Saúde e Pesquisa
DOI: 10.17765/2176-9206.2023v16n1.e11402

Exposure to the pesticide glyphosate and the occurrence of autistic spectrum disorder: is there an association?

Exposição ao praguicida glifosato e a ocorrência do transtorno do espectro autista: existe associação?

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RESUMO

O presente estudo teve como objetivo estudar a associação entre a exposição ao glifosato e a ocorrência do Transtorno do Espectro Autista (TEA). Trata-se de um estudo documental com busca de dados acerca da prevalência do TEA (Centers of Disease Control and Prevention) e de um levantamento para verificar o princípio ativo do praguicida mais usado no Brasil (Instituto Brasileiro do Meio Ambiente e dos Recursos Naturais Renováveis) e no mundo (United States Evironmental Prevention Agency). Os resultados mostraram que a prevalência do TEA aumentou ao longo dos anos. Do mesmo modo, o uso e a compra de praguicidas também aumentaram, sendo o glifosato o princípio ativo mais usado. Ainda que os resultados apontem a existência de uma relação entre a exposição ao glifosato e a ocorrência de autismo, são necessários mais estudos para afirmar o potencial neurotóxico do glifosato e sua associação com o nascimento de crianças autistas.

Palavras-chave: Autismo. Agrotóxico. Transtorno do espectro autista. Transtornos do neurodesenvolvimento.

ABSTRACT

The present study aimed to analyze the association between exposure to glyphosate and the occurrence of Autistic Spectrum Disorder (ASD). This is a documentary study with search for data about the prevalence of ASD (Centers of Disease Control and Prevention) and a survey to verify the active ingredient of the most used pesticide in Brazil (Brazilian Institute for the Environment and Renewable Natural Resources) and worldwide (United States Environmental Prevention Agency). The results showed that the prevalence of ASD increased over the years. Likewise, the use and purchase of pesticides have also increased, and glyphosate has been the most widely used active ingredient in the world. Although the results point to the existence of a relationship between exposure to glyphosate and the occurrence of autism, further studies are required to confirm the neurotoxic potential of glyphosate and its association with the birth of autistic children.

Keywords: Autism. Pesticides. Autistic Spectrum Disorder. Neurodevelopmental Disorder.

Received in December 21, 2022
Received in February 01, 2023

INTRODUCTION

Pesticides, weedkillers or bug-killers are chemical compounds intended for agricultural application, used to control living beings considered harmful, such as insects, fungi, larvae and weeds[1]. These compounds play a key role in increasing productivity, since by controlling harmful organisms, consequently, they reduce crop losses in different plantations[2]. In the context of use, Brazil is the largest consumer of pesticides in the world, and also one of the countries that most approves new agrochemicals[3]. In 2020 alone, 493 substances were registered by the Ministry of Agriculture, Livestock and Supply (MAPA), which is considered the highest number in history[4].

Among the most used pesticides in the world is the organophosphate called glyphosate, an herbicide used to control weeds[5]. Although the World Health Organization (WHO) classifies glyphosate as slightly toxic to humans, residues of this herbicide can remain in food and animals consumed by humans. Through food, as well as long-term and high-dose exposure, it can lead to chronic toxicity to exposed individuals.[6]

Despite the benefits of pesticides, their constant use in agriculture has raised questions about their consequences for both the environment and the health of the population[7]. The literature describes a series of toxic damages resulting from chronic exposure to pesticides, including various types of cancer, such as leukemia, cervical cancer, ovarian and prostate cancer, respiratory, cardiovascular, reproductive, hormonal problems and also neurodevelopmental problems[8,9,10,11]. As for glyphosate, review studies have pointed to the capacity of this herbicide to induce the proliferation of human cells, through in vitro experiments, and to generate breast cancer in women, in addition to being able to cause functional alterations in the heart, kidneys, liver and brain[12,13,14].

Glyphosate was introduced in Brazil, along with other pesticides, in the mid-1950s, however, it was only in the 1990s that clinical and epidemiological studies were initiated on the risks of exposure to chemical compounds. Its main mechanism of action in plants is to inhibit the metabolism of amino acids, it is transported throughout the plant and reaches several enzymatic systems, thus resulting in the slow death of the plant[15,16].

Similarly, pesticides can be absorbed by humans and can cause neurological disorders. Modabbernia *et al.* (2017)[17] point out that environmental factors, such as exposure to chemical compounds and pollutants, contribute about 40-50% to the development of autism.

Autistic Spectrum Disorder (ASD), popularly known as autism, is a clinical and neurological condition in which the ability to socially interact and communicate is affected, and marked by repetitive behaviors that appear in childhood, but can extend throughout adult life[18]. Although the pathophysiological causes of ASD are still unclear, genetic and environmental factors are seen as contributing conditions[19].

Some in vivo, in vitro, experimental studies in animals and observational studies in humans, such as the study by He *et al.* (2022)[20], a review including all types of study cited, have been analyzing the possible association between exposure to pesticides and the occurrence of ASD, since when there is contact with these substances at the beginning of life, especially during pregnancy or lactation, the fetus may suffer severe damage to the Central Nervous System. Bertoletti *et al.* (2022)[21] concluded, in their study, that exposure of children to pesticides, including organophosphates, is one of the environmental factors associated with a higher occurrence of ASD. Even though the neurological effects of pesticides in children have been described in the literature[22,23], few studies have analyzed the

association between exposure to glyphosate and ASD.

In this context, this study aimed to analyze data on the prevalence of ASD, the use and sales of glyphosate-based pesticides in Brazil and in the world, as well as the scientific evidence existing to date that associate exposure to glyphosate and the occurrence of ASD.

METHODOLOGY

The research is divided into two stages. The first consists of presenting data that corroborate to explain the reason for choosing the pesticide glyphosate and ASD as study subjects for this research. And, in the second part, the association between these two subjects was established.

DOCUMENTARY RESEARCH

Data and statistics about asd

Data regarding the prevalence (number of people in a population that have a condition in relation to all people in the population) of ASD were retrieved from the website of the Centers for Disease Control and Prevention – CDC[24]. This information was accessed through the indices: *Data & Stats > Autism Spectrum Disorder (ASD)* in July 2022.

Due to the fact that, until now, in Brazil, there are no official figures on the prevalence of autism[25], these data were collected from studies available in the literature.

DATA ON PESTICIDES

Worldwide, data regarding the sale, usage and active ingredient of pesticides were collected in the document "Pesticides Industry Sales and Usage 2008 – 2012 Market Estimates" available on the website of the United States Environmental Protection Agency – EPA[26]. The access to the document was carried out through the indices Pesticides > About pesticides > Sales and usage report.

In Brazil, the most recent data (2020) on the number of active ingredients of pesticides marketed in the country were retrieved from the website of the Brazilian Institute for the Environment and Renewable Natural Resources – IBAMA[27], through the indices *Boletins anuais de produção, importação, exportação e vendas de agrotóxicos no Brasil > Boletins anuais > Boletim 2020*.

LITERATURE SEARCH

Study design

The present study is an integrative literature review, a method based on bringing together several published studies in a given area of study and performing a synthesis of the general knowledge. To write an integrative review, a line of strategy was defined which is based on the elaboration of a question to be researched, establishment of criteria for inclusion and exclusion of studies, information and criteria of the studies to be selected, interpretation and presentation of the data obtained[28].

This review addressed studies relating exposure to glyphosate and ASD. To this end, the guiding question of the study was "Is there an association between exposure to glyphosate and the occurrence of ASD?".

Based on the guiding question, the "PECO" was used, with the study population (population): children of mothers exposed to glyphosate (observational studies) or offspring of mice exposed to the pesticide (experimental studies); exposure (Exposure): exposure to glyphosate; the control group (control): no

exposure to the pesticide; and the outcome (outcomes): the occurrence of ASD.

Search strategy

The search for studies was carried out in five databases: PubMed, Biblioteca Virtual em Saude (BVS), Scientific Electronic Library Online (SciELO), Science Direct and Google Scholar, from June 1, 2022 to June 13, 2022. The descriptors, in English, "autism", "autist", "autistic spectrum disorder", "asd" and "glyphosate, and also in Portuguese "autismo", "autista", "transtorno do espectro autista", "tea" and "glyphosate, combined together with the Boolean operators "AND" and "OR" ("autism" OR "autist" OR "autistic spectrum disorder" OR "asd" AND "glyphosate") (autismo" OR "austista" OR "transtorno do espectro autista" or "tea" AND "glifosato"). No filter was selected for years of publication.

Selection of studies

After searches in the five databases listed in the previous topic, from June 1, 2022 to June 13, 2022, duplicate publications were excluded. Next, the titles and abstracts were read, excluding articles that did not fit the theme of this review, and the remaining articles were read in full. In addition, to locate articles that had not been found in the databases used, a search was carried out in the reference lists of the selected articles. This selection was carried out blindly and independently by two of the authors of this review.

Eligibility criteria

Articles published in English, Portuguese and Spanish and that answered the guiding question of the study were considered eligible. Book chapters, literature reviews, dissertations, theses, monographs, books, editorials, manuals, news, reports and comments were excluded.

Data collection

After reading the full articles that met the inclusion criteria, some data were collected, which are later listed in Chart 1 and 2. Chart 2 lists general information about all the studies included in the review (author, year, country, database, title and objectives of the study), while Chart 2 contains detailed information about each selected study (author, year, type of study, control group, main results found, limitations of the study).

RESULTS

DATA AND STATISTICS ABOUT ASD

According to information provided by the CDC's Autism and Developmental Disabilities Monitoring Network (ADDM)[24], the most recent estimate, from the year 2018, is that around one in every 44 eight-year-olds has ASD. The document also mentions that ASD can affect all racial, ethnic and socioeconomic groups, and is about 4.2 times more common in males when compared to females[24]. Table 1 lists data and statistics regarding ASD in eight-year-old children provided by the CDC from 2000 to 2018.

Table 1. Data and Statistics on the Prevalence of Autistic Spectrum Disorder in eight-year-old children

Year of surveillance	Year of birth	Pooled prevalence per 1,000 children (interval between sites ADDM [1])	Conversion of data to 1 in X children
2000	1992	6.7 (4.5-9.9)	1 in 150
2002	1994	6.6 (3.3-10.6)	1 in 150
2004	1996	8.0 (4.6-9.8)	1 in 125
2006	1998	9.0 (4.2-12.1)	1 in 110
2008	2000	11.3 (4.8-21.2)	1 in 88
2010	2002	14.7 (5.7-21.9)	1 in 68
2012	2004	14.5 (8.2-24.6)	1 in 69
2014	2006	16.8 (13.1-29.3)	1 in 59
2016	2008	18.5 (18.0-19.1)	1 in 54
2018	2010	23.0 (16.5-38.9)	1 in 44

[1] Autism and Developmental Disabilities Monitoring Network
Source: *Centers for Disease Control and Prevention* (CDC), 2022.

According to the information in Table 1, the number of children with ASD has been increasing significantly in 18 years of registration. The increase in the prevalence of children with ASD is notable compared to the years 2000 and 2018, rising, respectively, from 6.7 to 23.0 in a thousand children, and following the conversion of the data, there was an increase of one in every 150 children diagnosed with ASD in 2000 to one in every 44 children in 2018[24].

In Brazil, one of the only population-based studies on the prevalence of ASD was carried out by Paula *et al.* (2011)[29], who estimated 500,000 people with ASD in the country, with a prevalence equal to 25/10,000 children born. Furthermore, the study by Salgado *et al.* (2022)[30] favors elucidating the factors on which to base the increase in the diagnosis of ASD, such as the Psychiatric Reform, advances in ASD diagnostic criteria, training of multidisciplinary teams and the epidemiological transition.

Data on pesticides in the world and in Brazil

Table 2 lists data referring to sales, usage amount and the most used active ingredient worldwide, according to the EPA.

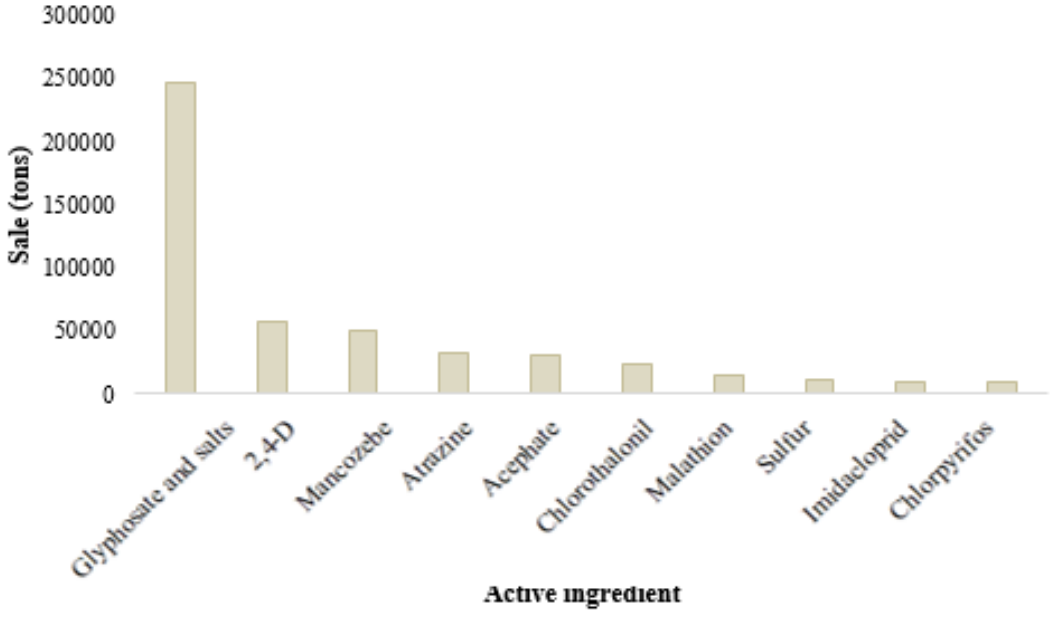
Table 2. Worldwide data on market, usage and active ingredient of pesticides

Year	World market	Usage of pesticides in the world	Most used active ingredient in the world agricultural market
	Millions $	Thousand pounds	
2012	55,921	5,821	Glyphosate
2011	52,829	5,414	Glyphosate
2010	47,171	5,177	Glyphosate
2009	46,007	5,008	Glyphosate
2008	48,842	4,850	Glyphosate

Source: *United States Environmental Protection Agency* (EPA), 2017.

According to data in Table 2, it was observed an increase in sales of pesticides worldwide, greater than 7 million dollars in five years. As for the use of pesticides, there was a linear increase between 2008 and 2012, reaching nearly 1,000 pounds over five years.

Of the pesticides marketed in 2012, almost 60% were herbicides, of which glyphosate was the most widely used representative of this class in the world this year and throughout the period from 2008 to 2012. This herbicide reached around 270 to 290 million pounds used in 2012, reality since 2001. Also, according to the EPA[26] based on an American study in 2012, about 52 million US families use herbicides, thus increasing contact with glyphosate[26]. With regard to Brazil, Figure 1 illustrates data on the sale of glyphosate in relation to the other active ingredients of herbicides used in the country.



* 2,4-D: Dichlorophenoxyacetic acid

Figura 1. Most used and sold active ingredients in Brazil in 2020.

Source: Brazilian Institute for the Environment and Renewable Natural Resources (IBAMA), 2020.

At the Brazilian level, according to information from IBAMA, glyphosate and its salts are in first place among the ten best-selling active ingredients of herbicides in the country since 2009[27].

In addition, glyphosate and its derivative salts have a significantly higher number of sales than the second place in the ranking, dichlorophenoxyacetic acid (2,4-D), with a difference of almost 200 thousand tons. In 2020 alone, glyphosate reached more than 245 thousand tons in sales, while 2,4-D around 57 thousand tons (Figure 1).

Integrative review

In the present study, a total of 2,292 articles were found in the analyzed databases, of which 2,210 were excluded because they were duplicates, totaling 82 unique records. Of these, 36 were excluded by title and/or abstract (n=46). In the full reading, 44 were excluded according to the eligibility criteria, and two articles were found by searching the references of selected articles. Thus, four articles were included in this review. Figure 2 shows the flowchart used in the selection of articles included in this review.

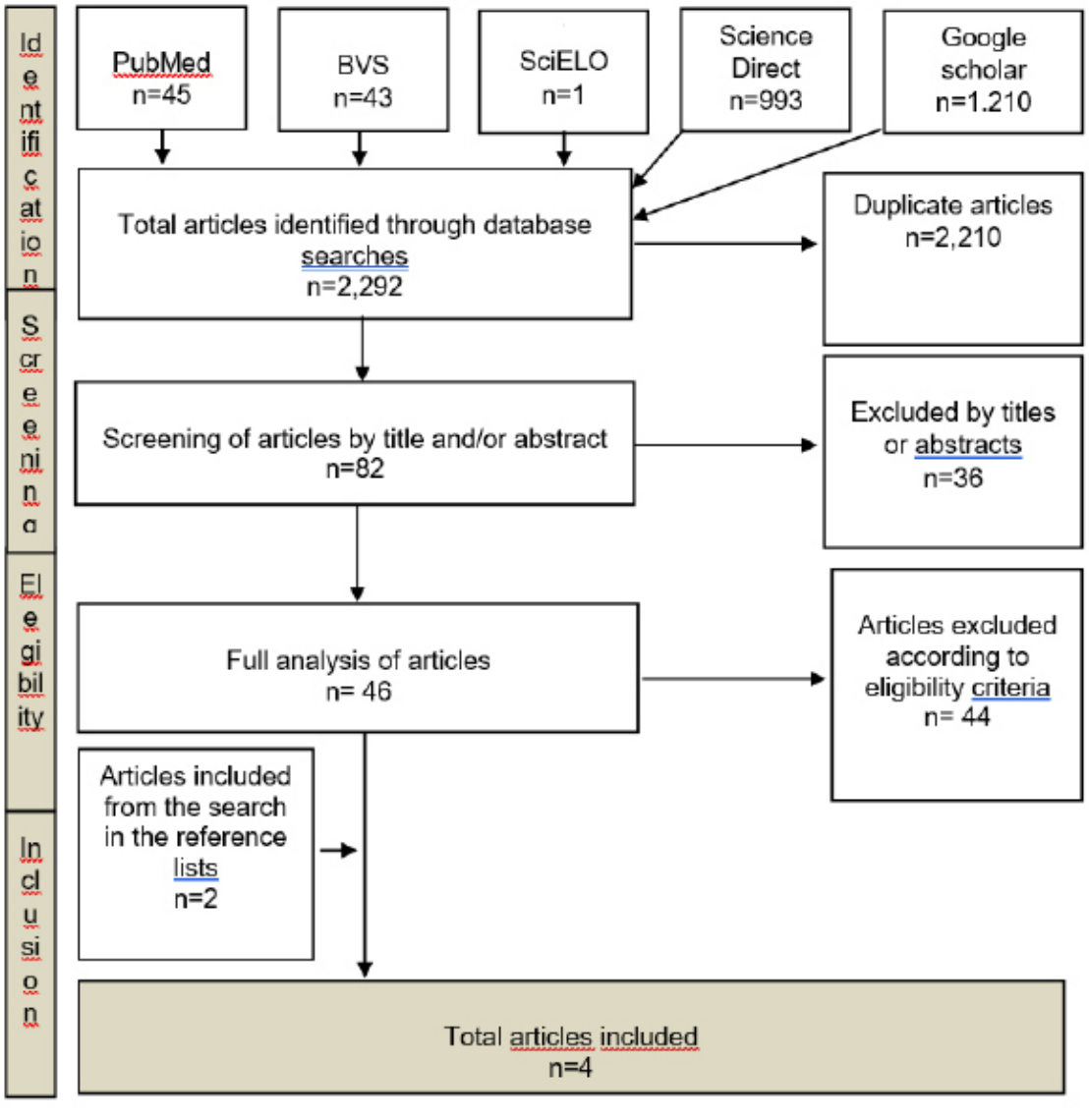


Figure 2. Flowchart for the methodology used in this integrative review.
Source: Prepared by the authors.

Chart 1 presents general data about the articles selected to the present study. In addition, the corresponding table shows that the selected articles are recent and that all studies were carried out in the United States (Chart 1).

Chart 1. General information about selected articles

Author/ year	Country	Database	Title	Objectives
PU *et al.* (2021)	United States	Gray literature	Autism-like Behaviors in Male Juvenile Offspring after Maternal Glyphosate Exposure	To analyze whether maternal exposure to pure glyphosate can cause ASD-like behaviors.
PU *et al.* (2020)	United States	Gray literature	Maternal glyphosate exposure causes autism-like behaviors in offspring through increased expression of soluble epoxide hydrolase	To examine the role of soluble epoxide hydrolase in the pathogenesis of ASD in offspring after maternal exposure to glyphosate.
VON EHRENSTEIN *et al.* (2019)	United States	Pubmed	Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children: population based case-control study	To examine associations between early exposure to environmental pesticides and ASD.
SHAW (2017)	United States	Pubmed	Elevated urinary glyphosate and Clostridia Metabolites with altered dopamine metabolism in triplets with autistic spectrum disorder or suspected seizure disorder: A case study	Determine excess glyphosate present in triplets and their parents and evaluate findings to determine potential effects.

Source: Prepared by the authors.

Chart 2 below lists, in detail, the information present in the selected articles.

Chart 2. Detailed information on each of the studies selected in this review that link exposure to glyphosate and the occurrence of Autistic Spectrum Disorder (ASD)

STUDY		METHOD		RESULTS	
Author/ year	**Type of study**	**Participants**	**Control group**	**Main findings**	**Study limitations**
PU *et al.* (2021)	Experimental study	Female, pregnant mice housed in cages and their male offspring	Female, pregnant mice treated with drinking water only	Mice exposed to glyphosate showed deficits in social interaction compared to control mice and data obtained suggest behavior similar to ASD in male offspring after exposure to glyphosate during pregnancy	Study analyzed only male offspring, since the highest prevalence of ASD is concentrated in male mice.
PU *et al.* (2020)	Experimental study	Female, pregnant mice (E5) and male mice separated from their dams at weaning (P21)	Female, pregnant mice treated with drinking water only	High concentrations of glyphosate during pregnancy cause ASD-like behaviors in male offspring; The highest concentration of soluble epoxide hydrolase in the prefrontal cortex was found in animals treated with glyphosate, in relation to the control group; Changes in the intestinal microbiota of male mice exposed to glyphosate.	Not specified
VON EHRENSTEIN *et al.* (2019)	Population-based case-control study	2,961 individuals diagnosed with ASD, including 445 with comorbid intellectual disability, identified through birth records	Controls derived from birth records were matched with cases 10:1 by sex and year of birth	Study suggests that the risk of having children with ASD is higher after prenatal exposure to environmental pesticides within 2,000 meters of the mother's residence during pregnancy, compared to women in the same region without such exposure; ASD risk was associated with prenatal exposure to glyphosate; For ASD with intellectual disability the estimated odds ratios were about 30% higher for prenatal exposure to glyphosate	The study relied only on available birth addresses and 9-30% families could have moved during pregnancy; No information on exposure to pesticides, or other sources, such as diet or occupation; No information about passive and active smoking
SHAW (2017)	Case study	03-year-old triplets, 02 boys (with autism) and 01 girl (suspected seizure disorder) and their parents.	Reference values for glyphosate in urine	All triplets had high levels of glyphosate in their urine; The 02 boys with autism showed abnormalities in at least 01 test of organic acids and elevated phenolic compounds; The girl with a suspected seizure disorder did not present any of these results, however, there was a significantly higher value of the metabolite tiglylglycine, a marker of mitochondrial dysfunction and/or mutations.	Not specified

Source: Prepared by the authors.

All four studies included in this review, observational[31,32] or experimental with animals[33,34] (Pu *et al*., 2021; Pu *et al*., 2020) were evaluated in relation to offspring (offspring) with exposure of mothers to the glyphosate-based herbicide (Chart 2).

Pu *et al.* (2021)[33] carried out a study on the social analysis of male mice exposed to glyphosate at 0.098% during pregnancy and lactation, in relation to mice that had the same period mentioned in treatment only with drinking water. Mice (pregnant females) were kept in separate cages from male offspring. Each mouse was placed separately in a transparent box to perform a social interaction test lasting 10 minutes, timed and recorded by three video cameras. After that time, a strange mouse was placed in the box along with the test mouse and sociability was evaluated for another 10 minutes. Finally, one more strange mouse was placed in the box for social evaluation for another 10 minutes. After analyzing the videos taken from the experiment, a deficit of social interaction was concluded in the male offspring exposed to glyphosate.

The study by Pu *et al*. (2020)[34] followed the same method as the study above. However, the way of evaluating data differed in blood and tissue analysis (from the central nervous system) of male rats exposed to glyphosate, and the concentration of glyphosate was 0.38% (wt/vol) during pregnancy and 0.39% (wt/vol) during lactation. According to the study, the concentration of 0.39% (wt/vol) resulted in 100% mortality. With that, a new concentration of 0.098% glyphosate was used in the lactation of the mice and the result was a lower weight of dams in relation to the control group treated with water, and a deficit in social interaction in the male offspring. Furthermore, mice exposed to glyphosate during pregnancy and lactation showed higher expression of soluble epoxide hydrolase (sEH) in the prefrontal cortex and lower concentrations of epoxy fatty acids. According to the study, this favored the increase of inflammatory reactions. In addition, changes were found in the intestinal microbiota of the test mice, with a smaller number of bacteria capable of using the shikimic acid pathway.

Von Ehresntein et al. (2019)[31] presented results based on pregnant women who live within 2,000 meters of agricultural services and are exposed to pesticides and women not exposed. Glyphosate was the herbicide most related to the birth of children with ASD including intellectual disability comorbidity with an odds ratio of 1.60 during pregnancy, 1.09 before pregnancy and 2.34 after birth compared to other pesticides, such as diazinon (1.45; 1.11 and 1.89), malathion (1.29; 1.00 and 1.65) and bifenthrin (1.33; 1.03 and 1.72). According to the study, exposure in the three months prior to pregnancy had weaker associations with ASD than exposure during pregnancy or in the first year of life. Exposure to glyphosate during pregnancy increased the odds of ASD by 10% (1.16; 95% confidence interval 1.06 to 1.27), while exposure to other pesticides dropped below[1]. And, finally, greater chances of ASD with intellectual disability were reported at 30-40% in prenatal exposure or after birth to glyphosate and the other pesticides mentioned above (Chart 2).

Shaw (2017)[32] conducted tests with toxic chemicals, organic acids, and glyphosate in the urine of triplet participants on a non-organic diet as a possible source of glyphosate exposure. One of the triplets, male, showed loss of developmental ability and after metabolic tests, showed elevated aspartate aminotransferase (AST), which is a marker of mitochondrial dysfunction for ASD. Triplet 1 was diagnosed with ASD at 34 months of age. Triplet 2, also male, lost some developmental skills that had already been gained at 25 months of age and was diagnosed

with ASD. The female triplet had a suspicious condition of seizures and developmental delay up to two years of age. Immunoenzymatic tests (ELIZA) were performed to detect glyphosate and all children excreted this herbicide in the urine at high doses of 34.4 micrograms glyphosate/gram creatinine (μg/g), before the organic diet provided by their parents, with a median value of 1.35 μg/g. The mother's glyphosate levels were 6.7 μg/g and the father's within normal limits. After an organic diet, glyphosate in the urine of triplet 2 dropped to 2.25 μg/g and the children's mother concluded that the new diet reduced their stress and irritability and complaints of fatigue (Chart 2).

DISCUSSION

The results found in this documentary research demonstrate the increase in the prevalence of ASD at an international level (Table 1), as well as the growing number of sale and usage of pesticides worldwide over the years (Table 2). In addition, glyphosate was the main active ingredient of pesticides used both in Brazil (figure 1) and worldwide (Table 2).

Epidemiological information on the prevalence of ASD in Brazil and in other Latin American countries is questionable because it presents data obtained from few studies[35], which leads to a large difference between the available data. Based on the most current results (2018) of ASD prevalence internationally published by the CDC, the estimate is that one in every 44 children are autistic, and transposing this prevalence (2.3% population) to Brazil, it is estimated that there are about 4.84 million autistic people in the country[25].

Although until now there is no database about ASD in Brazil, in 2019, Law 13861 was enacted, which includes ASD in the demographic census carried out by the Brazilian Institute of Geography and Statistics (IBGE), starting in 2022[36]. In the same year, bill 969/2019 established the Census of People with Autism Spectrum Disorder and their Families Program, which will bring great advances to the analysis of the prevalence of this disease. In addition, federal law 12764/2012, which ordered the National Policy for the Protection of the Rights of Persons with Autistic Spectrum Disorder, underwent changes in 2020, Law 13977, which included the Identification Card for Persons with Autistic Spectrum Disorder (CIPTEA), in order to guarantee integrated care and priority in care and access to public and private services[30].

All studies included in the literature search demonstrated the association between mother exposure to glyphosate and the occurrence of ASD in offspring/children. According to Dong *et al*. (2022)[37], pesticides, in general, cause serious health effects, especially in cases of mothers and fetuses. The exposure of pregnant women to pesticides culminates in transfer through the placenta and breastfeeding after the birth of the baby, this study proved the presence of high secretion of pesticides in the breast milk of women living in an exposure zone for at least five years, becoming a public health case[37].

Along with the growing consumption of pesticides, in Brazil and in the world, the number of children diagnosed with ASD has also been increasing[38]. In addition to genetic factors, studies indicate that the older parents' age and, above all, exposure to toxins resulting from environmental pollution influence the predisposition to the occurrence of ASD. The latter case is exhibited through mutagenic and genotoxic evidence in humans and animals from the breakage of DNA double strands promoted by exposure to pollutants[39].

It is possible to associate exposure to pesticides, mainly glyphosate-based herbicides,

with the neurodevelopmental disorders characteristic of ASD, based on the occurrence of cellular oxidative stress generated by the toxic agent. It is believed that the association between ASD and exposure to environmental pollution caused by glyphosate is due to direct interaction with genetic material, impaired DNA repair or oxidative damage. Environmental toxicants are capable of double bonding hydroxyl to nucleobases of DNA and abstracting hydrogen atoms from the carbon-hydrogen bonds of 2'-deoxyribose and the methyl groups of thymine nucleotides, resulting in DNA changes[13,39].

Although ASD does not have a well-defined etiology, it is related to damage to the development of the nervous system[40]. In the literature, the study by Souza et al. (2019)[41] elucidates the association between the occurrence of ASD through the mechanism of oxidative stress and inflammation of the cortex and cerebellum caused in animal cells due to exposure to glyphosate. Increased oxidative stress causes increased expression of reactive oxygen (ROS) and nitrogen (RNS) species, responsible for the maintenance and death of cortex cells. This increase in ROS and RNS makes the CNS prone to attack by free radicals and consequent neurodevelopmental disorders, since exposure to glyphosate results in a decrease in the expression of enzymes that combat oxidative stress: enzyme superoxide dismutase 1 (SOD1) and 2 (SOD2), catalase and glutathione.

The uncontrolled formation of ROS and RNS imply the induction of an inflammatory response in the CNS, however other globular proteins act in the detoxification control of ROS and RNS, called neuroglobin, cytoglobin, hemoglobin and myoglobin, responsible for carrying oxygen. However, neuroglobin and cytoglobin have their expression reduced together with SOD1 and SOD2 and other enzymes responsible for controlling oxidative stress, after cortical analysis of rats exposed to glyphosate in the aforementioned study[41].

On the other hand, there are other hypotheses for the mechanism of occurrence of ASD associated with exposure to glyphosate, during pregnancy and lactation. The increase in the concentration of soluble epoxide hydrolase in the prefrontal cortex, due to the reduction in the plasma concentration of epoxyeicosatrienoic acid, parallel to the increase in its concentration in tissues, induces behavioral neurological damage after the induction of maternal immune activation. In addition, glyphosate inhibits the shikimic acid pathway, responsible for the production of essential amino acids for animals, but absent in human cells, acquired through food[42]. However, the shikimic acid pathway is carried out by microorganisms and, taking into account the abnormality caused in the intestinal microbiota of humans by glyphosate, aromatic amino acids cannot be synthesized in the organism. As a result, the precursor of tyrosine, tryptophan and phenylalanine, chorismate, is not synthesized, preventing the formation of secondary metabolites such as ubiquinone, menaquinone, tannins and flavonoids[43].

Although the results found suggest that there may be an association between exposure to glyphosate and the occurrence of ASD, further studies are required in order to make it possible to trace an association between the increasing usage of pesticides, in particular glyphosate, and the increase in children with the disease studied.

Some limitations during the development of this study, such as the low number of studies relating the potential of glyphosate to trigger ASD, the lack of a national database to notify the number of autistic children born and registered in the country, and the difference in the periods analyzed regarding the prevalence of ASD (2000-2018), sale and usage (2008-2012) and the most used active ingredient in Brazil (2020), make it

difficult to draw an assertive association between the data.

CONCLUSION

This study demonstrated that both the number of people with ASD and the usage of pesticides has been growing over the years, in which glyphosate is the most used active ingredient in Brazil and in the world during the analysis period.

Although the data found suggest an association between glyphosate exposure and ASD characteristics, experimental data including neurological toxicity and the consequent occurrence of ASD are still scarce. Therefore, further studies are required to prove this association.

Such information is extremely important so that, once a possible association is proven, actions are carried out to raise awareness among the population, especially pregnant women. And so that preventive measures are also taken, through greater inspection by regulatory agencies, which analyze whether the level of this pesticide in food, made available for human consumption, is within the maximum residue limit allowed. These actions allow pesticides to be used rationally, especially glyphosate, thus avoiding the occurrence of harmful effects on human health.

ACKNOWLEDGEMENTS

The authors would like to thank the Federal University of São João del-Rei, Centro-Oeste Dona Lindu campus (UFSJ/CCO) for their support.

FINANCING SOURCE

This work was carried out with the support and funding of the Minas Gerais Research Foundation (FAPEMIG, process APQ-01220-22), and the Coordination for the Improvement of Higher Education Personnel – Brazil (CAPES) – Funding Code 001.

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