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RESEARCH ARTICLE

Trends in science on glyphosate toxicity: a scientometric study

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Abstract

As part of the most used herbicides, glyphosate is the most successful ingredient of agrochemical companies. The main objective of this study was to demonstrate research trends related to the glyphosate toxicity and its main effects on human and environmental health. For this purpose, 443 articles published, from 1995 to 2020, on the platform Web of Science™ Thomson Reuters were selected. The main toxicity results related in literature are genotoxicity, cytotoxicity, and endocrine disruption. The environmental effects come mostly from the contamination of groundwater and soils. Several studies have concluded that herbicide concentrations right below the official safety limits induced toxic effects. The results presented a highlighted harmful effect of glyphosate on both human and environmental health. It has been observed that countries where publish the most about the glyphosate toxicity are great investors in large-scale agriculture. It is important to ponder that these countries are in a route of ecosystem exploitation that includes not only fauna and flora, but also human beings. Unfortunately, science does not provide concise data for these pesticide disapproval in the global consumer market. It is necessary to search sustainable global interest alternatives to increase agriculture production based on peoples' food sovereignty.

Keywords Agriculture · Pesticides · Symptoms · Contamination · Health · Herbicide

Introduction

Biotechnology, applied through mutagenesis and genetic engineering, can be used to create and recreate crop varieties by inserting genes of different species into plants. Currently, there are transgenic varieties, seeds, and food, such as corn, soybeans, cotton, and canola, grown on millions of hectares worldwide (Peterson and Shama 2005). The production of genetically modified (GM) crops has increased significantly from 1990 to present day, contributing to the change in the dynamics and trends in the general use of agrochemicals (Coupea and Capelb 2016).

The global area on which transgenic crops are grown has increased by more than 50 times in a decade (from 1996 to 2005) in over 20 countries. Crops are genetically modified in different ways, with diverse characteristics. However, tolerance to herbicides and insecticides is the most common genetic modification carried out, with corn and soybeans being the major crops in which this is performed (Sung et al. 2006).

However, weed management began after World War II with the introduction of 2, 4-D. Currently, the advent of transgenic crops has placed glyphosate-based herbicides at the peak of commercialization and use in agropastoral fields in urban environments (Duke and Powles 2008; Carneiro 2015).

Consequently, questions about the clash between public health problems and the indiscriminate use of pesticides have become recurrent, which, despite known harmfulness, are increasingly used, especially in Latin America (Augusto 2012). There are several governmental organs in different countries responsible for the study and approval or disapproval of agrochemical compounds. These agencies include the US Animal and Plant Health Inspection Service (APHIS), Brazil's ANVISA (National Agency for Sanitary Surveillance), and the European Commission of Agriculture, responsible for disseminating statistics, news, and relevant legislation to the member countries of the economic European Union bloc (National Research Council (US) Committee on Genetically Modified Pest-Protected Plants 2000; ANVISA 2020; European Commission 2020).

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Herbicides constitute one of the agrochemical categories, with some of the most commercialized herbicides worldwide based on the ingredient, glyphosate (Carneiro 2015). The first glyphosate was synthesized by Henri Martin of the Swiss pharmaceutical company, Cilag, but was not tested or patented for use as a herbicide. John Franz of the Monsanto company was the first to synthesize and test a glyphosate for use as a herbicide in 1970, which soon required patenting (Duke and Powles 2008; Monsanto 2020).

In Brazil, the first record of a glyphosate-based herbicide dates to October 9, 1984, under the number 8,405,091. The applicant, FBC LTD, the existence as a legal entity of which is currently uncertain, was defined by the New Scientist magazine, as an "international company in the field of agrochemicals and livestock products" in the same year's edition (NEW SCIENTIST 1897).

From then on, the clashes have been constant, and confrontations between multinationals, trade unionists, environmentalists, and government authorities are increasingly drastic (IARC 2018; ANVISA 2020). Discussions on the authorization and prohibition of the commercialization of glyphosate-based herbicides have also affected the economies of countries, especially in the last 20 years (Gottems 2017).

In health sciences, numerous effects have been observed. According to the Dossiê Abrasco (Carneiro 2015), although the consumption of agrochemicals has increased, the rate of acute herbicide intoxications has not increased in the same proportion. This may be due to difficulties in recognizing acute intoxications, diagnostic failures, obsolete information systems, and inadequate notification services (Carneiro 2015). As concerns direct environmental toxicity, studies have demonstrated its effects in decreasing ecosystem services such as pollination, soil nitrification (Cycoń et al. 2013; Sebiomo et al. 2011), functional diversity of microorganisms (Fang et al. 2009), and decreases of the multiple uses of water (e.g., algal bloom and the production of toxic compounds by algae) (Zhang et al. 2016; Dabney and Patiño 2018).

Therefore, the main objective of this study was to demonstrate research trends in science in relation to the toxicity of glyphosate and herbicides with glyphosate as active ingredient. Some of the secondary objectives were to establish similarities between the findings of authors with the highest number of publications on the subject, highlighting the core of their research, the journals that stand out in the promotion of studies, and to consider the evolution of publications on glyphosate over the years (e.g., dosage used in the experiments) and its main effects on human and environmental health.

Regarding the evaluation of glyphosate dosage trends, we were motivated to select the year 2012 as a "break point" due to a seminal, controversial paper that was published that time and later retracted and republished. The originality of this study was due to the long animal follow-up period (2 years), the evaluation of the complete herbicide formulation, and the use of other doses aside from those recommended. Low environmentally relevant doses below the range of levels permitted by regulatory authorities in drinking water and GM feed were evaluated. Increased mortality was observed in females rat as compared to controls, mainly due to breast tumors. Considering the findings of Séralini et al. and the impact of the author's publications on the subject, the controversial 2012 study could be considered a watershed on the use of lower herbicide experimental doses in glyphosate toxicity research.

Methodology

The data used in this study were obtained from the Web of Science ™ Thomson Reuters database. Filtering was applied to selected articles published between 1995 and 2020. The search was performed using the terms "glyphosat*" and "toxicit*," and we selected papers that contained the terms in the titles, abstracts, and keywords. Only articles were considered; revisions and other scientific papers were excluded.

The address of the first author of each article was used to identify the top 20 countries with the highest number of publications. The top 5 journals with the highest number of published works were also identified through their impact factors.

The effects of exposure to glyphosate were also evaluated. For this, we considered the main experimental model categories used in each study. Thus, it was possible to establish 5 main experimental models, i.e., mammals (animal in vivo studies and culture cells), fish, amphibians, invertebrates, and the environment. The environmental category was composed of 2 subcategories, plants, and water/soil microorganisms. The experimental herbicide doses were also collected and analyzed.

The specific product used (whether pure glyphosate or a glyphosate formulation) in the experiments were mostly found in the methodology field in a subtopic called "chemicals". "Glyphosate" refers to the pure chemical without adjuvants. The names between parentheses are the laboratories in which they were purchased.

Finally, we evaluated whether the inference scale of each article was international, national, geared towards communities belonging to the European Union, or local. This scale of inference was determined for each article after reading a large portion of it. Relationship was established based on the applicability of the results of each study. Many surveys are directed to local communities or made through biomonitoring in a particular region of a country. The worth of other studies, especially those performed in laboratories, is of international scale to the scientific or commercial community of the evaluated product.

Statistical analysis

To determine the temporal tendency of publications on the subject, the number of articles was related to the respective years of publication in a regression analysis. To analyze and compare data obtained from glyphosate dosage models between "up to 2012" and "after 2012," a nonparametric Kruskal–Wallis test and t test were used. Differences between groups were considered significant at a P-value < 0.05. Statistical analyses were performed using GraphPad Prism 6.0 (GraphPad Software, Inc., San Diego, CA) and the R software (R Development Core Team, 2021). The year 2012 was considered the benchmark for comparing dosages because in this year, long-term surveys, which used herbicide doses recommended by regulatory authorities, were carried out (Séralini et al. 2012).

The frequency of toxicity symptoms reported in the articles analyzed was associated with the organism model through a heatmap analysis in the R software (R Development Core Team, 2021), using the "pheatmap" add-in (Kolde 2019). A heatmap (or heat map) is a way to visualize hierarchical clustering, in which data values are transformed into a color scale (Kassambara 2017). In this way, heatmaps permit simultaneous visualization of clusters of samples (organisms) and features (frequency of the toxicity symptoms). The organisms and toxicity symptoms were re-ordered according to the results obtained by hierarchical clustering, placing similar observations close to each other. By visualizing the data matrix in this way, it is possible to identify the symptoms that are most associated with each organism.

Results and discussion

Within the period considered, 443 articles containing the words "glyphosat*" and "toxicit*" were found, with a progressive increase in the number of publications (R^2 = 0.82, p = 0.0001). In 1995 and 1998, no articles that evaluated the toxic effects of glyphosate on humans or the environment were published (Fig. 1).

In 1996 (n = 3), transgenic soybeans, corn, and cotton seeds, tolerant to glyphosate herbicides, were approved for planting in the USA. In 2005 (n = 10) and 2008 (n = 13), the planting and trade of glyphosate-tolerant alfalfa and GM beet, respectively, were approved. The US Environmental Protection Agency (EPA) reports, publicizing the use of pesticides, had a time span of 14 years without concise information. Since 2009, the world's agricultural use of glyphosate has grown alarmingly, especially with the planting of GM crops since 1995 (Benbrook 2016).

The correlation between the percentage of publications and the percentage of agricultural area was positive and significant (r = 0.84; p < 0.05). Of the three countries with the highest number of published articles, the People's Republic of China has 54.99% of its territory composed of agricultural areas, followed by France (44.61%) and the USA (41.27%). Countries not found among those with the highest publications but which have considerable agricultural areas are England (71.22%), Denmark (60.43%), and India (54.67%) with respect to the total territorial extension. Canada does not follow this rule as it occupies the seventh place in the ranking of publications and the first place in territorial extension and has the smallest agricultural area, i.e., only 6.28% of its territory, followed in ascending order, by Japan with 11.90% and South Korea with 17.06% of extensions for agricultural purposes (Table 1).

According to the CIA database, the main commodities for exportation in these countries (Table 1) are chemicals, machinery, foodstuffs, pharmaceutical products, computers, motor vehicles, plastics, and textiles. As concerns agricultural products, the most produced commodities were wheat, fish, dairy products, fruits, potatoes, poultry, vegetables, and other foods (Central Intelligence Agency (CIA) 2020).

With the sale of transgenic seeds worldwide for use in agriculture and livestock farming, increased trade, purchase, and sale of agrochemicals have incited a growing international discussion around these genetically modified organisms (GMOs) (Coupea and Capelb 2016; Duke and Powles 2008; Carneiro 2015; European Food Safety Authority (EFSA) 2016). The excessive use of pesticides can hardly be discussed without first linking it to GMOs.

Main authors and journals

Of the twenty-five researchers with the highest number of authorships in scientific articles, Gilles-Eric Séralini (n = 15) was the first to publish an article in this category. Robin Mesnage (n = 9) and Emile Clair (n = 5) published a little later (Fig. 2). The three (alongside other authors) co-authored a controversial article, which after much debate, had its publication portrayed and was republished in 2014 (Séralini et al. 2014). The budget for the study was €3 million, and it was conducted at the University of Caen, funded by and executed with the collaboration of CRIIGEN (Butler 2012).

Many authors among those with the highest number of authorial publications were co-authors of the same studies. An article can have more than one highlighted author. Among the five journals with the highest number of article publications, Science of The Total Environment had the highest impact factor (= 6.551), followed by Chemosphere (IF 5.778), Ecotoxicology and Environmental Safety (IF 4.872), Environmental Toxicology and Chemistry (IF 3.152), and Environmental Science and Pollution Research (IF 3.056) in 2019/2020, according to the Bioxbio database (Bioxbio 2020).

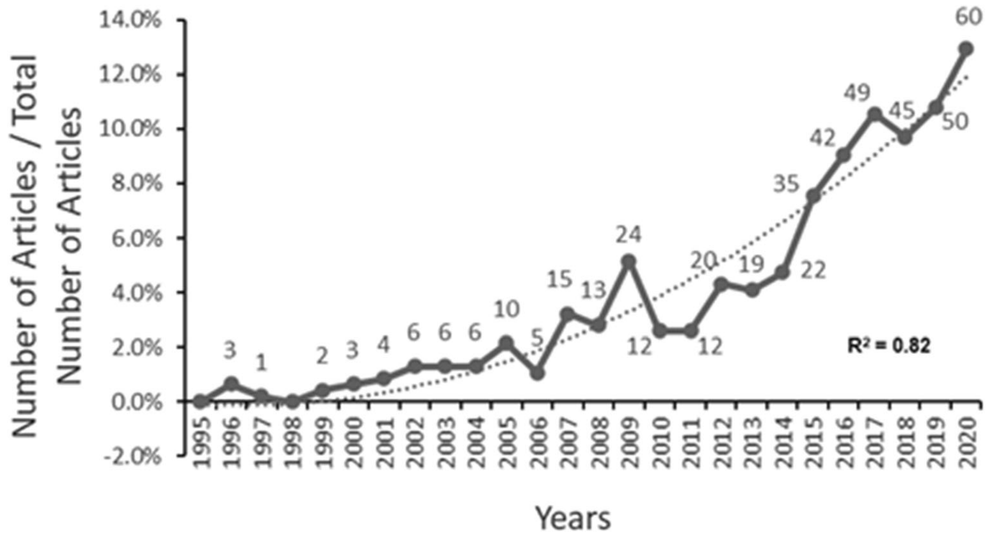

Fig. 1 Number of articles published between 1995 and December 2020 in the ISI database. To standardize the number of articles containing the words "glyphosat*" and "toxicit*," the number of articles in each year containing these words was divided by the total number of articles in the ISI database for that year and multiplied by 100. The absolute number of publications on this subject per year is given above each point.

Some scientific articles were like "hot papers." An article by Séralini et al. (2012) had 533 citations but was not part of the search results in the Web of Science ™ database. This paper was retracted under much pressure from sources with vested interests in safeguarding Roundup as a product. There were 2 other articles published by Richard et al. (2005), with 527 citations, and Benachour and Séralini (2009), with 451 citations, according to search results in the National Center for Biotechnology Information (NCBI) 2020

Main herbicides

Among the 20 main herbicides used in these studies, 11 were part of the Roundup line of the transnational, Monsanto (Fig. 3). The use of Roundup has increased mainly in countries where GM seeds are grown, especially Roundup Ready seeds resistant to the herbicide. Roundup herbicides commonly contain polyoxyethyleneamine as the main surfactant, making them more cytotoxic than pure glyphosate (Koller et al. 2012).

Table 1 Twenty countries with the highest number of articles published, in descending order, according to the Web of Science™ Thomson Reuters database. Territorial extensions per country, were collected from the CIA database (Central Intelligence Agency (CIA) 2020), and information on agricultural areas was obtained from the World Bank database for the year 2019 (THE WORLD BANK GROUP 2019)

Country	Number of published articles	Percentage of published articles	Total area (Km^2)	Agricultural area (Km^2)	Percentage of agricultural area
USA	110	24.83%	9,833,517	4,058,625	41.27%
France	46	10.38%	643,801	287,180	44.61%
China	41	9.25%	9,596,960	5,277,330	54.99%
Brazil	26	5.86%	8,515,770	2,835,460	33.30%
UK	25	5.64%	243,610	173,500	71.22%
Argentina	23	5.19%	2,780,400	1,487,000	53.48%
Germany	23	5.19%	357,022	166,570	46.66%
Italy	20	4.51%	301,340	127,170	42.20%
Canada	18	4.06%	9,984,670	626,562	6.28%
South Korea	13	2.93%	99,720	17,008	17.06%
Mexico	12	2.70%	1,964,375	1,067,050	54.32%
Spain	12	2.70%	505,370	262,657	51.97%
Denmark	11	2.48%	43,094	26,040	60.43%
Poland	11	2.48%	312,685	143,740	45.97%
Colombia	10	2.26%	1,138,910	446,656	39.22%
Japan	10	2.26%	377,915	44,960	11.90%
Belgium	9	2.03%	30,528	13,508	44.25%
Australia	9	2.03%	7,741,220	3,710,780	47.94%
India	7	1.58%	3,287,263	1,797,210	54.67%
Portugal	7	1.58%	92,090	36,141	39.25%

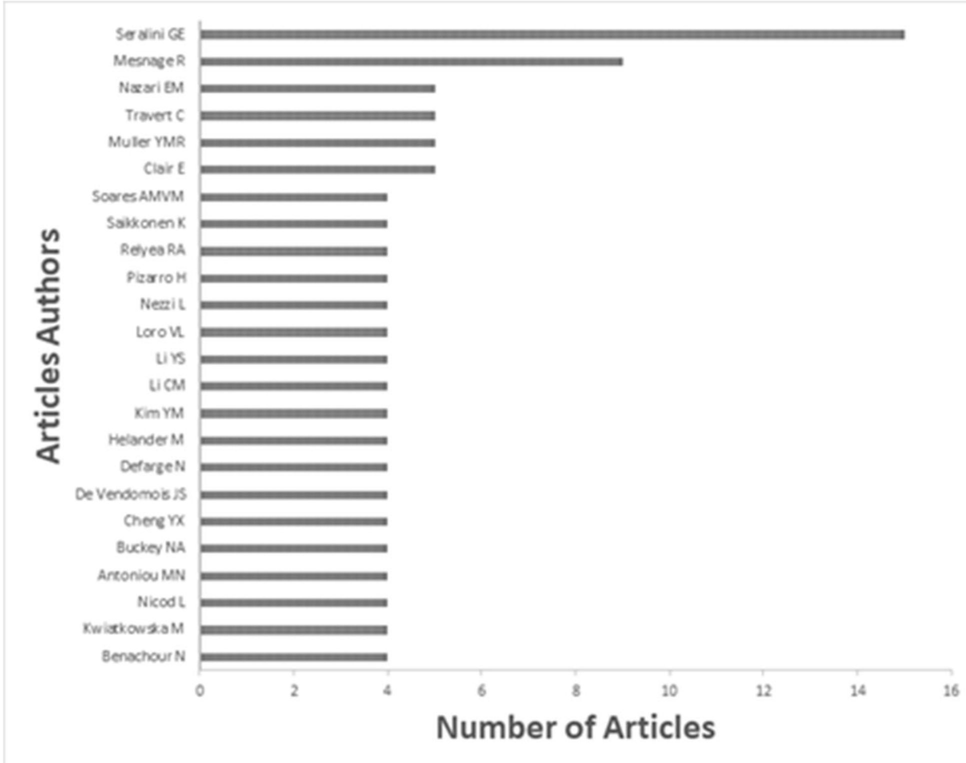

Fig. 2 Twenty-five authors with the highest number of publications, according to the Web of Science™ Thomson Reuters database. The axis Y is the author name and the X the number of articles attributed to these authors. The order presented is in agreement with the data downloaded directly from the platform and takes into account the authorship itself, dispensing the authorial order contained in the header of each article

Glyphosate-based herbicides were extensively used in the "hot papers," studies. In a study by Séralini et al. (2012), a GM corn field was treated with the herbicide, WeatherMAX, and the herbicide, GT Plus, was diluted in portable water for the experiments. Richard et al. (2005) used glyphosate from Sigma Aldrich and Monsanto's Roundup herbicide. Finally, Benachour and Séralini (2009) used 4 Roundups in their experiments, i.e., Express, Bioforce, GrandTravaux, and

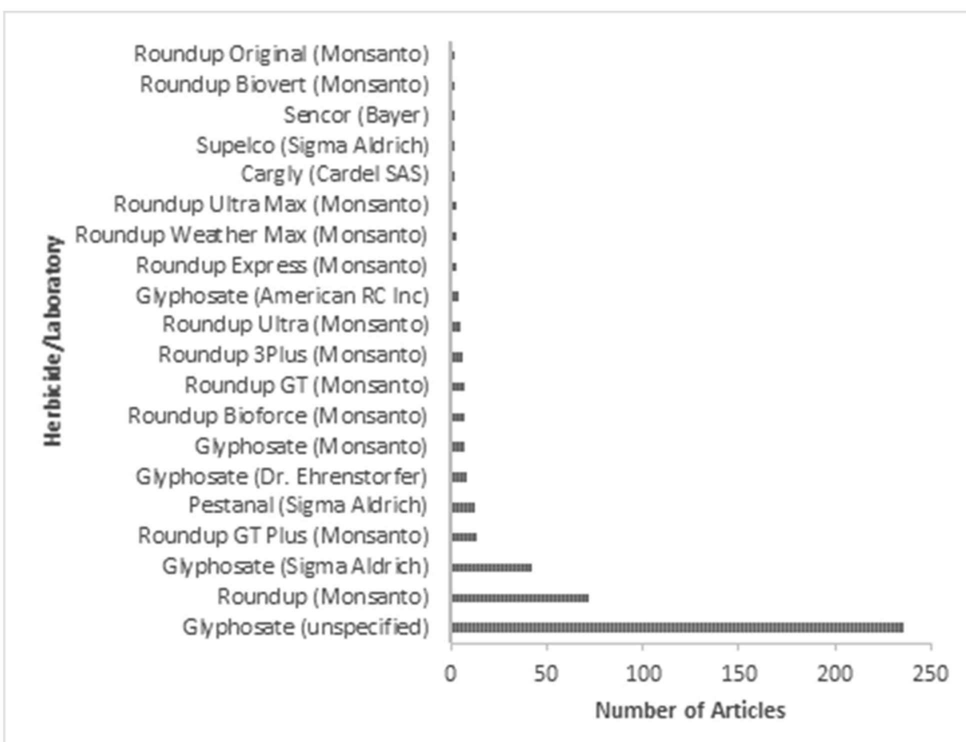

Fig. 3 Herbicide agents most used in studies with glyphosate as a pure chemical without adjuvants. The names of the laboratories where they were purchased are written in parentheses. The names before those of the herbicides are those of the manufacturers or marketers.

GrandTravaux Plus (Séralini et al. 2014; Richard et al. 2005; Benachour and Séralini 2009).

This leads to a number of problems, especially considering that the ingredients in agrochemicals can be divided into two categories, active and "inert". The so-called inert ingredients may be biologically or chemically active, even though tests for the release of pesticides are carried out only on the active ingredient and not on molecules considered secondary in the compound (Cox and Surgan 2006).

Glyphosate dosage

Regarding information obtained on glyphosate toxicity, the results were divided with respect to the 5 main experimental model categories studied, i.e., mammals (in vivo and cells), fish, amphibians, invertebrates, and the environment. In addition to the main toxic effects, the experimental herbicide dosages used during the years surveyed were also evaluated. When the median dosage values used for all models until 2012 and after 2012 were compared, we found a significant reduction in dosage (Fig. 4).

There was a significant reduction in herbicide experimental doses in studies performed on mammals and fish. This reduction has been more pronounced in the last 8 years (Table 2). When evaluating the median herbicide doses used in the studies in this review before and after 2012, we observed a significant reduction in glyphosate doses and a significant change in formulations in experiments involving mammals and fish.

When the dosages were separated with respect to the model used, the minimum dosage values were significantly different in the experiments with mammals and fish between the period up to 2012 and after 2012. Plants, fish, and invertebrates showed differences in dosage between these periods when the median dosage was used. When the maximum values were considered, no model showed differences between these periods (Table 2).

Glyphosate toxicity

In contrast to the decrease in glyphosate dosage used in toxicity studies in recent years (after 2012), an increase in the variety of disorders associated with glyphosate has been observed in recent years.

Among the symptoms reported in the articles analyzed, the most common was associated to alterations in the endocrine and reproductive systems (Fig. 5). This symptom was most common in mammals but was reported in all the model organisms. Another condition that was reported in all models was oxidative stress. In Fig. 5, the symptoms are presented in order of the frequency of their occurrence and with respect to the model organism. The organism with the highest number of identified symptoms was fish, followed by amphibians. For soil and water microbiota, the most common symptoms were decreased growth rate, followed by population dynamics, and endocrine and reproductive disorders. For invertebrates, the most common symptom was alteration in metabolism. For mammals and mammalian cells, the most frequently encountered problems were cytotoxicity, endocrine and reproductive disorders, and genotoxicity. A significant increase in the number of articles that reported endocrine disorders, genotoxicity, and oxidative stress was observed after 2012. Such findings are correlated to the use of low herbicide experimental doses. Only a few studies were carried out on plants, and consequently, only a few symptoms were reported (Fig. 6).

Main effects of glyphosate in mammals and mammalian cells

The main toxic effects of glyphosate reported in in vivo studies performed on mammals were endocrine and reproductive disorders, hepatotoxicity, oxidative stress (Benedetti et al. 2004), and neurotoxicity (Coullery et al.,2020). After 2012, gut microbiome disturbances have also been reported. Rats were most frequently used as experimental models (67%). To a lesser extent, mice, cattle, and pigs were also used.

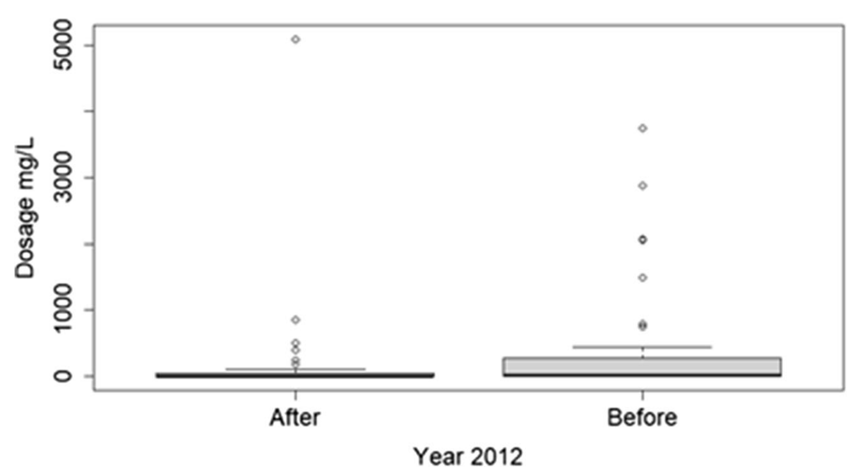

Fig. 4 Kruskal–Wallis test comparing the median dosage values (mg/L) used up to 2012 and after 2012 in the articles published from 1995 to 2020 on glyphosate and toxicity from the Web of Science database

Table 2 Test t comparing the doses (mg/Kg for mammals and mg/L for others) used in models up to 2012 and after 2012. The significant values of $p < 0.05$ are in boldface

		Mean	Median	Minimum	Maximum	p value
Mammals	Up to 2012	417.75	350.00	5.00	1340.00	**0.046**
	After 2012	370.99	50.40	0.1×10^{-2}	5000.00	
Fish	Up to 2012	60.24	10.00	1.16×10^{-1}	410.00	**0.001**
	After 2012	45.10	1.80	0.1×10^{-3}	1647.00	
Amphibian	Up to 2012	68.33	3.77	0.25	845.00	0.302
	After 2012	17673.89	5.75	1.8×10^{-2}	480000.00	
Water and soil microbiota	Up to 2012	127.02	12.00	0.01	1000.00	**0.016**
	After 2012	2952.00	101.00	0.20	36000.00	
Invertebrates	Up to 2012	22.27	2.16	1.2×10^{-2}	192.00	0.351
	After 2012	290.92	2,80	1.6×10^{-7}	11400.00	
Mammals culture cells	Up to 2012	308.90	5.00	1.6×10^{-3}	5000.00	0.329
	After 2012	292.78	5.00	0.01	4146.00	
Plants	Up to 2012	1135.46	200.00	1.00	7200.00	**< 0.001**
	After 2012	76.34	10.00	0.1×10^{-2}	1000.00	

Disruption in endocrine function was one of the most cited effects of glyphosate in studies involving mammals. The main endocrine disturbances observed were testosterone level alterations, increased 17β-estradiol levels in males serum, delayed sexual maturation in females, reduced spermatogenesis, and alterations in pituitary hormone levels (Dallegrave et al.

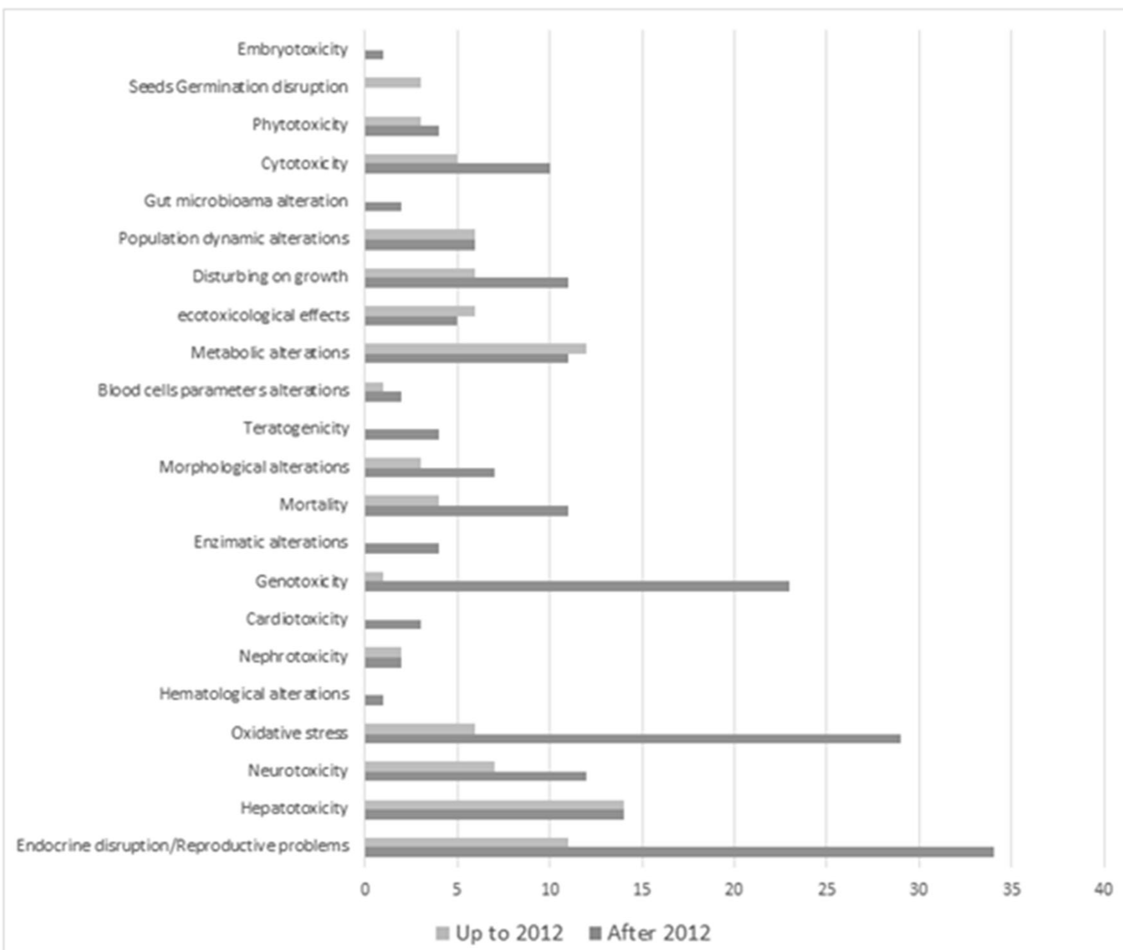

Fig. 5 Main symptoms most reported in scientific articles. Data in published articles on experiments performed on mammals, fish, amphibians, soil and water ecosystems, invertebrates, plants and mammalian cells cultures

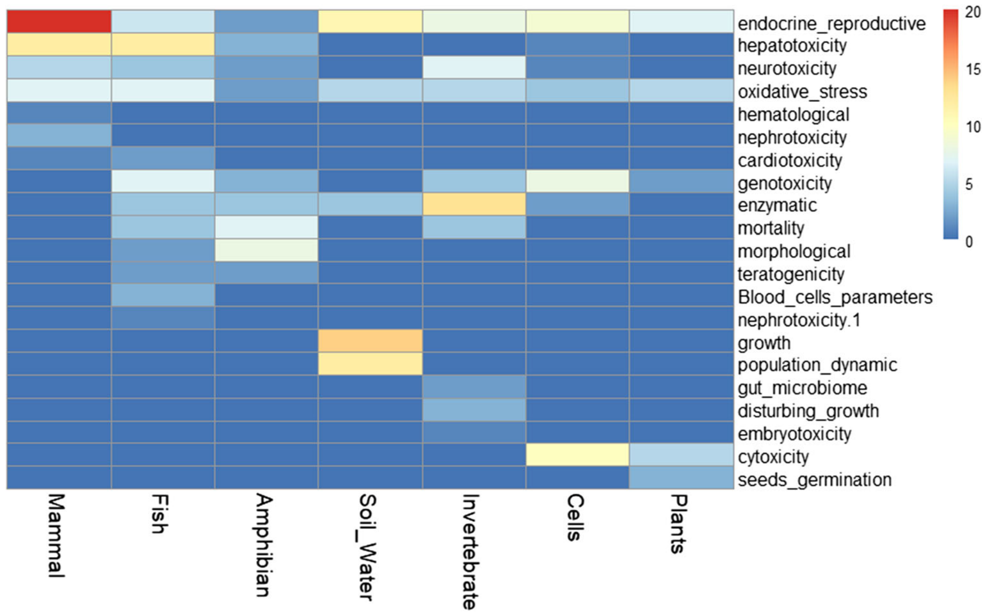

Fig. 6 Heatmap showing the relationship between toxicity symptoms and model organisms. The deep colors represent the most frequent toxicity symptom per organism. Similar organisms showed similar toxicity symptoms

2007; Romano et al. 2012; Owagboriaye et al. 2017). Many studies have investigated the effects of high Roundup doses. However, recently, some studies began to examine whether exposure to glyphosate, which is considered safe, could elicit some toxic effects. Manservisi et al. (2019) investigated the effects of exposure to low glyphosate doses in Sprague Dawley rats across different life stages. Glyphosate and commercial formulations were administered in drinking water at a dose of 1.75 mg/kg bw/day from the prenatal period to adulthood. Endocrine disorders and altered reproductive development were observed in both male and female rats.

Worthy of note, in 2012, Séralini et al. (2012) conducted a very controversial study on rats fed GM maize grains (NK603), which, according to updated Acquisition of Agri-Biotech Applications (ISAAA) data, was the glyphosate-resistant GM maize with the highest number of approvals for cultivation worldwide (ISAAA, 2017). Low environmentally relevant doses below the range of levels permitted by regulatory authorities in drinking water and GM feed were evaluated. Increased mortality was observed in females as compared to controls, mainly due to breast tumors. The second most affected organ was the pituitary gland. Females were more sensitive to the presence of the herbicide in drinking water than males. In males, the most affected organs were the liver, the digestive tract, and kidneys. Séralini et al. (2012) concluded that low levels of the complete herbicide formulation, at concentrations well below officially set safety limits, induced severe hormone-dependent mammary, hepatic, and kidney disturbances (Séralini et al. 2012).

Manservisi et al. (2019) showed that chronic exposure to low doses of glyphosate and commercial formulations caused deleterious effects as well. These findings raised the question of whether such effects could be transgenerational. In this light, Kubsad et al. (2019) investigated the effects of transient exposure in gestating F0 generation female rats. The authors demonstrated that glyphosate had negligible effects on the directly exposed F0 or F1 (offspring) generations. In contrast, dramatic increase in pathology was observed in the F2 generation (grand-offspring) and in F3 transgenerational great-grand-offspring. The transgenerational pathologies observed included prostate disease, obesity, kidney disease, ovarian disease, parturition abnormalities, and differential DNA methylation in sperm. Manservisi et al. showed that glyphosate could promote transgenerational epigenetic inheritance of disease and pathology through germline epimutations.

The second most reported effects of glyphosate were liver toxicity and oxidative stress. Benedetti et al. (2004) showed that long-term treatment of rats with low doses of glyphosate-Biocarb® increased the release of hepatic aspartate aminotransferase (AST) and alanine aminotransferase (ALT) into rat serum. Changes in liver tissue were also observed, with an increase in the number of Kupffer cells. In El-Shenawy 2009 evaluated the cytotoxic potential of glyphosate and Roundup. Male albino rats were intraperitoneally treated with sublethal concentrations of both herbicide formulations. Treatment with Roundup induced leakage of the intracellular hepatic enzymes, indicating irreversible damage to hepatocytes. In addition, Roundup induced oxidative stress in hepatic tissues. In 2017, Mesnage and Antoniou (2017) performed a combined analysis of the proteome and metabolome profiles of rat livers following long-term (2 years) exposure to an environmentally relevant Roundup dose. Proteome disturbances were observed to be associated with organonitrogen metabolism and fatty acid β-oxidation. Metabolome analyses confirmed the occurrence of lipotoxic conditions and oxidative stress. These alterations could be clearly associated with non-alcoholic fatty liver disease and its progression to non-alcoholic steatohepatitis. This study provides important revelations about exposure to extremely low glyphosate doses. Non-alcoholic fatty liver disease is becoming an epidemic and has been linked to the rapid increase in other diseases, such as diabetes, obesity, and metabolic syndromes (Sherif et al. 2016). Chronic exposure to active environmental pollutants via contaminated food cannot be neglected.

Neurotoxicity was the third most reported effect. Recently, Coullery et al. (2020) evaluated the effects of glyphosate on the nervous systems of neonate rats after gestational exposure. Dose-dependent changes in reflex development, motor activity, and cognitive function were observed. These results suggested that glyphosate could induce developmental neurotoxicity, as evidenced by deficits in behavioral and cognitive functions in rat pups.

Finally, it is important to discuss the effects of glyphosate on gut microbiome. The primary mechanism by which glyphosate elicits its herbicidal effects is by the inhibition of aromatic amino acid synthesis through the shikimate pathway. The shikimate pathway is absent in animal cells but exists in some microorganisms (Knaggs 2001). Mesnage et al. (2021) used a multi-omics strategy to evaluate the effects glyphosate or its commercial formulations on rat gut microbial metabolism and found that glyphosate inhibited the shikimate pathway in rat gut microbiome. The inhibition of the shikimate pathway by glyphosate can lead to the increase in shikimic acid levels. Some studies have associated shikimic acid to deleterious health effects, such as cancer development (Ma and Ning 2019). In addition, the authors observed an oxidative stress process.

Concerning articles that performed experimental assays using mammalian cells, similar effects to those demonstrated in vivo were observed. The most frequently observed effects were endocrine and reproductive disorders (Clair et al. 2012), genotoxicity (Kwiatkowska et al. 2014), and cytotoxicity (Hao et al. 2020). Human cell model experiments were conducted in most of the studies (78.5%). Mouse, rat, cow, and frog cells were used to a lesser extent.

Some studies published in high-impact journals can be cited, as exemplified by the study conducted by Clair et al. (2012). In this study, an in vitro mature rat testicular cell experimental model was used. The cells were treated with glyphosate levels permitted in human urine and European agricultural environments. The herbicide caused necrotic damage to Leydig cells and other cells. The main endocrine disorder observed at low Roundup and glyphosate concentrations (1 ppm) was a 35% decrease in testosterone levels.

Kwiatkowska et al. (2014), in an article published in Food and Chemical Toxicology, discussed on glyphosate-induced DNA damage and methylation in human blood mononuclear cells. They found firsthand that high glyphosate concentrations could induce DNA damage in leukocytes and cause DNA methylation in human cells (Kwiatkowska et al. 2014). Hao et al. (2020) associated genotoxicity and cytotoxicity with Roundup adjuvant treatment. Oxidative stress and DNA damage were observed in human lung A549 cells after treatment with the Roundup adjuvant, polyethoxylated tallow amine. These effects were not observed in cells treated with glyphosate alone.

Neurotoxic effects have also been observed in cell culture experiments. Chorfa et al. (2013) evaluated the relationship between Parkinson's disease and occupational exposure to pesticides by assessing changes in α-syn levels in human neuroblastoma (SH-SY5Y) and melanoma (SK-MEL-2) cell lines after acute exposure to different pesticides and confirmed the hypothesis that pesticides are propellants of the molecular effects associated with Parkinson's disease. Exposure to the pesticides was also associated with the occurrence of malignant melanoma (Chorfa et al. 2013).

Main effects of glyphosate in fish

The extensive use of herbicides in agriculture can cause contamination of aquatic environments, thereby affecting non-target organisms, such as fish. Aside from the loss of food supply and habitat, the toxic effects of herbicides on fish have been demonstrated. The effect most reported in the articles analyzed was hepatotoxicity (Fig. 6). Endocrine disorders (Davico et al. 2020), hepatotoxicity (Rezende dos Santos et al. 2017), genotoxicity (Rodrigues et al. 2019), neurotoxicity (Lanzarin et al. 2020), cardiotoxicity, and mortality (Lanzarin et al. 2019) have been described as toxic effects of glyphosate in fish. *Danio rerio* is one of the most commonly used species in experiments involving treatment with glyphosate and its formulations.

Nesković et al. (1996) published one of the first studies on glyphosate toxicity in fish. The specimen studied was *Cyprinus carpio L.*, an important commercial fish. High doses of glyphosate were used, and hepatotoxicity was the main toxic effect observed. There has been a significant reduction in treatment doses in recent studies. However, despite this reduction in doses, deleterious effects are still observed. For example, in the study by Davico et al. (2020), adult *D. rerio* female fish were exposed to low Roundup concentrations (0.065, 0.65, and 6.5 mg L^{-1}) for 15 days, and reproductive system toxicity was the main toxic effect observed.

Lanzarin et al. (2019) observed an increase in mortality and malformations in *D. rerio* embryos exposed to concentrations above 8.5 μg a.i. mL^{-1}. In addition, a dose-dependent decrease in heart rate, although not inducing significant developmental changes, was observed. The study demonstrated the different toxicity levels of the Roundup formulation components. The authors concluded that it is important to evaluate different toxicological endpoints and use different non-target organisms to predict the hazards of glyphosate-based formulations, their components, and breakdown products in aquatic biota.

Moustafa et al. (2016) investigated the oxidative and immunotoxic stress effects of the herbicides, Roundup (Monsanto) and Stomp (BASF) on catfish of the Nile River. This fish species is highly consumed by the local and surrounding populations. The experiment was performed on 120 fish exposed to each individual herbicide and the combination both. The results revealed a significant decrease in the phagocytic activity of fish, with elevated levels of superoxide dismutase, catalase, and glutathione peroxidase. They concluded that the combination of both herbicides led to increased toxicity by affecting the human food chain (Moustafa et al. 2016). Therefore, studies demonstrating the effects of glyphosate contamination in non-target aquatic organisms have led to discussions on food chain contamination and its possible deleterious effects.

Main effects of glyphosate in amphibians

Herbicides have been shown to be hazardous to non-target species, including amphibians. Several effects of glyphosate and its commercial formulations have been reported in amphibians (see Fig. 6). The most commonly reported effects were morphological alterations and mortality (Fig. 4). Morphological alterations and mortality (Herek et al. 2020), genotoxicity (Carvalho et al. 2019), alterations in embryonic development (Lanctôt et al. 2014), and hepatotoxicity (Riaño et al. 2020) have been associated with herbicide contamination.

Herek et al. (2020) evaluated the effects of acute and chronic exposure to commercial glyphosate formulations in two tadpole species. For chronic toxicity testing, tadpoles were exposed for over 14 days to the 2 doses permitted by the Brazilian legislation and to glyphosate concentrations found in natural environmental Brazilian and Argentinian waters. Increased mortality was observed in both studied species. Tadpoles that survived presented with growth rate and weight reduction. The maximum acceptable toxicant concentration of glyphosate for mortality and malformation was lower than the level permitted in Brazilian waters. This study demonstrated that the tested glyphosate formulation presented a high environmental and acute risk for the evaluated amphibian species.

Riaño et al. (2020) evaluated tadpole exposure to usual environmental herbicide doses for a period of 1 month. Exposure to 325 μg a.i./L caused liver histological alterations. Recent studies on the toxic effects of exposure to environmental herbicide doses warn of threats to the survival of non-target organisms. The decline in amphibian populations may be caused by the contamination of water sources in ecosystems with high anthropic activity, especially by pesticides used in agriculture (Relyea 2005). Amphibians are particularly sensitive to environmental contamination due to their high skin permeability, shell-less eggs, and the fact that some species have biphasic life cycles, with aquatic and terrestrial life stages (Wagner et al. 2015). For this reason, these organisms are key to determining the state of the ecosystem (Simon et al. 2011).

Main effects of glyphosate in invertebrates

Invertebrates have been used as experimental models in several studies on herbicide toxicity. Some of the studied organisms include prawns, crabs, bees, worms, snails, arthropods, etc. The toxic effects of herbicides observed in invertebrates are similar to those observed in other experimental models. The most common symptom reported in the studies analyzed was alteration in enzyme function (Fig. 6). Endocrine and reproductive system disorders (Suppa et al. 2020), neurotoxicity (Balbuena et al. 2015), and metabolic and gut microbiome alterations (Blot et al. 2019) were among the most observed effects.

It is worth highlighting that some studies demonstrated the action of herbicides on non-target invertebrates and their impact on the environment. Their impact on pollinating bees, which are essential for maintaining the ecosystem, is a good example of this. These bees have been affected by the increase in agricultural areas and the application of agrochemicals (Potts et al. 2010). Balbuena et al. (2015) demonstrated that infield-realistic doses inhibited the recovery of memory acquired during exploratory orientation flights, causing disorientation and deterioration of associative learning in worker *Apis mellifera* bees. Increased mortality (Abraham et al. 2018) and delay in bee development after exposure to sublethal doses of glyphosate have been reported (Vázquez et al. 2018). Blot et al. (2019) showed that glyphosate induces significant changes in the relative abundance of major gut bacterial taxa in *A. mellifera*. Interestingly, aminomethylphosphonic acid (primary degradation product of the glyphosate) did not induce any significant changes in honeybee microbiota, suggesting that glyphosate is the component responsible for gut community modification. These results indicate the production risks of current agricultural models . The use of large amounts of agrochemicals can affect biodiversity reservoirs and many non-target organisms in agroecosystems.

Water and soil ecosystems

Glyphosate can enter aquatic systems through many ways. However, information on the potential risks posed by glyphosate at environmentally relevant levels in aquatic systems remains limited (Zhang et al. 2016). Pesticides cause serious hazards to the soil environment and human health because many pesticides and their derivatives remain in the soil system for considerable periods. Most pesticides negatively affect the biological functions, diversity, composition, and biochemical processes of microbes. Pesticides can cause an imbalance in the soil microbiome, which directly affects agricultural production (Meena et al. 2020). The presence of glyphosate in the soil causes considerable changes in the growth and development of soil microorganisms. The pattern of change may vary because of differences in the exposure period, the concentration of the active ingredient in the formulation, time of exposure, and many other environmental factors (Adomako and Akyeampong 2016).

In recent years, some studies have focused on the bioremediation potential of some indigenous soil and water microorganism communities with different levels of adaptation for the degradation of glyphosate (Ermakova et al. 2010). A study demonstrated that microbial activity increased as an adaptation to the stress caused by increased herbicide concentrations over weeks of treatment. The results obtained demonstrate the potential adaptation capacity of microorganisms in soils, when large amounts of herbicides are added (Sebiomo et al. 2011). In present times, these types of studies can be performed using higher doses to verify this effect, independent of the environmentally relevant concentration.

Glyphosate inhibits the enzyme, EPSP synthase, in the shikimate pathway, which is present in plant cells and some microorganisms, but not in human or other animal cells. While the EPSP synthase of some bacteria is sensitive to glyphosate, in in vivo or in vitro dynamic culture systems with mixed bacteria, and media that resemble rumen digesta, the addition of glyphosate has been shown not to have an impact on microbial function (Vicini et al. 2019). However, this is a simplistic perspective, as when important metrics of the community are measured, the impact is shown. For instance, a study demonstrated alterations in *Microcystis aeruginosa* populations (aquatic microalgae) and a consequent increase in microcystin production at environmentally relevant glyphosate concentrations (0.1–2 mg/L). These occurred mainly because of the effects of glyphosate on *M. aeruginosa* cell density (Zhang et al. 2016). In another study, the influence of glyphosate on algal bloom development was evaluated, and a positive but non-linear relationship was found between glyphosate concentration and gold algal density at low environmentally relevant concentrations. This provided evidence of the effects of glyphosate through glyphosate-contaminated runoff discharge or the direct application in aquatic environments (e.g., to control nuisance macrophytes) (Dabney and Patiño 2018). The studies presented above clearly associated glyphosate to a decrease in environmental services, which should incite great concerns about eutrophication problems and the multiple uses of water.

A study on soil microbiota and pesticides showed a decrease in soil richness and diversity and inhibition of the nitrification process with increased pesticide concentrations (Cycoń et al. 2013). Another study showed that bacterial, fungal, and actinomycete populations decreased upon treatment with herbicides when compared to control populations. Herbicide treatment resulted in a significant decrease in soil dehydrogenase activity compared to control soil samples (Sebiomo et al. 2011). In an in situ study, glyphosate was found to have no effects on soil microbiota richness, but a decrease in functional diversity was found (Fang et al. 2009). Again, these studies showed a loss or decrease in ecosystem services.

Plants

Glyphosate has phytotoxic effects on plants. Its formulations inhibit antioxidant enzyme activities and induce oxidative stress, resulting in physiological dysfunction and cell damage. Decreased photosynthesis was observed due to increased degradation and reduced biosynthesis of chlorophyll, resulting in yellowing and necrosis of foliage (Gomes et al. 2016). However, only a small number of plant toxicity studies were found (Fig. 6).

In addition, herbicides can reduce plant resistance. Consequently, glyphosate-treated plants frequently die from infection by root pathogens that are universally present in the soil (Rosenbaum 2013). Another problem caused by the extensive use of glyphosate is weed resistance. Beilin and Suryanarayanan (2017), through a search in multidisciplinary archives, fieldwork, and interviews, sought to identify weeds resistant to glyphosate because they grew in the same fields as GM soybeans in Argentina. The main glyphosate weed-resistant range was amaranth, which has edible varieties. They are weeds with a high number of mutations and a high level of resistance to herbicides (Beilin and Suryanarayanan 2017). Owing to weed resistance, there is an increase in the dose and frequency of glyphosate being applied.

Impact of glyphosate on human health

In the 1990s, the first studies on the effects of glyphosate in humans demonstrated the symptoms of acute poisoning. Gastrointestinal symptoms, respiratory distress, hypotension, altered level of consciousness, acute renal failure, extensive chemical burns, and death have been reported (Roberts et al. 2010).

Osten and Dzul-Caamal (2017) performed an innovative study in which glyphosate residues in groundwater, bottled drinking water, and the urine of farmers in various locations in the municipality of Hopelchén, Campeche, Mexico, obtained through biomonitoring, were analyzed. The highest glyphosate concentrations were found in groundwater and the urine of rural workers. These values indicated exposure to and excessive use of glyphosate in nearby farming communities (Osten and Dzul-Caamal 2017). According to Williams et al. (2016), the prevalence rate and mean glyphosate concentration in human urine significantly increased between 1993 and 2016 from 0.00001 to 0.001 mg kg bw^{-1} 226 day^{-1}. Jayasumana et al. (2014)

hypothesized the association between glyphosate use and its unique metal-chelating properties with a chronic kidney disease epidemic in Sri Lanka. Most scientists conclude that the major health issue in rice paddy farming areas in Sri Lanka is toxic nephropathy.

Worthy of note, Aris and Leblanc (2011) evaluated maternal and fetal exposure to pesticides associated with GM foods. Blood was collected from pregnant and non-pregnant women, who were not living with their partners, working on herbicides in Sherbrooke, Canada. The diet considered included several foods, such as meat, margarine, canola oil, rice, corn, grains, peanuts, potatoes, fruits and vegetables, eggs, poultry, fish, milk, juice, tea, coffee, mineral water, soda, and beer. Glyphosate was not detected in maternal and fetal blood but was present in the blood of some non-pregnant women (5%); this could be explained by the absence of exposure, elimination efficiency, or limitations of the detection method (Aris and Leblanc 2011). In contrast, Arbuckle et al. (2001) demonstrated a significant association between preconception exposure to glyphosate-based herbicides and increased risk of spontaneous abortion.

Despite the large number of observational studies carried out on populations exposed to herbicides, the toxic effects of glyphosate in humans have been demonstrated mainly through experiments using human cell cultures, as mentioned above. The most frequently observed effects were endocrine disorders, oxidative stress, genotoxicity, and cytotoxicity.

As concerns reported symptoms related to human toxicity, the "probable carcinogenic" maxim is highlighted. The article by Dieter Schrenk (2018) provides a detailed explanation of the classification of carcinogenic chemicals. As an example, the author cites the difficulty in explaining the carcinogenicity of glyphosate in humans, as the data compared were obtained from experiments on mixed exposure to various chemicals (Schrenk 2018).

This was previously presented in a study by Jennings and Li (2017), who examined the values applied to pesticides considered to be carcinogenic or not, commonly used in world agriculture. The results showed that most of the pesticides did not follow the soil application patterns known as soil regulatory guidance values (RGVs). They finally reported that in 1991, USEPA/OPP concluded that glyphosate showed "evidence of carcinogenicity to humans." However, USEPA/IRIS denied any kind of "human carcinogenicity" (Jennings and Li 2017).

In Hardell et al. 2002 evaluated whether exposure to pesticides was a risk factor for non-Hodgkin's lymphoma (NKL) and hairy cell leukemia. In this study, glyphosate was found to be a risk factor for NHL. In Roos et al. 2003 performed an integrative assessment of multiple pesticides as risk factors for NHL among men. They found that several individual pesticides, including glyphosate, were associated with increased NHL incidence.

In 2018, Monsanto was ordered to pay $289 million in damages to Dewayne Johnson, who had non-Hodgkin's lymphoma. A San Francisco jury found that Monsanto had failed to adequately warn consumers of the cancer risks posed by the herbicide (Bellon 2018). In March 2019, a man was paid $80 million in a lawsuit for claiming that Roundup was a substantial factor responsible for his cancer. In the same year, a jury in California ordered Bayer to pay a couple $2 billion in damages after finding that the company had failed to adequately inform consumers of the possible carcinogenic effects of Roundup. Later, the sentence value was reduced to $86.7 million. In 2020, Bayer agreed to settle over a hundred thousand Roundup lawsuits (Thacker 2019). The company agreed to pay $8.8 to $9.6 billion to settle those claims and $1.5 billion for any future claims (Chappell 2020).

Legislation

The last piece of information presented concerns aspects of legislation cited in the content and bibliographic references of scientific articles. Some could not be specified because they contained only a cursory citation of some international documents and were not included in the final references of the articles (n = 38). Others did not refer to any type of government document or agency (n = 95).

Studies on treatment using continuous renal replacement therapy (Lee and Choi 2017) and the determination of the levels of glyphosate and its metabolites in emergency patients in Korea (Han et al. 2016) are examples of studies that did not contain citations, references, or content on legislation. Two articles that did not specify some type of legislation in their references can be cited; the first is the study on the toxic effects of Grassate herbicides in mollusks and earthworms (Ogeleka et al. 2017), and the second evaluated the toxicity of selected pesticides in human organelles (Huras 2016).

The European Food Safety Authority's (EFSA) technical opinions are highlighted. Among the twenty authors with the highest number of publications, Antoine Messéan, Hanspeter Naegeli, Nils Rostoks, and Christoph Tebbe (n = 4) jointly authored four EFSA technical opinions on authorizations to market GM glyphosate-tolerant soybeans for use in feed processing and as food and feed produced by Pioneer (European Food Safety Authority (EFSA) 2016), Monsanto (European Food Safety Authority (EFSA) 2015a), Bayer CropScience (European Food Safety Authority (EFSA) 2017a), and Dow AgroSciences LLC (European Food Safety Authority (EFSA) 2017b). There is also the "conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate" (European Food Safety Authority (EFSA) 2015b).

Other articles cited reports from international organizations, such as the FAO panel of experts, the WHO Basic Evaluation Group on Pesticide Residues (JMPR) (Mink et al. 2011), agrochemical assessments from agencies such as the International Agency for Research on Cancer (IARC), EFSA Technical Assessment Opinions (GMO-NL-2007-47) (European Food Safety Authority (EFSA) 2016), and other documents related to professional organizations such as the United Nations Office on Drugs and Crime (UNODC) (Rincón-Ruiz and Kallis 2013).

Another example is the study by Almeida et al. (2017) on the use of GM seeds and the increasing consumption of agrochemicals in Brazil. The relevant data presented in this study were not only obtained from the national legislation or the Brazilian Institute of Geography and Statistics (IBGE) database, but also from the International Service for the Acquisition of ISAAA database and a review monograph on insecticides and herbicides from the International Agency for Research on Cancer (IARC) (Almeida et al. 2017).

Combining data from official documents cited in the articles with their respective inference scales, the information obtained demonstrated four possible destinations for the results contained in each article, i.e., international, national, European Union communities, and local. Articles classified as unspecified ($n = 12$) were those resulting from reports or simply from comparative studies.

Articles with a national scope include those concerning nations, with the focus of these studies being research and approaches launched, e.g., the use of GM seeds and agrochemicals in Brazil (Almeida et al. 2017), the control of the main species of oilseed crops in Finland (Salonen et al. 2011), and the war between amaranth and soybeans in Argentinian cultures (Beilin and Suryanarayanan 2017). Such studies are very specific in terms of the applicability of their results.

Articles published at the local scale ($n = 68$) are those in which the methodology and experiments were carried out in a specific place, and the results of which can only serve to change everyday habits in the same circumscription, such as the population of Eastern Quebec, Sherbrooke, Canada (Aris and Leblanc 2011). Data for communities of the European Union nations are generally related to the EFSA (International Service for the Acquisition of Agri-biotech Applications (ISAAA) 2017).

Conclusion

Based on scientific literature, it was observed that countries that publish the most on glyphosate toxicity are great investors in the field of large-scale agriculture. The herbicide agents most used in scientific experiments are those of the transnational, Monsanto, which highly invests in the trade of transgenic seeds and agrochemicals.

The most prominent authors suggest that France has a high decision-making power regarding the evaluation of permissions to commercialize these pesticides in the European Union. Unfortunately, science does not provide concise data for the total disapproval of these pesticides in the global consumer market.

Earlier studies (before 2012) analyzed used doses that were not environmentally acceptable; however, even with the decrease in the dosage values after 2012, the range of symptoms identified still increased. Some glyphosate toxicity symptoms, such as reproductive and endocrine disorders and oxidative stress, have been identified in all model organisms.

The reported symptoms draw attention and raise concerns. Organic agriculture should be broadly promoted and financed by international government agencies, especially at country level. Populations must increasingly seek sustainable exit routes to produce their own food or at least reduce the consumption of GM foods and other glyphosate-contaminated foods (e.g., from preharvest application).

Finally, based data on the most produced commodities and commodities of export and production of countries with the highest number of publications on the subject, it is important to note that these countries are in the process of exploiting other aspects of the ecosystem, including not only fauna and flora, but human beings as well. Only time will tell if agricultural methods will return to a less chemical-based standard in the future.

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