and CHU, 2003). In general, commercial formulations have higher toxicity compared to the active ingredient alone due to the addition of adjuvants and surfactants (CHAUFAN *et al.*, 2014).

Exposure to glyphosate or its commercial formulations causes several physiological disorders in organisms from different taxonomic groups, including humans (Table 2). In *in vitro* studies with sublethal glyphosate concentrations, brown mussel (*Perna perna*) and zebrafish (*Danio rerio*), used as experimental models for human diseases, and a killifish species found in water bodies of Brazilian agricultural areas (*Jenynsia multidentata*), showed a decrease in acetylcholinesterase activity, i.e., the enzyme responsible for the degradation of acetylcholine in synaptic clefts, causing cholinergic stress in these animals (SANDRINI *et al.*, 2013). Moreover, glyphosate concentrations of 10 $mg.L^{-1}$ were sufficient to cause reproductive toxicity in zebrafish, increasing the mortality rate and premature egg hatching due to alterations in gene expression during gametogenesis (UREN WEBSTER *et al.*, 2014). Finally, bullfrog tadpoles exposed to Roundup Original® at sublethal concentrations showed reduced ventricular mass, leading to reduced cardiac output and high levels of adrenergic stress (COSTA *et al.*, 2008), in addition to reduced body mass and histopathological changes in the heart (LIMA *et al.*, 2020).

Although ANVISA classified glyphosate formulations as having medium to low toxicity, several harmful effects on human health have been reported in the literature (ANDREOTTI *et al.*, 2018; VAN BRUGGEN *et al.*, 2018; AGOSTINI *et al.*, 2020). Even at low concentrations, glyphosate and its commercial formulation impair the action of the aromatase enzyme, which is responsible for estrogen synthesis and toxic to human placental cells. There are reports of farmers with fertility problems due to glyphosate exposure (RICHARD *et al.*, 2005). Skeletal malformation has also been reported in Wistar rats subjected to perinatal glyphosate exposure (DALLEGRAVE *et al.*, 2003) as well as stimulation of the proliferation of breast cancer cells (THONGPRAKAISANG *et al.*, 2013). Glyphosate exposure reduces the CDK1/cyclin B complex activity. CDKs are monomeric proteins that are inactive in the cell until they bind to a cyclin. Activation of this enzyme complex is responsible for the progression of the cell cycle phases, and in each phase, there are specific CDK's and cyclins, which signal event starts (MARC *et al.*, 2002). In addition to the direct toxicity caused by glyphosate, the development of neurological diseases is associated with manganese depletion caused by the ingestion of glyphosate due to its chelating action (SAMSEL and SENEFF, 2015).

Due to its non-selectivity to target organisms, continuously applied glyphosate can change the structure of the primary producer community of aquatic ecosystems (planktonic and benthic algae, aquatic macrophytes) (POWLES, 2008; BAKER *et al.*, 2012; SMEDBOL *et al.*, 2018) and may therefore also affect the structure of the consumer food web and the functionality of aquatic ecosystems, despite Monsanto's claim that glyphosate poses a low environmental risk (TSUI and CHU, 2003). Albeit referring to different concentration ranges, the classification of the product as harmless appears to be in contrast with the technical instructions that accompany the product. The manufacturer instructs the user to label the product as "poison", to avoid accidental ingestion and warns of the danger of eye and skin irritation, in addition to informing that if the product is spilled into water bodies, the collection of water for consumption must be interrupted. Besides that, the superficial soil layers must be removed in the case of contamination and stored in closed containers to be collected by the company (MONSANTO, 2010).

Table 2: Toxic effects of glyphosate and its commercial formulations on species from different trophic levels.

Species	Concentration	Form	Exposure	Effects	Trophic level	References
Scenedesmus acutus	5 mg.L^{-1} w.	Analytical standard	Acute	Inhibition of culture growth	Producer	SÁENZ *et al.*, 1997
Scenedesmus quadricauda	5 mg.L^{-1} w.	Analytical standard	Acute	Inhibition of culture growth	Producer	SÁENZ *et al.*, 1997
Scenedesmus quadricauda	50 mg.L^{-1} w.	Analytical standard	Acute	Reduction of chlorophyll *a* content	Producer	SÁENZ *et al.*, 1997
Oscilatoria limnetica	20 mg.L^{-1} w.	Roundup®	Acute	Reduction of carbohydrate, protein and flavonoid content	Producer	SALMAN *et al.*, 2016
Prymnesium parvum	100 µg.L^{-1} w.	Roundup SC®	Acute	Enhanced growth rate	Producer	DABNEY and PATIÑO, 2018
Prymnesium parvum	100 µg.L^{-1} w.	Analytical standard	Acute	Enhanced growth rate	Producer	DABNEY and PATIÑO, 2018
Perna perna	0.68 mM w.	Analytical standard	Acute	Reduction of cholinesterase activity	Consumer	SANDRINI *et al.*, 2013
Lumbriculus variegatus	0.05–5.0 mg.L^{-1} w.	Roundup®/Analytical standard	Acute	Bioaccumulation, oxidative stress	Consumer	CONTARDO-JARA *et al.*, 2009
Apis mellifera	2.5 mg.L^{-1} of bee bread or royal/worker jelly	Analytical standard	Chronic	Altered gene expression, oxidative stress	Consumer	VÁZQUEZ *et al.*, 2020
Sphaerechinus granularis	8 mM w.	Roundup®	Acute	Deregulation of the cell cycle due to inactivation of the CDK1/cyclin B complex	Consumer	MARC *et al.*, 2002
Anguilla anguilla	58 µg.L^{-1} w.	Roundup® Ultra	Acute	DNA damage and oxidative stress	Consumer	GUILHERME *et al.*, 2012
Danio rerio	10 mg.L^{-1} w.	Roundup®/Analytical standard	Chronic	Reproductive disorders	Consumer	UREN WEBSTER *et al.*, 2014
Danio rerio	50 µg.L^{-1} w.	Analytical standard	Acute	Cardiotoxicity	Consumer	ROY *et al.*, 2016
Danio rerio	2.43 mM w.	Analytical standard	Acute	Reduction of cholinesterase activity	Consumer	SANDRINI *et al.*, 2013
Oreochromis niloticus	36 ppm w.	Roundup®	Acute	Histopathological damage to gills, liver, and kidneys	Consumer	JIRAUNGKOORSKUL *et al.*, 2002
Jenynsia multidentata	4.26 mM w.	Analytical standard	Acute	Reduction of cholinesterase activity	Consumer	SANDRINI *et al.*, 2013
Cnesterodon decemmaculatus	1 mg.L^{-1} w.	Analytical standard	Acute	Reduction of acetylcholinesterase activity	Consumer	BERNAL-REY *et al.*, 2020

w. = water in experimental tanks

Table 2 (continued) – Toxic effects of glyphosate and its commercial formulations on species from different trophic levels.

Species	Concentration	Form	Exposure	Effects	Trophic level	References
Xenopus laevis	250 $mg.L^{-1}$ w.	Roundup® Star	Acute	Embryo length reduction, reduction of carboxylesterase activity	Consumer	TURHAN *et al.*, 2020
Lithobates catesbeianus	1 ppm w.	Roundup®	Acute	Adrenergic stress and tachycardia	Consumer	COSTA *et al.*, 2008
Lithobates catesbeianus	1 $mg.L^{-1}$ w.	Roundup®	Acute	Reduction of cardiomyocyte diameter, body mass, and length	Consumer	LIMA *et al.*, 2020
Salvator merianae	400 $\mu g.egg^{-1}$	Roundup®	Acute	Increase in the number of lymphocytes and reduction of heterophiles	Consumer	MESTRE *et al.*, 2020
Rattus novergicus	1 $g.kg^{-1}$ body mass	Roundup®	Acute	Death of 50% of pregnant females in the study and less weight gain throughout pregnancy	Consumer	DALLEGRAVE *et al.*, 2003
Rattus novergicus	500 $mg.kg^{-1}$ body mass	Roundup®	Acute	Skeleton malformation	Consumer	DALLEGRAVE *et al.*, 2003
Homo sapiens	250 mL purposely ingested	Commercial formulation not specified	Acute	Upper-airway obstruction with reduced partial oxygen pressure	Consumer	YANG, 2020
Homo sapiens	34.69 $mg.L^{-1}$ blood	Roundup UltraMax	Acute	Oxidative stress in hepatocytes	Consumer	CHAUFAN *et al.*, 2014
Homo sapiens	0.6–150 $mg.L^{-1}$ blood	Commercial formulation not specified	Acute	Oropharyngeal tissue damage, respiratory and cardiovascular disregulation, hepato- and nephrotoxicity, alteration of consciousness	Consumer	ZOUAOUI *et al.*, 2013
Homo sapiens	6.90–7.48 $g.L^{-1}$ blood	Commercial formulation not specified	Acute	Death: cardiorespiratory arrest, intravascular coagulation, shock, and multiple organ failure	Consumer	ZOUAOUI *et al.*, 2013

w. = water in experimental tanks

The effects of toxic substances on different primary producers can vary considerably and may be associated with phylogenetic differences between taxonomic groups (WÄNGBERG and BLANCK, 1988). In a comprehensive mesocosm study in a shallow Pampa lake in Argentina, glyphosate additions of 8 $mg.L^{-1}$ caused algal (mainly diatom) mortality. However, increases in total phosphorus concentration due to glyphosate mineralization led to eutrophication, increased cyanobacteria growth as well as high turbidity (VERA *et al.*, 2010). Glyphosate has also been reported to be toxic to some microalgae species, such as *Skeletonema costatum* (Bacillariophyceae) and *Selenastrum capricornutum* (Chlorophyta) (TSUI and CHU, 2003), thereby affecting the primary productivity of aquatic systems. Further, glyphosate may interfere with cell cycle regulation and embryonic development of some aquatic consumer species such as *Sphaerechinus granularis* (Echinacea), a marine invertebrate widely used as an animal model to evaluate effects of pesticide exposure (MARC *et al.,* 2002).

Several factors influence the ecophysiology of aquatic herbivores throughout their developmental stages. Aquatic macroinvertebrates and vertebrate larvae, for example, besides being under constant predation pressure from higher trophic level consumers, are extremely susceptible to changes in their habitat (SOLOMON and THOMPSON, 2003), either in water quality characteristics, such as temperature, pH, salinity, and dissolved oxygen concentration, or in physical habitat structure (e.g., sediment structure, presence of shelter sites, breeding sites) (AL-SHAMI *et al.,* 2011; REID *et al.*, 2019). To overcome such pressures, individuals must expend a lot of energy to be able to acclimatize to the environmental conditions, especially if disturbed by the presence of contaminants, and to avoid population declines in the medium and long term (PATHIRATNE and KROON, 2016), which limits the secondary production in aquatic systems (BENKE and HURYN, 2010). Therefore, aquatic herbivores are especially susceptible to both direct contaminant effects, and effects that contaminants, such as glyphosate, may have on their food resources and habitat (e.g., phosphorus pollution and pH) (BRAUNS *et al.*, 2011).

Further up the food web, harmful effects of glyphosate have also been recorded, e.g., in fish. In the European eel (*Anguilla anguilla*), exposure to Roundup® concentrations similar to those found in the environment caused oxidative stress and DNA damage to liver and gill cells (GUILHERME *et al.,* 2010). Histopathological changes have also been reported in gills (hyperplasia), liver (hepatocyte vacuolation), and kidneys (Bowman capsule dilation) of Nile tilapia (*Oreochromis niloticus*) exposed to a Roundup® formulation (SAMANTA *et al.*, 2018). Glyphosate bioaccumulation was observed in *Lumbriculus variegatus*, a terrestrial annelid, concomitantly with significantly increased superoxide dismutase enzyme activity, indicating the presence of oxidative stress (CONTARDO-JARA *et al.*, 2009). In native fish species in rice fields in Argentina, bioaccumulation, oxidative stress and neurotoxic effects were observed following a fumigation event (ROSSI *et al.*, 2020). The possibility of bioaccumulation becomes worrying, also because humans may become ultimately affected by the consumption of contaminated aquatic organisms, in addition to direct contamination caused by the ingestion of fruits, vegetables, and water. Continued exposure to glyphosate in humans could be a trigger for several physiological and reproductive problems (ROMANO *et al.*, 2012), and its detection in food and drinking water may become necessary for the control of its harmful potential to human health.

3. CONCLUSIONS

The use of glyphosate-based herbicides, even without regulation, e.g., in urban areas, is a common practice in Brazil. Several studies have shown glyphosate contamination of water resources and soil, and the time required for the degradation of glyphosate in the environment can vary greatly, depending on environmental conditions as its degradation occurs mainly due to microbial activity. Despite being classified by regulatory agencies as a low-risk substance, the literature shows that glyphosate is capable of causing toxic effects in many species. It affects the structure and functioning of aquatic ecosystems due to its toxicity to organisms on different trophic levels. The presence of glyphosate in water resources used for drinking water supply and bioaccumulation in animals represent a risk for human health. The dynamics of this pesticide in the environment must be better understood to control its harmful effects. Efficient mitigation measures aiming at long-term harm reduction are needed, while the massive and indiscriminate use of this herbicide is still allowed in Brazil and other countries.

ACKNOWLEDGMENTS

I.B.L. received an M.Sc. fellowship by the Federal University of São João del-Rei. We thank the Research Foundation of the State of Minas Gerais (FAPEMIG, CRA PPM-00596/16 and PPM-00386/18) and the Brazilian National Council for Scientific and Technological Development (CNPq 305712/2018-7) for financial support.

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