Pre and postnatal exposure to glyphosate-based herbicides and potential neurodevelopmental outcomes: a systematic review of animal and epidemiological studies

Article *in* Toxicological Research · May 2025

DOI: 10.1007/s43188-025-00294-z

7 authors, including:

Nathália Ribeiro Dos Santos
Federal University of Bahia
34 PUBLICATIONS **390** CITATIONS
SEE PROFILE

Homègnon Antonin Ferréol Bah
Henry Ford Health System
27 PUBLICATIONS **155** CITATIONS
SEE PROFILE

Victor Martinez
Federal University of Bahia
20 PUBLICATIONS **151** CITATIONS
SEE PROFILE

Daisy Oliveira Costa
Federal University of Bahia
17 PUBLICATIONS **92** CITATIONS
SEE PROFILE

Toxicol Res.
https://doi.org/10.1007/s43188-025-00294-z

Online ISSN 2234-2753
Print ISSN 1976-8257

REVIEW ARTICLE

Pre and postnatal exposure to glyphosate-based herbicides and potential neurodevelopmental outcomes: a systematic review of animal and epidemiological studies

Nathália Ribeiro dos Santos[1,2] · Homegnon Antonin Ferréol Bah[1,3,4] · Erival Amorim Gomes-Júnior[1,5] · Victor Otero Martinez[2] · Daisy Oliveira Costa[2] · Elis Macedo Pires[1] · José Antonio Menezes-Filho[1,2,3,5]

Received: 14 October 2024 / Revised: 2 March 2025 / Accepted: 23 April 2025

Abstract

Emerging evidence indicates potential adverse effects on infant neurodevelopment from exposure to glyphosate during prenatal and postnatal periods. This systematic review examines the scientific literature to explore links between prenatal/postnatal glyphosate exposure and neurodevelopmental abnormalities in humans and non-humans. Twenty-five original articles were reviewed, focusing on the following descriptors: glyphosate-based herbicides, pre and postnatal exposure, and neurodevelopmental outcomes. Risk of bias assessment was conducted to quality of studies. Experimental studies commonly used tests such as open field and novel object recognition, while epidemiological studies relied on medical records for diagnoses of conditions like depression and autism-like behavior. Surprisingly, only one experimental study directly measured glyphosate levels, and one of the epidemiological studies included a biomarker measure. In rodents, GLY exposure was associated to impaired cognition, motor function, memory, as well as ASD and anxiety-like behavior. In fish models, impairment of swimming activity was predominant. Overall, findings suggest possible associations between glyphosate exposure and neurodevelopmental deficits, emphasizing the need for further research to comprehend the extent of glyphosate's impact on developmental functioning.

✉ Nathália Ribeiro dos Santos
nathalia.ribeiro.farma@gmail.com

1 Laboratory of Toxicology, College of Pharmacy, Federal University of Bahia, Salvador 40170-115, Brazil

2 Graduate Program in Pharmacy, Federal University of Bahia, Salvador 40170-115, Brazil

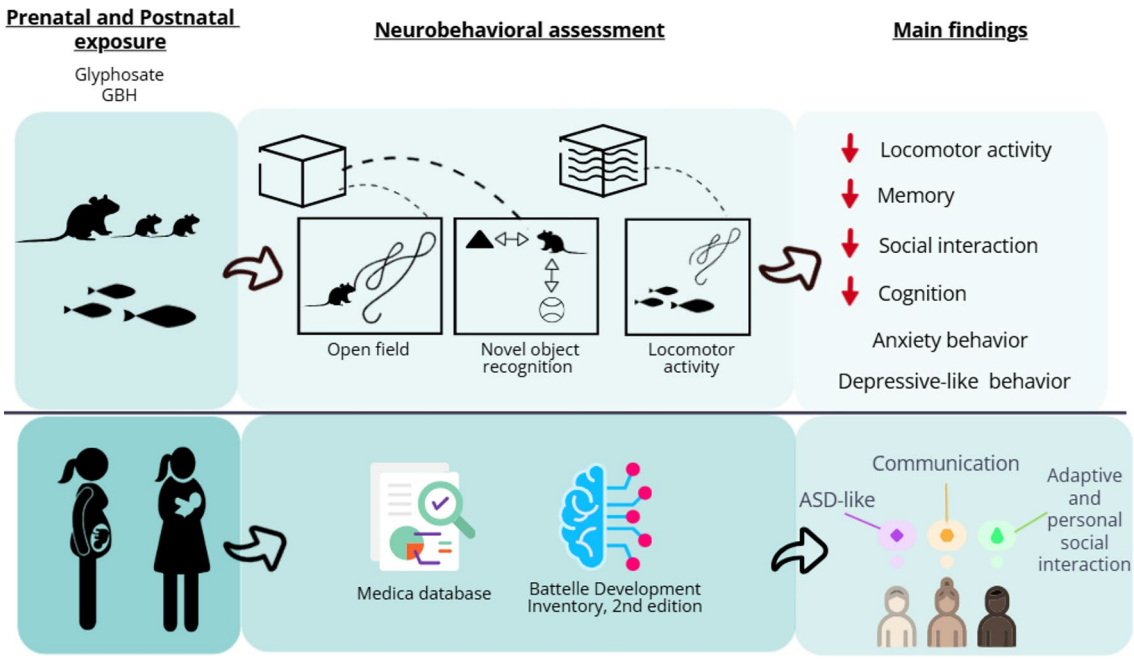
3 Graduate Program in Collective Health, Federal University of Bahia, Salvador 40110-040, Brazil

4 Department of Public Health Sciences, Henry Ford Health, Detroit 48202, USA

5 Graduate Program in Food Science, Federal University of Bahia, Salvador 40170-115, Brazil

Published online: 09 May 2025

Graphical abstract



Keywords Prenatal care · Child development disorders · Maternal exposure · Pesticide exposure

Introduction

Pesticides have been widely used globally to increase agricultural production and protect crops. However, they are recognized as environmental and food chemical contaminants associated with health problems for humans and animals. Evidence indicates that adult exposure to pesticides is linked to carcinogenic, reproductive, immunological, genotoxic, and neurological effects [1–3]. Recent epidemiological studies have reported higher risks of reproductive effects and impairments in children's neurodevelopment due to prenatal and postnatal pesticide exposure, affecting the early stages of fetal and infant brain development. A high prevalence (17%) of developmental disabilities (DD) also has been observed in individuals aged 3–17 years [4] and the proportion of children diagnosed with any DD in the United States rose from 7.4 to 8.5% [5]. Additionally, a recent study found that 12% of Brazilian children up to 5 years old exhibited suspected delayed development and did not show behaviors or abilities expected for their age [6].

Glyphosate (GLY, N-phosphonomethyl-glycine) is a systemic and non-selective herbicide used in various commercial pesticides known as glyphosate-based herbicides (GBH) [7]. GLY is the most widely used herbicide worldwide, including in Brazil, with its use having increased significantly over the past five years due to more favorable political conditions. This increase in use means that a significant portion of the population is potentially exposed to it. Problems have also aroused such as the development of glyphosate-resistant weeds prompting farmers to spray higher amounts of GLY or mix it with other toxic chemicals such as 2,4-D [8]. Several concerns have been raised regarding its intense agricultural use due to the severe environmental and human health impairments it may cause, as residues are increasingly being detected on consumed food items [9] and drinking water supplies [10].

The North Carolina Birth Defects Monitoring Program (USA) found a positive association between higher GLY levels and heart defects [11]. Parvez et al. [12] showed a significant correlation between GLY urine levels and shortened gestational length but not fetal growth indicators, while the Pregnancy Environmental Exposures Study associated increased GLY levels during the first trimester with lower birth weight and a higher risk or neonatal intensive care unit admission [13]. Spontaneous abortions later in pregnancy have been linked to perinatal GLY exposure on an Ontario farm in the USA [14]. However, none of these studies investigated neurodevelopmental outcomes. Other studies have examined pregnancy exposure and neurobehavioral effects, but during adolescence and adulthood [15, 16].

Research into the neurotoxicity mechanisms of GLY exposure during pregnancy and lactation began only a few years ago with experimental studies [17] and still little is known. The central nervous system (CNS) of children is more susceptible to environmental contaminants than that of adults, making this a critical window of development [18–22].

Williams and collaborators [23] reviewed GLY exposure and its impact on developmental and reproductive outcomes, assessing various outcomes, including spontaneous abortions, neural tube defects, congenital disabilities, fetal deaths, miscarriages, infertility, and time to pregnancy. This current review primarily focuses on neurobehavioral outcomes.

The relationship between prenatal or early postnatal exposure to GLY and infant neurobehavioral outcomes remains limited and inconclusive, highlighting critical gaps in this knowledge. Our research group is currently conducting a Birth Cohort study called DSAN-12 m (Socio-environmental Determinants of Neurodevelopment at 12 months), investigating GLY pre and postnatal exposure and its relation to neurodevelopment in children. We identified the need for this review aiming to synthesize the existing evidence and pinpoint future research directions. Due to limited information regarding GLY exposure during pregnancy and its impact on children's neurodevelopment, we systematically reviewed the available literature to examine the relationship between prenatal and postnatal GLY exposure and its effects on neurodevelopment in both humans and non-humans.

Methodology

Search strategy

A systematic review was conducted using the PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) to guide the preparation of the study. It was researched in the available scientific literature studies that have examined *uterus* and postnatal exposure to glyphosate compounds and its relation with neurobehavioral outcomes in offspring. Medline (National Library of Medicine, Bethesda, MD, USA), Scopus (Elsevier, Oxford, UK), Scientific Electronic Library Online (São Paulo, Brazil), LILACS (Latin American and Caribbean Literature in Health Sciences, São Paulo, Brazil), and Web of Science (Thomson Reuters Scientific, Clarivate Analytics, Boston, USA) databases were searched.

The following descriptors were used: glyphosate or glyphosate-based herbicides, prenatal and postnatal exposure, children neurodevelopment, infant neurodevelopment, and neurobehavioral.

After the search, title and abstract of all articles were read and those duplicated or as a review were excluded. The methodology was evaluated as well as their outcome assessed. Then, the studies went through a full reading and separated by epidemiological (humans) and experimental (non-humans) categories. Two researchers worked independently to perform the searching and analyses.

Inclusion and exclusion criteria

Articles selected for this review met the following inclusion criteria: (a) original research articles; (b) full-text; (c) published between the years 2000 and 2024; (d) written in English, Spanish, or Portuguese; (e) epidemiological and experimental studies; (f) evaluating prenatal and postnatal exposure to glyphosate and neurodevelopmental outcomes in children or animal offspring.

The main neurodevelopmental parameters searched were attention deficit disorder, autism spectrum disorder, and behavioral, cognitive, and social interaction alterations. Experimental studies that had carried out at least one test to assess these parameters were included in this review.

Studies approaching parameters such as birth outcomes or abnormalities, immunochemical or gene expression but did not apply any behavioral test were not considered for this review.

Risk of bias assessment

Risk of bias in the included studies was assessed using the SYRCLE's (SYstematic Review Centre for Laboratory animal Experimentation) risk of bias tool for animal studies [24] and The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case–control and cross-sectional studies [25], and cohort studies [26]. We also used additional guidance from the Cochrane Collaboration's tool for assessing risk of bias in animal studies [27] and from JBI Manual for Evidence Synthesis for epidemiological studies [28].

Basically, for SYRCLE tool evaluates ten items across to six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases. Each study was categorized as having "low risk" of bias ("yes") if there was clear evidence supporting specific criteria, "high risk" ("no") if there was evidence contrary to expectations, or "unclear" if the information provided was insufficient for judgment or not reported.

For the evaluation of epidemiological studies, the JBI Critical Appraisal tools were used, considering the responses "yes," "no," "unclear," and "not applicable." The biases assessed included selection, measurement, confounding, outcome assessment validity, and statistical analysis.

This analysis provides valuable insights into the reliability of study outcomes and guides future research

toward more rigorous and unbiased methodologies. Each study was independently assessed by two reviewers. Any discrepancies in judgments were resolved through discussion to reach a consensus. If consensus could not be reached, a third reviewer acted as an arbiter.

Results

A total of 323 articles were found, 135 were duplicates and were excluded, other 35 were review-type of study, abstracts of poster presentation, letters and were also excluded. After reading the title and abstract, 128 articles did not address the topic of interest and were excluded. Finally, twenty-five met the eligibility criteria and were included in the presented review. From these, twenty-two assessed prenatal and postnatal exposure to GLY in vivo (sixteen using rodents and six using fish models), and three were epidemiological studies. Experimental studies were, basically, conducted in Argentina (4), Brazil (8), Marocco (3), United States (4), Japan (1), China (2), Portugal (1), France (1) and Germany (1), while all three epidemiological studies were carried out in the United States. Figure 1 represents a PRISMA flow diagram that summarizes the process conducted to select the articles.

Risk of bias assessment

In our assessment of animal studies, we found varying levels of bias across the studies reviewed (Fig. 2). Only two studies detailed the type of randomization used for sequence generation, while all others did not or failed to mention it altogether, increasing risk of bias (question 1). To create similar groups at baseline, all studies reported at least the age and housing conditions of pregnant rats and in offspring before exposure, so they were considered as low risk of bias (question 2). A total of 20 studies showed an unclear risk of allocation concealment (question 3) because they did not

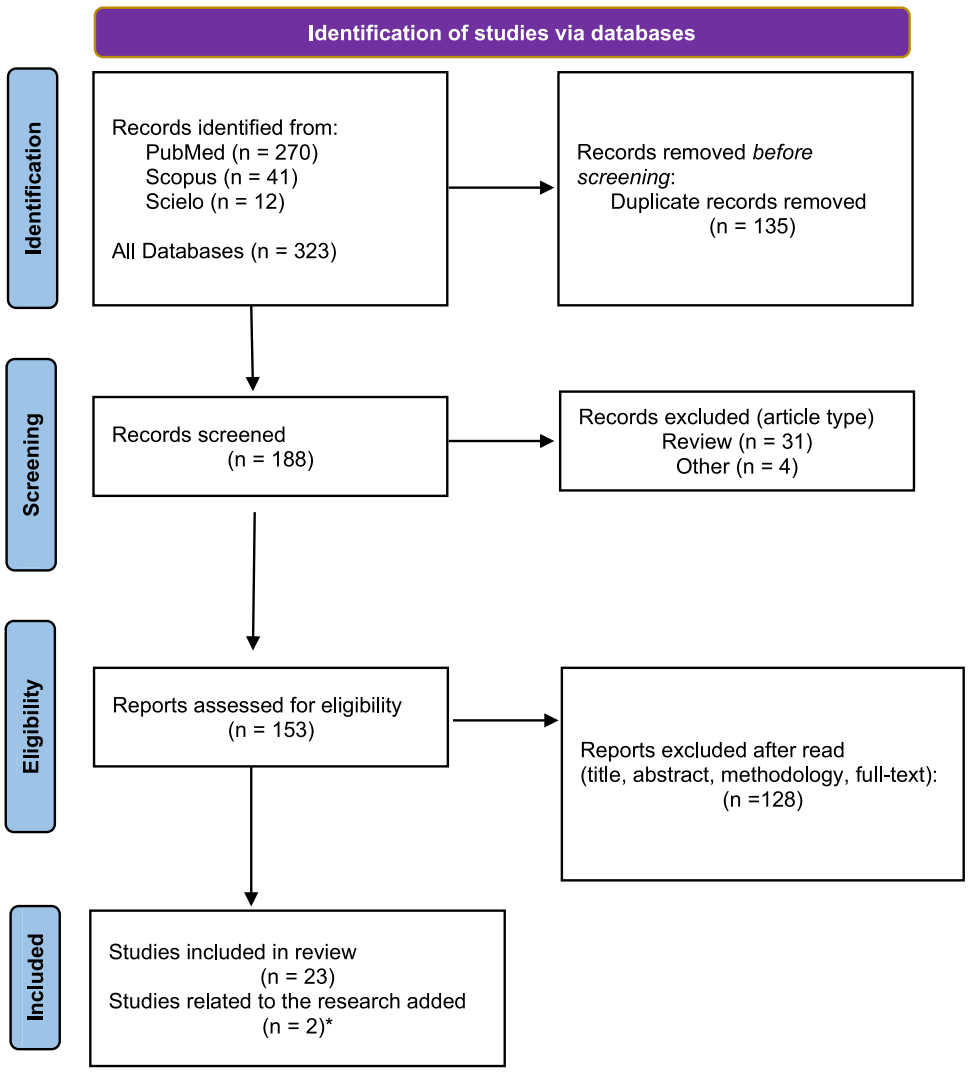


Fig. 1 Scheme of PRISMA flow diagram of the process for selecting articles discussed in this review. Note: *studies that were found a part the research, but went through the same entire PRISMA method

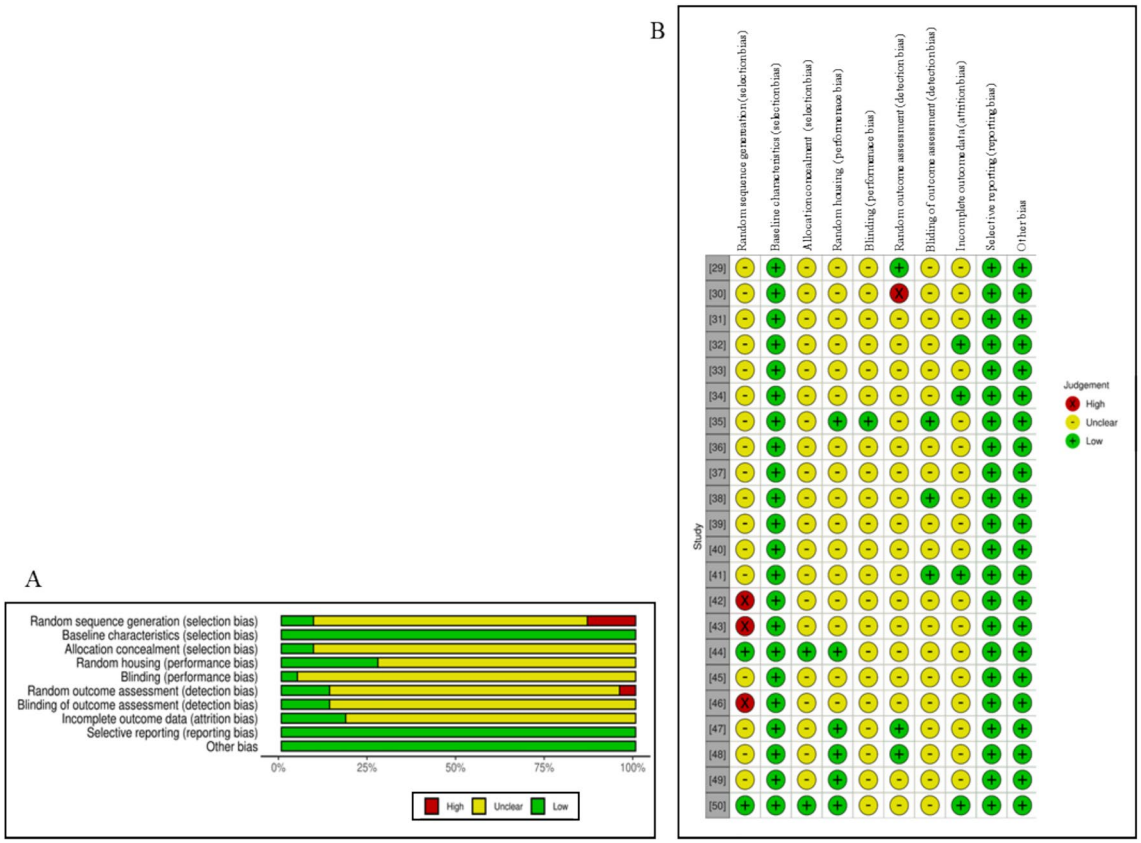


Fig. 2 Risk of bias for experimental studies. Overall RoB for each item in the SYRCLE tool for included studies (**a**). Individual RoB for each included study (**b**)

specify whether the investigator was unaware of the next treatment allocation.

Regarding performance bias (question 4, 5), most of the studies were not clear about their random housing of animals or blinded investigators, that could directly influence animal behavior and outcome assessment. They superficially mentioned that animals were randomly housed either individually or in small groups but did not specify any other characteristic, and did not make clear of blinding caregivers or did not even mention it. Only six of them specified the type randomization used and one study mentioned about blinding caregivers.

For detection bias (question 6, 7), most studies were unclear because they did not provide sufficient information about randomly picking animals during outcome assessment or blinding outcome assessor despite of well describing their methodology. About incomplete outcome data (question 8), for eighteen studies it was unclear whether all animals were used in the analysis, while only 4 studies were considered low risk which authors reported the total animals used for each test. In addition, there were studies that only mentioned if there were mortality or other loss but did not report how they handled it. All studies reported the expected outcomes (question 9) and appeared to be free of other problems that could lead to a high risk of bias (question 10) (Fig. 2A and B); Table S1 in Supplementary material).

Regarding epidemiological studies, all of them presented a low risk of bias assessment since they described all the standard information required (Table S2 in Supplementary material). However, we considered the exposure measure (question 3) as high risk of bias since they just interviewed parents use of pesticides or used informatic tools for estimating exposure, and not literally measured pesticide levels in biological matrices. Only one study measured biomarkers of exposure in biological matrices.

Experimental studies

Table 1 presents details on the behavioral tests applied, their purpose, a brief execution, and interpretation of the results, as reported by each study in this review. In summary, the tests were conducted to evaluate the following aspects: proprioceptive abilities, motor skills, reflex development, locomotor activity, emotionality, anxiety, depressive-like behavior, recognition memory, social interaction,

Table 1 Main characteristics and purpose of applied neurobehavioral tests, from the reviewed articles

Neurobehavioral test applied	Aim of test	Execution and interpretation
Righting reflex	Proprioceptive abilities	A rat is placed on its back on a tabletop, and the time taken to right itself through 180° is measured Longer time to regain an upright position – worst evaluation
Cliff aversion	Integrity of their motor output and sensory input Vestibular imbalance	A rat is placed with its nose and foreleg over the edge of a wooden platform, and the time spent moving away from the cliff is recorded Longer time: worst evaluation
Negative geotaxis	Reflex development Motor coordination	A rat is placed on an inclined wood plane with its head facing downwards, and the time spent to change its orientation (face up) is recorded Longer time: worst evaluation
Open field	general activity levels, gross locomotor activity, exploration habits and emotionality	A rat is placed in a box arena and allowed to move freely. Its behavior is analyzed as well as time spent in the central area e amount of access to the central area Lower levels of locomotion mean anxiety-like behavior
Plus-maze	Anxiety e locomotor levels	A rat is placed in a maze with an open roof and four elevated arms (two arms open and two arms closed – forming a plus sign) to freely explore it and other areas. Open arms represent unprotected and exposed area situation and closed arms mean protected and enclosed areas situation Increased time spent in open arms: anti-anxiety-like behavior (explore aversive, open spaces)
Forced swimming	Study of depressive-like behavior	A rat is placed in a tank filled with water, and its behavior (immobility, swimming, climbing) is analyzed Increased immobility time/decreased climbing time: worsen evaluation
Rotarod test	Motor coordination and balance	A rat is placed on a rod that rotates at a low speed. If it loses balance and falls, the rod stops, and the latency to fall and the speed is recorded Decreased time: worst evaluation
Novel object recognition test	Recognition memory	In the first moment, a rat is placed in an empty box. Later, the animal is placed in a similar arena with two objects to explore. In a second moment, the same happens but with one different object to test recognition memory. The time exploring and discriminating it is recorded Less time and lower discrimination: worst evaluation
Three-chambered sociability test	Social interaction	A rat is placed in the middle of a chamber. In the left side, rat 1 is placed under a wire cage; right side is empty (1st moment). Plastic rat (or other real rat), now, is placed in the right side (2nd moment). Time that the test rat spends in each side and sniffing the other rats is measured Less time with conspecific rat: worst social interaction
Y-maze	Willingness to explore new environments. Working memory performances	A rat is placed in the center of a Y-shaped maze to explore the 3 arms freely. The number of entries in arms and alternation was recorded Reduced number: worst evaluation
Passive avoidance test	Learning and memory	A rat is placed in a two-compartment chamber: one gives an electrical mild foot shock, and the other does not. A rat with regular learning and memory will avoid entering the side with foot shock. The latency to cross between sides is recorded Decrease of latency: worst evaluation

Table 1 (continued)

Neurobehavioral test applied	Aim of test	Execution and interpretation
Grooming test	Anxiety, stress, neurological disorder	A rat is placed in a cage, and its behavior is observed. The time spent in self-grooming was counted Increased grooming time: ASD-like behavior
Locomotor activity	Locomotor ability	A rat is placed in activity chambers and allowed one hour of free exploration, and the total activity and time spent in the center of the arena is measured Reduced exploratory activity: worst evaluation
Pre-pulse inhibition (PPI)	Startle reflex (involuntary contractions of whole-body musculature by sudden and intense stimuli)	Different levels of pulse or no stimulus are given to a rat. The amount of PPI is expressed as the percentage decrease in the startle reactivity amplitude caused by the prepulse's presentation Reduced pre-pulse: worst evaluation
Morris water maze test	Spatial learning and memory	A rat is placed in a pool of water and required to find a hidden platform using spatial cues. The rat has to learn the location of the platform Standard learning and memory: decreased time to find the platform and more time spent in the target space where the platform used to be
Conditioned fear test	Emotional memory	A rat is placed in a new environment, introducing an aversive stimulus and re-exposing the animal to the same environment. Its freezing behavior (as a response to fear) is observed Longer freezing behavior: stronger fear memory
Marble-burying	Anxiety and compulsive-like behavior	A rat is placed in an empty cage (1st moment) and then with 20 dark glass marbles (2nd moment). The number of marbles with the most area covered with bedding was counted More marbles buried: repetitive behavior
Homing behavior test	Social cognitive abilities mediated by olfactory responses	It measures the pup´s ability to find the nest when displaced from it. The time to locate and enter the nest side is recorded Increased latency to reach dam's shavings: worst evaluation
Hole-board test	Repetitive movements	A rat is placed in a squared arena with a black background and 16 holes, and its behavior is observed. The number of head dips is registered Increased number of head dips: repetitive behavior
Social play behavior	Social and play interaction	Two animals with no social experience are placed in a test cage, and their behavior is observed. The time of social play is measured Reduction time in social interaction: delay in maturation of the early social interaction
Play fighting behavior	Social behavior	The behavior of rats kept isolated or in a group previously and then put together to assess how social interactions and isolation impact the play their behavior. Pinning behavior, rotation, attacks, counterattacks, dodges, and immobility are measured Impaired pinning behavior/fewer attacks and counterattacks/ higher immobility: decreased social behavior ability
Light dark test	Anxiety-like behavior	A chamber with two compartments (dark and bright) is used. A rat can move freely between them. The number of transits into the lit and the latency to enter the lit is measured Reduced number of transitions to the light compartment: anxiety-like behavior

Table 1 (continued)

Neurobehavioral test applied	Aim of test	Execution and interpretation
Locomotor activity in fish model	Locomotor function	Fish into a multi-well plate incubator. Locomotor behavior observed in dark and light environment Reduced movement: hypoactivity Increased movement: hyperactivity
Social interaction in fish model	Social interaction	The distance between individuals in the group is measured, and also the distance to the closest individual (known as inter-individual distance and nearest neighbor distance) Higher distances: impaired social interaction ability, social avoidance, anxiety-like behavior
Response to stimuli in fish model	Risk perception	A Microsoft PowerPoint presentation with visual different stimulus moving on the half of the screen was presented. Also, periods of dark and light were conducted to evaluate anxiety-like behavior Higher number of fish that remained in the stimulus area: reduced risk perception

Information obtained from the studies to be discussed

exploratory skills, learning and memory, social behavior, repetitive movements, and swimming pattern.

Firstly, regarding rodents models, Gallegos et al. [29] evaluated the neurobehavioral effects of chronic exposure to GBH during pregnancy and lactation of rats and found that offspring exposed to GBH exhibited a significant decrease in locomotor activity, as evidenced by crossing fewer squares in the open field test. In the plus maze test, 45-day-old female and 90-day-old (both male and female) offspring that were treated with GBH showed reduced anxiety-like behaviors, as indicated by spending more time in the open arms.

On the other hand, Cattani et al. [30] investigated the effects of sub-chronic exposure to GBH on neurochemical and behavioral parameters in immature and adult rat offspring. Their study revealed that GBH exposure led to increased immobility time in the forced swimming test, indicating a depressive-like profile, as evidenced by decreased climbing time. However, no significant effects were observed on locomotor activity.

Complementing the previous study, Gallegos et al. [31] explored the neurotoxic mechanisms of chronic GBH exposure during pregnancy and lactation. The study revealed that adult offspring perinatally exposed to GBH exhibited impaired recognition memory, as indicated by reduced exploratory ability compared to control animals in the novel object recognition test.

Similarly, Ait-Bali et al. [32] assessed the developmental impact of GBH exposure on female mice during pregnancy and lactation. Behavioral tests revealed that GBH exposure led to a slower righting reflex and shorter fall-down latencies in traction and rotarod tests at both 250 and 500 mg/kg doses, and higher negative geotaxis time and slower cliff avoidance at 500 mg/kg. Attesting these animals motor and sensory development impairment. In the open field test, the 500 mg/kg group showed a significant decrease in distance traveled, showing poor locomotor activity. Additionally, these mice spent less time in the elevated plus maze, presenting higher anxiety index. Social interaction was reduced, and novel object recognition test revealed less exploration of the novel object.

Interestingly, as an innovative approach, Pu and collaborators [33] explored the role of soluble epoxide hydrolase (sEH) in the pathogenesis of autism spectrum disorder in offspring mice prenatally exposed to GLY and its effects on maternal behavior. Blood GLY levels were measured in both mothers and male offspring. Offspring exposed to GLY showed cognitive impairment in recognition tests and social interaction deficits in the three-chamber test. Additionally, the sHE expression in brain areas of prenatally exposed mice was significantly higher compared to controls, suggesting that sEH may play a role in behavioral outcomes observed in this context.

Coullery et al. [34] investigated the effects of early postnatal GLY exposure on the neurobehavior of rat offspring and assessed its impact on the Wnt5a-CaMKII pathway, which is involved in embryonic development. This study found that GLY exposure led to delayed righting reflex and longer time in the negative geotaxis test, indicating impaired reflex development in neonates. Additionally, locomotion and memory were adversely affected in GLY-exposed groups. The findings also suggested that GLY exposure could downregulate Wnt5a-CaMKII pathway activity in the brains of embryonic rats, potentially contributing to neurodevelopmental issues.

Luna et al. [35] interestingly assessed if postnatal GLY exposure-induced cognition impairment was related to changes in synapse formation and maturation. Results showed that GLY exposed pups spent less time exploring

the novel object recognition test, and they also had longer time to locate the hidden platform, as well as when it was removed, suggesting that the learning and memory abilities were impaired.

Pu et al. [36] examined whether maternal exposure to pure GLY could induce autism spectrum disorder (ASD)-like behavior in male offspring. Mice prenatally exposed to GLY exhibited increased grooming time and demonstrated social interaction deficits compared to the control group, suggesting ASD like abnormalities.

Another study by Del Castilo et al. [37] investigated the impact of low doses of GLY exposure on the developing brain, and assessed behavioral changes in adult mice. Their study found no alterations in locomotor activity, anxiety behaviors, or spatial memory acquisition. However, mice exposed to GLY exhibited decreased social interest and increased repetitive behavior.

de Oliveira et al. [38] introduced a rat model to investigate the impact of perinatal exposure to GBH on neurodevelopmental disorders. In the Homing behavior test, both female and male offspring exhibited increased time to reach the dam's shavings suggesting impaired olfactory discrimination used to initiate social behaviors. In the Hole board test, GBH-exposed offspring showed an increase in the number of head dips, indicating repetitive movements. The Social Play Behavior test revealed a reduction in social play behavior among GBH-exposed offspring. Additionally, in the Object Recognition Test, males in the GBH group displayed reduced short-term and long-term object recognition compared to controls.

Ricci et al. [39] investigated the impact of perinatal exposure to GLY on behavior in rats. Their study, particularly in the playing fighting behavior test, revealed differential effects of GLY on male and female offspring. GLY impaired pinning behavior in female offspring. They also exhibited lower aggressive behaviors (attacks and counterattacks) and higher immobility time, indicating reduced mobility compared to males. No significant differences were observed in the open-field test.

Recently, Buchenauer et al. [40] explored the impact of GLY exposure during pregnancy and lactation on offspring behavior. Their findings suggest that maternal exposure to GLY had a more noticeable effect on the neurobehavior of female offspring, resulting in depression and anxiety-related behaviors. The study also noted changes in sociability among female offspring, while male offspring did not exhibit alterations in sociability in response to glyphosate exposure.

Carneiro et al. [41] investigated the effects of toxicity in mice offspring that were exposed to GBH during the intrauterine period. It was observed increased hyperactivity in the open field test and increased anxious behavior in the Marble-burying test for those exposed to GLY.

Anarghou and collaborators [42] conducted a study to determine the behavioral effects of GBH during gestation and lactation in mice. Their findings revealed that offspring exposed to both 25 and 50 mg/L of GBH exhibited increased anxiety behavior, impaired sociability, memory and learning deficits. These effects were evidenced by a lower number of entries in the Y-maze alternation test, decreased object recognition, increased time spent in the periphery of the open field test, and social deficits in the social interaction test. Notably, maternal behavior was also adversely affected by GBH exposure.

El Hamzaoui et al. [43] investigated the impact of exposure to GBH during gestation and lactation on behavioral disorders and memory deficits in rats. In the open field test, GLY exposure reduced time spent in central area and number of returns to the center parameters. In the forced swimming test, pre- and postnatally exposure increased immobility time. In the Y-maze test, pre- and postnatally exposure decrease the percentage of alternation in both females and males. In the Morris water maze, GBH exposed spent much more time finding the platform (spatial learning). Altogether, theses finding showed anxiety and depressive-like behavior in offspring, as well as impairment in memory.

He and collaborators [44] maternally exposed mice to GBH and evaluated the effects on ASD-like behaviors. Offspring prenatally exposed to GBH presented impaired interaction behavior as evidenced by the three-chamber social test. Additionally, offspring exposed to 0.25%, 0.50% and 1% GBH exhibited increased number of repetitions and grooming time, and buried more marbles, as observed by the T-maze, buried marbles, and grooming tests, showing repetitive behavior. Furthermore, the open field test showed that offspring exposed to GBH presented decreased number of entries and duration, indicating anxiety-like behavior.

Fish models were also used to explore the association between GLY exposure and neurobehavioral outcomes in offspring. Zhang et al. [45] investigated GLY exposure in larval Zebrafish and its impact on behavioral analyses. Results showed that there was an increase in locomotor activity during day time in groups exposed to GBH as increased activity and decreased resting were observed in the activity behavior test.

Forner-Piquer et al. [46] evaluated GLY exposure in Zebrafish larvae and its effect on locomotor behavior. Regarding exposure concentrations varying from 0.05 to 10.000 µg/L, the ones higher than 1000 µg/L revealed impairment on their locomotor activity considering distance traveled, velocity, number of rotations and body mobility, which were all decreased.

Lanzarin and collaborators [47] assessed Zebrafish embryos exposure to GBH formulation and its impact on behavioral performance. Exploratory behavior in larvae

exposed were considered similar to control group and there were no changes in social behavior. In the stimulus response test, the higher exposed GBH group presented reduced fear behavior. In the group exposed to the highest concentration of GBH (5 µg/mL) it was observed changes in swimming activity with decrease traveled distance. Interestingly, this study measured GLY concentrations used in the exposure experiment, by fluorescence spectrophotometer, as well as measuring it in 100 larvae.

Furthermore, Pompermaier et al. [48] aimed to describe the effects of GBH exposure on larval behavioral in Zebrafish. As results, in the open field test, the exposed GBH group increased number of rotations, time spent and entries in central zone, and distance traveled, while in the aversive stimulus test a greater number of larvae remained in the stimulated area than control group. All these together reflects a hyperactivity, anxiolytic-like behavior, and impaired avoidance capacity of risk situation in those GBH exposed.

Recently, Moraes and collaborators [49] evaluated pure GLY exposure in early life of Jenynsia multidentate (fish) and its effect on locomotor function, and they observed that GLY exposure caused altered swimming performance, with reduced travel distance and velocity, as well as hypolocomotion in light conditions (for all concentrations tested) and in dark (in both 30 and 100 µg/L). This same research group, Moraes and colleagues [50], assessed the effects of chronically exposed fish model (Jenynsia lineata) to pure GLY and a formulated GBH form (RTR) on locomotor activity. Offspring exposed to GLY showed higher distance traveled and velocity, meaning a hyperlocomotion pattern. On the other hand, offspring exposed to RTR showed decreasing distance traveled and velocity (hypolocomotion). It is noteworthy that GLY concentration measurements were conducted in each treatment solution using a high sensitivity instrument, High Performance Liquid Chromatography with Diode Array Detection (HPLC–DAD), by this group.

Table 2 shows a schematic summary of studies with animals presenting their general characteristics, such as animal models, treatment, outcome measures, and main findings.

Epidemiological studies

In the cross-sectional study by Garry et al. [51], it was provided more detailed information on the reproductive health of pesticide applicators and their families, from 1997 to 1998 in Red River Valley, Minnesota, USA. They had access to the licensed applicators at that time frame and randomly selected individuals or subjects to answer a general health and pesticide use survey. Every vital medical record and birth anomalies were registered, and confounding variables such as maternal smoking, drinking age, and chronic diseases were examined. This study also evaluated family disease history, the medication used during pregnancy, and nonmedicinal drug use. The authors observed that when parents reported applying GLY, there was a significant association with a higher likelihood of neurobehavioral disorders occurring in their children. Specifically, the odds ratio (OR) was 3.6, which means that the risk of developing such disorders was almost four times higher in the group of parents who manipulated GLY compared to those who did not.

In a case–control study by von Ehrenstein et al. [52], the associations between early developmental exposure to pesticides and autism spectrum disorder (ASD) were evaluated in California's Central Valley, an agricultural region. The study used birth data from 1998 to 2010 from the Office of Vital Statistics and ASD records from the state Department of Developmental Services. The control group was randomly selected, matching the birth year and sex of the cases. An algorithm was developed to generate period-specific averages of pesticide use based on geocoded residential birth addresses, covering periods before gestation, during gestation, and the first year of life. The study found that exposure to GLY during pregnancy and infancy was associated with a 10% increase in the odds of ASD (OR = 1.16, 95% CI = 1.06–1.27). Furthermore, ASD cases with intellectual disability showed even more significant increases in odds, with ORs ranging from 30 to 40% for exposure during pregnancy and infancy.

A recent birth cohort study was conducted in Puerto Rico to investigate the relation between prenatal GLY exposure and early childhood neurodevelopmental impacts [53]. Participants were recruited at mean of 14 weeks of gestation and born-children were monitored through 4 years of age. GLY and AMPA were measured in maternal urine at three time-points during pregnancy. Neurobehavioral assessment of children was conducted using The Battelle Developmental Inventory, 2nd edition in Spanish (BDI2) at 6, 12 and 24 months-old. Authors found no significant associations at 6 months. However, at 12 months, negative associations were observed between AMPA and receptive communication. In addition, at 24 months, also negative associations were observed, especially with AMPA, affecting expressive and receptive communication scores, cognitive scores (regarding attention and memory, and perception and concepts subdomains), as well as adaptive and personal-social domains. Furthermore, both AMPA and GLY were linked to fine motor performance at 24 months. Additionally, GLY was associated with the expressive subdomain at 24 months. In summary, this study suggested that prenatal exposure to glyphosate is related with neurodevelopmental impairment in children.

Table 3 summarizes the epidemiological studies, presenting their general characteristics, such as country of origin,

Table 2 Studies of animal exposure, in both rats and fish models, during pregnancy and main neurodevelopmental findings

Animal model/ Strain	Period of exposure	GLY/GBH formulation	Treatment (dosage of exposure)	Behavioral assessments	Main findings	References
Rodents' models						
Wistar rats	From pregnancy until weaning (GD 0 to PND 21)	Glifloglex®	Pregnant: control group received tap water; GBH group 1: 0.65 g/L (0.065%); GBH group 2: 1.30 g/L (0.13%), in drinking water	Righting reflex, cliff aversion, negative geotaxis, open field, plus-maze Behavioral tests were applied on PND 45 and 90	Both PND 45 and 90 offspring exposed to the two GBH concentrations presented decreased locomotor activity and anxiety behavior	[29]
Wistar rats	Pregnant rats: from GD 5 until PND 15 or up to PND 60 Offspring: in utero and PND1 to PND 21	Roundup Original®	Pregnant: control group received tap water. GBH group: exposed to 1% GBH in drinking water (corresponding to 0.36% of GLY)	Forced swimming, open field, rotarod Behavioral tests applied on PND 60	Depressive-like behavior was observed by the forced swimming test which showed that GLY exposure increased the immobility time in the test and decreased climbing time	[30]
Wistar rats	From GD 0 until PND 21	Glifloglex®	Pregnant: control group received tap water, GBH-1: 0.65 g/L (100 mg/kg/day) and GBH-2: 1.30 g/l (200 mg/kg/day)	Novel object recognition test Memory test applied on PND 90	Female rats showed impaired memory for both doses of GLY and in male rats exposed to higher GLY dose	[31]
Swiss mice	From GD 0 until PND 21	Roundup®	Pregnant: control group received tap water; GBH lower dose group: 250 mg/kg; GBH higher dose group: 500 mg/kg	Negative geotaxis, righting reflex, cliff avoidance, and rotarod tests. Open-field, elevated plus-maze, three-chambered sociability, Y-maze, novel object recognition, and passive avoidance test Behavioral tests: PND 60	GBH caused a deficit in motor development in offspring treated with both 250 mg/kg and 500 mg/kg. At an adult age, the exposed groups showed impairment in locomotor activity, sociability, learning. Memory was impaired only in the group with higher dose	[32]
ddY mice	From GD 5 to PND 21	Roundup® Maxload	Pregnant: received water or formulated glyphosate (0.1, 0.25, 0.50, 0.75, 1.0%)	Locomotor activity, novel object recognition, PPI, three-chamber social interaction, grooming Behavioral tests between PND 28 and PND 35	Offspring after maternal glyphosate exposure showed cognitive and social interaction deficits, mainly with 0.25% treated group Increased activity of sEH might play a role in ASD-like behavior	[33]

Table 2 (continued)

Animal model/ Strain	Period of exposure	GLY/GBH formulation	Treatment (dosage of exposure)	Behavioral assessments	Main findings	References
Wistar rats	From GD 8 until GD20	40% water solution GLY salt	Pregnant: control received vehicle; GLY 24 mg/kg, and the other group received GLY 35 mg/kg	Righting reflex test, negative geotactic reaction; locomotor activity. Morris water maze test, conditioned fear test Behavioral test from PND 25 Expression level of Wnt5a-CaMKII in brain tissue	GBH caused inhibition of the Wnt5a-CaMKII signaling pathway and affected developmental reflexes, motor activity, and cognitive function, in a dose-dependent manner	[34]
Wistar rats	From PND 7 to PND 27	40% water solution GLY salt	Control group: PBS GBH exposed groups: 35 and 70 mg/kg	Novel object recognition and Morris water maze	Both GLY–treated pups presented impaired learning and memory functions	[35]
ddY mice	From GD5 to PND21	GLY standard solution	Pregnant mice were treated with water or 0.098% GLY	Grooming test and three-chamber social interaction Behavioral tests performed from PND28 to PND 35	Prenatal GLY exposure caused behavioral alteration in male offspring suggesting a relation with ASD-like event	[36]
Swiss mice	From pregnancy, lactation, weaning until offspring adulthood	Roundup®	Female mice were treated with 0.075% w/v GBH. Control received regular drinking water	Open field test, novel object recognition test, social approach test, marble burying test, and Morris water maze Behavioral tests were done between PND 60 and PND 80	GBH exposure led to decreased social interest and repetitive behavior, sex- specific	[37]
Wistar rats	From GD 0 to PND 22	Zapp QI 620 Syngenta®	Female control (oral gavage with 5 mL/kg of saline per day) and GBH (oral gavage with 50 mg/kg saline solubilized GBH per day)	Offspring Homing behavior test (PND 13); and hole board, social play behavior, open field, and object recognition tests (PND 28–32) Maternal behavioral tests from PND 2 to 6 Offspring behavioral tests from PND 28 to 32	Perinatal GBH exposure induced impairment on social play behavior, repetitive behavior, social interaction time and early cognitive abilities on offspring	[38]

Table 2 (continued)

Animal model/ Strain	Period of exposure	GLY/GBH formulation	Treatment (dosage of exposure)	Behavioral assessments	Main findings	References
Wistar rats	From GD 15 to PND 7	Roundup Transorb®	The doses administered were 50 and 150 mg/kg of GLY. Control group received water	Play fighting behavior, open field behavior and social interaction test Behavioral tests on PND 31 and PND 90 to 95	In the playing fighting behavior, both doses showed lower levels of aggressive behaviors in females, and less mobility was also observed more in females compared to males, at 50 mg mg/kg	[39]
Balb/cByJ mice	From before mating with males until weaning of the pups	GLY standard solution	Pregnant control: received distilled water Exposed group: 0.5 and 50 mg/kg/day of GLY	Open field test, three-chamber test and light dark test Behavioral tests from week 9 in offspring	GLY exposure to 50 mg/kg/day induced depression and anxiety type behavior, and also, social deficits, mainly in female offspring	[40]
Swiss mice	From GD 1 to GD 18–22	Roundup Original®	Pregnant control group: distilled water Exposed group: GLY at 0.3 mg/kg	Open field, social interaction, Y-maze, and Marble-burying Behavioral tests on PND 25–28	Prenatal exposure to GLY may induce hyperactivity and anxious behavior in mice offspring	[41]
Swiss albino mice	Daily from GD0 to PND21	Roundup®	GLY formulation: 25 or 50 mg/L of GBH Control group: non-treated water	Open Field, Y-maze, object recognition task, and social interaction tests Behavioral tests on PND23	For both treated groups, GBH exposure resulted in altered memory, decreased object recognition, and increase in anxiety behavior. Only the 50 mg/kg GBH exposed group presented reduced social interactions	[42]
Wistar rats	From mating until weaning on PND21	Barbarian Super 360	GLY formulation: Control group: NaCl GBH-exposed group: 75 mg/kg	Open field, elevated maze, Y-maze, forced swimming, Morris water maze Behavioral tests on PND58	GBH during gestation and lactation caused anxiety and depressive-like behavior in offspring	[43]
BALB/c mice	From GD 0 to PND21	Roundup Maxload	Control group: normal purified water, GBH-exposed groups: 0.10%, 0.25%, 0.50%, and 1.00%	Grooming test, T-maze test, Buried marbles test, Three-chamber social test and Open field test Behavioral tests on PND 24 and PND 41	Exposure groups, mainly 0.25%, 0.50% and 1.0%, reduced social interaction, repetitive, anxiety and ASD-like behaviors	[44]
Fish models						

Table 2 (continued)

Animal model/ Strain	Period of exposure	GLY/GBH formulation	Treatment (dosage of exposure)	Behavioral assessments	Main findings	References
Zebrafish (AB strain)	From 0.75 to 96 hpf	GLY analytical standard	Exposed groups: 0.01, 0.1. 0.5, 1, 5, 10, 100, 200, 400, 600 mg/L Control group: 0 mg/L	Diel activity behavior assay of larvae conducted from 96 to 144 hpf	GLY exposure contributed to increased locomotor activity, at lower concentrations of 0.01, 0.5 and 5 mg/L	[45]
Danio rerio (Zebrafish)	From 1.5 to 120 hpf	GLY analytical standard	Exposure concentrations: 0.05, 0.1, 0.5, 1, 10, 100, 1000, 10.000 µg/L	Locomotor behavioral activity conducted at 120 hpf	Equal or higher level than 1000 µg/L GLY exposure presented impaired locomotion activity: distance, velocity and mobility were decreased	[46]
Danio rerio (Zebrafish)	From 2.5 to 75 hpf	RoundUp® UltraMax	Exposed groups: 0, 1, 2 and 5 µg/mL	Behavior, exploratory patterns, social interaction, response to stimulus Conducted at 144 hpf	GBH exposure caused negative impact in swimming activity and changes in behavior in the presence of an aversive stimuli, in offspring exposed to 5 µg/mL	[47]
Danio rerio (Zebrafish)	From 3 to 120 hpf	Roundup®	Exposed group: 4.8 µg/L	Open field and aversive stimulus test were conducted at 6 and 7 day-post fertilization, respectively	GBH exposure caused hypermobility and anxiolytic-like behavior	[48]
Jenynsia multidentate (fish)	Offspring with 20 and 24 h of age were exposed for 96 h	GLY Pestanal® analytical standard	GLY formulation: Control group: filtered dechlorinated tap water with a salinity of 5.0 ppt Exposed groups: 30, 65, and 100 µg/L	Locomotor activity was conducted during the last hour of exposure	GLY exposure altered the swimming function of fish, with reduced travel distance executed at 30 µg/L, and velocity in all concentration during light. In the dark, activity was reduced at 30 µg/L and increased at 65 µg/L	[49]
Jenynsia lineata (fish)	Mature and virgin fishes exposed for 21 days	GLY Pestanal® analytical standard and Roundup Transorb R® (RTR)	Control group: water at salinity 5 ppm Exposed groups: 65 ug/L of GLY standard and 65 ug/L of RTR	Locomotor activity conducted with offspring at 120 h post-birth	Prenatal exposure of GLY caused hyperlocomotion, while GBH resulted in hypolocomotion in offspring	[50]

PND postnatal day; *hpf* hours post-fertilization; *GD* gestational day

Table 3 Studies on prenatal and postnatal exposure to GLY and neurodevelopmental outcomes in children

Study design	State, country	Study population	Exposure assessment	Behavioral assessment	Main findings	References
Cross-sectional	Minnesota, USA	Pesticide applicators and their partners Live births fathered by a pesticide applicator = 536 Family participants = 695	Self-reported pesticide application by interview	Medical record examination data	GLY exposure was associated with children's neurobehavior 43% of children who had parent-reported ADD/ADHD used GLY	[51]
Case–control	California, USA	2961 cases with ASD diagnosis, including 445 with intellectual disability comorbidity; 339.210 controls	Mathematically estimated based on birth addresses geocode, pesticide applications (data, location, amount)	Records of Autism spectrum disorder were retrieved from the California Department of Developmental Services database	GLY prenatal exposure was associated with a higher risk of ASD (odds ratio 1.16, 95% confidential interval 1.06 to 1.27)	[52]
Birth cohort	Puerto Rico, northern region, USA	PROTECT ongoing research 143 mother–child pairs	GLY and AMPA measurement in maternal urine by GC–MS/MS	Battelle Developmental Inventory, 2nd edition in Spanish (BDI2) was applied in children at 6, 12 and 24 months of age	GLY gestational exposure was associated with children's communication, cognitive, adaptive and personal social impairment, regarding both 12 and 24 months-old	[53]

ADD/ADHD attention deficit disorder/attention deficit hyperactivity disorder

study design, sample size, exposure assessment, behavioral assessment instrument, and the main findings of each study.

Discussion

While the number of articles explicitly examining the association between prenatal GLY exposure and neurodevelopmental outcomes in humans and non-humans is limited, the available evidence consistently suggests that both intrauterine and postnatal GLY exposure can affect neurobehavioral outcomes in offspring and infants, including cognitive and motor impairments.

First, regarding the quality of the animal studies reviewed, all presented well and easy understanding described protocols. However, they required improvement in reporting standardized information necessary for risk of bias assessment, as indicated by the SYRCLE tool. Despite of all the given information, studies still need to detail and make some points clear for the quality enhancement. It is crucial for future research to address these methodological weaknesses to increase the validity of preclinical animal studies and minimize potential biases. In contrast, all epidemiological studies reported the required and sufficient information to be assessed as having a low risk of bias assessment.

Among the studies reviewed, only the experimental study conducted by Pu et al. [34] measured GLY concentrations in the blood of dams and their offspring, using this as a biomarker of exposure. The measurement of GLY levels in exposure studies is critical for accurately assessing the actual exposure, establishing dose–response relationships, correlating exposure with health outcomes, and ensuring the validity of research findings. Notably, only one of the epidemiological studies included in this review measured GLY in the biological matrices of participants [53], while the other two did not. This issue represents a current limitation in epidemiological studies related to exposure estimation and the study of its relationship with neurobehavioral outcomes. Other studies have previously assessed GLY concentrations in human biological samples but for different endpoints [54–58].

Regarding studies conducted using fish models to investigate GLY exposure on larvae/embryo and behavior, three of them measured GLY concentrations in water where the experiments were conducted [47, 49, 50]. This analysis is important to ensure that the actual concentration of exposure aligns with the intended concentration for the experiment. Notably, only one study reported concentrations higher than those expected in the beginning of the experiment, while later on the experiment a decrease was observed and GLY absorption in larvae was taken into consideration [47].

For rodents models, we found that only two studies evaluated GLY exposure, exclusively, during pregnancy [34, 41]. Also, that only two studies initiated exposure before mating females with males [40, 43]. In contrast, all other studies began exposure at started pregnancy continuing mostly until PND 21. Behavioral tests were primarily conducted from PND 25, with the latest applications occurring at PND 90. For fish models, exposure to GLY involved larvae/embryo of fish and the period of exposure was considered in hours post fertilization (hpf) from 0.75 hpf to 120 hpf, mainly. Despite the variations in the timing of exposure and the differing timeframes for assessing neurobehavioral effects, the studies were able to observe neurobehavioral outcomes. These effects were evident during early postnatal development and persisted into adulthood.

Additionally, varying doses of GLY exposure were used in the animal studies. Some selected theses doses based on the GLY no-observed adverse effect level (NOAEL) of 500 – 1000 mg/kg/day for maternal toxicity, r the acceptable daily intake (ADI) 0.3 mg/kg/day, from the US Environmental Protetion Agency (0.7 mg/L) or using previous LC_{50} [29–35, 38–42, 44, 46–48]. However, others studies did not specify the basis for their selected doses [36, 37, 43, 45, 49, 50]. Reporting based-dosage for experiments helps ensure that the exposure levels are relevant for assessing safety and risk without causing death or severe suffering to animals [59].

Another important factor to consider regarding GLY toxicity is its different formulations. GLY is commercially available either as pure salt or combined with surfactants, such as polyoxyethylene amine (POEA). The GBH formulations with surfactants present higher toxicity than GLY alone, and are known to increase GLY absorption through biological membranes, which may contribute to its increased toxicity [60]. Additionally, Sánchez et al. [61] confirmed that three different GBH formulations caused impairment on locomotor function, memory and depression-like behavior. Among the twenty-two animal studies reviewed here, fourteen reported using a GBH formulations containing additional ingredients and surfactants, making it challenging to determine if the observed effects were, in fact, due to the toxicity of GLY itself, the surfactants, or the combination of both.

Despite of that, Moraes and collaborators [50] was the only study to evaluate both GLY and GBH exposure in a fish model. The results showed that GLY exposed group exhibited greater locomotor ability (increased distance traveled and velocity), whereas the GBH exposed group presented decreased locomotor function (reduced distance traveled and velocity). This reduction in movement may be involved with developmental abnormalities observed in the GBH-exposed group, such as cervical deviation, vertebral agenesis, and muscle atrophy. Further research would be needed to better understand the role and implication of these various formulations into the overall toxicity.

All animal studies employed neurobehavioral tests to explore the effects of prenatal GLY exposure (as detailed in Table 2). Regarding rodents' models, eleven of them used open field and seven used novel object recognition tests, while for all fish models' locomotor activity was predominant. This current review revealed that prenatal exposure to GLY often led to significant alterations in locomotor activity, emotionality, memory, anxiety, social interaction deficits, depression-like behavior, and ASD-like behavior. The majority of the studies indicated that prenatal exposure was the most sensitive period for neurodevelopmental effects.

Only three epidemiological studies were included and the primary behavioral outcomes assessed were autism spectrum disorder (ASD) [52], attention deficit disorder [51] and impairment on communication, social interactions and cognitive function [53]. However, the first two studies relied on secondary data, which may be susceptible to information or classification bias. Neurobehavioral problems were gathered from file records in data services, birth certificates, or medical record examinations. Assessing exposure is challenging without direct measure of biomarkers in biological specimens of pregnant women. One population-based case–control study estimated exposure using high spatial and temporal resolution based on records of agricultural application records [52]. However, certain assumptions were necessary, such as parents being home during pesticide application and exposure occurring only during specified periods. Such retrospective studies risk information loss, such as exposure to pesticides from other sources (diet or occupation), potentially underestimating total exposure.

Similarly, the CHAMACOS birth cohort estimated agricultural pesticide use because direct measurements of pesticide exposure were unavailable. They incorporated a range of covariates as potential confounders and considered both pre- and postnatal exposure with neuro-assessments, enabling reasonable conclusions.

On the other hand, the birth cohort study [53] measured both GLY and its metabolite, aminomethylphosphonic acid (AMPA), in maternal urine, and used a reliable tool to assess children's neurodevelopment, The Battelle Developmental Inventory, 2nd edition. This tool evaluates personal-social, adaptive, motor, communication, and cognitive domains. By using sensitive neurodevelopmental assessment and biological exposure data allows researchers to more confidently identify correlations between exposure and developmental outcomes. This approach not only enhances understanding potential risks but also supports public health interventions based on real exposure and outcome data.

It is worth noting that other epidemiological studies have reported the impact of prenatal GLY exposure on behavior during adolescence and adulthood, not only in the short-medium term, such as childhood. Hyland et al. [15] observed increased maternal reports of internalizing problems, anxiety, and youth reports of depression in teenagers postnatally exposed to GLY, while Gunier et al. [16] found a correlation between prenatal residential proximity to GLY use and risk-taking behaviors in young adults. However, these studies also estimated glyphosate exposure geographically and focused on the impacts during adulthood, highlighting the scarcity of research in this age range. In addition, during our research, other population-based case control study was found and assessed the relationship between pesticide exposure (including GLY) and ASD from 2000 to 2021. While authors reported a higher prevalence rate of ASD in regions with increased pesticides use, it was not clear about the specific glyphosate-ASD relationship. Regarding the population's age, the mean age of those diagnosed with ASD in high pesticide use areas was 4.9 years, and low pesticide use was 5.1 years. However, once again, no specific association with GLY exposure was stablished [62].

In plants, GLY acts inhibiting the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) [63] causing the synthesis decrease of some amino acids such as tyrosine, phenylalanine, and tryptophan, and proteins. There is still limited information about GLY toxicokinetic in mammals. However, it has been reported that GLY is readily absorbed through the gastrointestinal tract in rats, only a small part is metabolized to AMPA, and is eliminated in the urine, majority, as the parent compound. In addition, GLY and AMPA present similar biological half-live (14 and 15 h post-oral administration, respectively) and there is no information if they can bioaccumulate [7, 64]. It would be interesting to further study GLY and AMPA toxicokinetic to better assess risks of exposure to humans and animals.

GLY-associated neurotoxicity may involve several mechanisms beyond oxidative stress, and Chávez-Reyes et al. [65] and Costas-Ferreira et al. [66] have deeply approached them. GBH can cross the placental barrier and disrupt both fetal development [67] and placental endocrine function [68], potentially affecting locomotor activity. Neurotoxicity may also be linked to dopaminergic system disruption, as decreased movement is associated with the loss of dopaminergic neurons in the central nervous system [69, 70]. Additionally, GLY exposure can induce dopaminergic neurotoxicity and interfere in signaling pathways important to neuronal growth and myelinization [66]. It can also affect the cerebellum, which plays a role in cognitive function and motor coordination, interfering with migration and differentiation of granule cells [60].

Moreover, GLY exposure is related to immune-glutamatergic dysfunction, impacting metabolism and neurotransmission, which are critical for cognitive functions like learning and memory and are linked to conditions such as ASD and other neurological disorders [17, 30, 32, 71]. Glutamate can induce excitotoxicity via the N-methyl-D-aspartate receptor (NMDAR) involving Ca^{2+} flux that plays a role in cellular stress and neurotoxicity [72]. Also, neuroinflammation involving tumor necrosis factor alpha (TNF-α) may play a role in neurotoxicity and neurodegeneration in exposure to GLY as well as induce cell death [65].

Also, Coullery and collaborators [34] observed that GLY exposure lead to a downregulation of the Wnt5a/CaMKII signaling pathway, which is important factor for neuronal growth and maturation as well as hippocampal connectivity and synaptic plasticity [73]. So, GLY exposure could play a role in neuronal differentiation and formation of synaptic connections.

GLY has also been related to downregulate the expression of brain-derived neurotrophic factor (BDNF) [32], essential for neurogenesis, growth and neuronal plasticity, in the prefrontal cortex and hippocampus [74]. Also, the nuclear factor kappa B (NF-kB) is affected by GLY exposure [30] implicating in functions such as cell survival, differentiation, synaptic plasticity, which are all involved with neurogenesis and development of CNS [75].

Another potential explanation for the association between behavioral outcomes and GLY exposure is its influence on gut microbiome composition. The gut microbiome has been linked to conditions like depression and anxiety, as certain bacteria are associated with impaired tryptophan metabolism, a factor implicated in various neurological disorders [40].

Research has highlighted an interesting connection between maternal immune activation (MIA) and soluble epoxide hydrolase (sEH). MIA is known to play role in developmental disorders like ASD [76], while sEH is involved in the inflammation processes associated with MIA [77]. In this context, Pu et al. [32] observed elevated levels of sEH in juvenile offspring after maternal GLY exposure. Despite this finding, there is a lack of studies exploring the relationship between prenatal GLY exposure, sEH, and neurodevelopmental outcomes. Further research is needed to understand these interactions and mechanisms. Notably, sEH is a promising therapeutic target for neurological diseases, as its inhibition may provide neuroprotective and anti-inflammatory benefits [78].

Conclusions

The reviewed studies indicate that exposure to glyphosate-based herbicides during pregnancy or early postnatal stages can have adverse effects on offspring's mental and motor development, leading to notable neurological disorders like depression and autism-like behaviors. Both prenatal and postnatal GLY exposure play significant roles in influencing neurodevelopmental outcomes. Further research regarding the types of GLY formulations should be evaluated to better understand their toxicity and related outcomes. As most findings come from animal studies, there is a need for more epidemiological investigations that comprehensively assess both exposure periods and their impact on children's neurodevelopment. Specifically, longitudinal cohort studies with direct biomarker measurements are essential to better understand exposure dynamics and associated risks. Considering various determinants of exposure and exploring ways to reduce it during pregnancy and postnatally is crucial for promoting healthier lives for both children and their mothers.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s43188-025-00294-z.

Author contributions NS: conceptualization, methodology, formal analysis, investigation, data curation, writing, reviewing and editing. HB: methodology, investigation, data curation, reviewing and editing. EG-J: methodology, investigation, reviewing and editing. VM: methodology, investigation, reviewing and editing. DC: methodology, investigation, reviewing and editing. EP: methodology, investigation, reviewing and editing. JM-F: methodology, investigation, supervision, conceptualization, writing, reviewing and editing.

Funding This review is part of the thesis of NRS, who had a scholarship from FAPESB and supported by a grant from CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) 421550/2018-0.

Data availability All data generated in this study are presented within this article. For any additional information, please contact the corresponding author.

Declarations

Conflict of interest The authors report there are no competing interests to declare.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent to publish Not applicable.

References

1. Kim K-H, Kabir E, Jahan SA (2017) Exposure to pesticides and the associated human health effects. Sci Total Environ 575:525–535. https://doi.org/10.1016/j.scitotenv.2016.09.009
2. Dardiotis E, Siokas V, Moza S et al (2019) Pesticide exposure and cognitive function: results from the Hellenic Longitudinal Investigation of Aging and Diet (HELIAD). Environ Res 177:108632. https://doi.org/10.1016/j.envres.2019.108632
3. Bassil KL, Frcpc DCC, Kaur JS, Dip KJK (2007) Cancer health effects of pesticides. Can Fam Physician 53:1704–1711. PMID: 17934034; PMCID: PMC2231435.
4. Li Q, Li Y, Zheng J et al (2023) Prevalence and trends of developmental disabilities among US children and adolescents aged 3 to 17 years, 2018–2021. Sci Rep 13:17254. https://doi.org/10.1038/s41598-023-44472-1
5. Zablotsky B, Ng AE, Black LI, Blumberg SJ (2023). Diagnosed Developmental Disabilities in Children Aged 3-17 Years: United States, 2019-2021. NCHS Data Brief 473:1-8. PMID: 37440277.
6. BRASIL (2023) Resumo Executivo - Projeto PIPAS 2022: Indicadores de desenvolvimento infantil integral nas capitais brasileiras. Ministério da Saúde, Fundação Maria Cecilia Souto Vidigal. Brasília: Ministério da Saúde. https://bvsms.saude.gov.br/bvs/publicacoes/projeto_pipas_2022_resumo_executivo.pdf
7. Agency for Toxic Substances and Disease Registry (ATSDR) (2020) Toxicological profile for Glyphosate. US Department of Health and Human Services. https://www.atsdr.cdc.gov/toxprofiles/tp214.pdf
8. Clapp J (2021) Explaining growing glyphosate use: the political economy of Herbicide-Dependent Agriculture. Glob Environ Chang 67:102239. https://doi.org/10.1016/j.gloenvcha.2021.102239
9. Xu J, Smith S, Smith G et al (2019) Glyphosate contamination in grains and foods: an overview. Food Control 106:106710. https://doi.org/10.1016/j.foodcont.2019.106710
10. Noori JS, Dimaki M, Mortensen J, Svendsen WE (2018) Detection of glyphosate in drinking water: a fast and direct detection method without sample pretreatment. Sensors 18:2961. https://doi.org/10.3390/s18092961
11. Rappazzo KM, Warren JL, Davalos AD et al (2019) Maternal residential exposure to specific agricultural pesticide active ingredients and birth defects in a 2003–2005 North Carolina birth cohort. Birth Defects Res 111:312–323. https://doi.org/10.1002/bdr2.1448
12. Parvez S, Gerona RR, Proctor C et al (2018) Glyphosate exposure in pregnancy and shortened gestational length: a prospective Indiana birth cohort study. Environ Health 17:23. https://doi.org/10.1186/s12940-018-0367-0
13. Gerona RR, Reiter JL, Zakharevich I et al (2022) Glyphosate exposure in early pregnancy and reduced fetal growth: a prospective observational study of high-risk pregnancies. Environ Health 21:95. https://doi.org/10.1186/s12940-022-00906-3
14. Arbuckle TE, Lin Z, Mery LS (2001) An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. Environ Health Perspect 109:851–857. https://doi.org/10.1289/ehp.01109851
15. Hyland C, Bradshaw PT, Gunier RB et al (2021) Associations between pesticide mixtures applied near home during pregnancy and early childhood with adolescent behavioral and emotional problems in the CHAMACOS study. Environ Epidemiol 5:e150. https://doi.org/10.1097/EE9.0000000000000150
16. Gunier RB, Deardorff J, Rauch S et al (2022) Residential proximity to agricultural pesticide use and risk-taking behaviors in young adults from the CHAMACOS study. Environ Res 215:114356. https://doi.org/10.1016/j.envres.2022.114356

17. Cattani D, de Liz Oliveira Cavalli VL, Heinz Rieg CE et al (2014) Mechanisms underlying the neurotoxicity induced by glyphosate-based herbicide in immature rat hippocampus: involvement of glutamate excitotoxicity. Toxicology 320:34–45. https://doi.org/10.1016/j.tox.2014.03.001
18. Liu J, Schelar E (2012) Pesticide exposure and child neurodevelopment. Workplace Health Saf 60:235–243. https://doi.org/10.3928/21650799-20120426-73
19. González-Alzaga B, Lacasaña M, Aguilar-Garduño C et al (2014) A systematic review of neurodevelopmental effects of prenatal and postnatal organophosphate pesticide exposure. Toxicol Lett 230:104–121. https://doi.org/10.1016/j.toxlet.2013.11.019
20. Heyer DB, Meredith RM (2017) Environmental toxicology: sensitive periods of development and neurodevelopmental disorders. Neurotoxicology 58:23–41. https://doi.org/10.1016/j.neuro.2016.10.017
21. Hertz-Picciotto I, Sass JB, Engel S et al (2018) Organophosphate exposures during pregnancy and child neurodevelopment: recommendations for essential policy reforms. PLoS Med 15:e1002671. https://doi.org/10.1371/journal.pmed.1002671
22. Biosca-Brull J, Pérez-Fernández C, Mora S et al (2021) Relationship between autism spectrum disorder and pesticides: a systematic review of human and preclinical models. IJERPH 18:5190. https://doi.org/10.3390/ijerph18105190
23. Williams AL, Watson RE, DeSesso JM (2012) Developmental and reproductive outcomes in humans and animals after glyphosate exposure: a critical analysis. J Toxicol Environ Health Part B 15:39–96. https://doi.org/10.1080/10937404.2012.632361
24. Hooijmans CR, Rovers MM, De Vries RB et al (2014) SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 14:43. https://doi.org/10.1186/1471-2288-14-43
25. JBI (2020) JBI critical appraisal tools. https://jbi.global/critical-appraisal-tools
26. JBI (2017) JBI Critical Appraisal checklist for cohort studies. http://joannabriggs.org/research/critical-appraisal-tools.html
27. O'Neil ME, Peterson K, Low A et al (2012) Suicide prevention interventions and referral/follow-up services: a systematic review. Washington DC: Department of Veterans Affairs (US); Appendix C, Criteria used in quality assessment of systematic reviews. https://www.ncbi.nlm.nih.gov/books/NBK92651/
28. Aromataris E, Lockwood C, Porritt K et al. (2024) JBI manual for evidence synthesis. https://synthesismanual.jbi.global
29. Gallegos CE, Bartos M, Bras C et al (2016) Exposure to a glyphosate-based herbicide during pregnancy and lactation induces neurobehavioral alterations in rat offspring. Neurotoxicology 53:20–28. https://doi.org/10.1016/j.neuro.2015.11.015
30. Cattani D, Cesconetto PA, Tavares MK et al (2017) Developmental exposure to glyphosate-based herbicide and depressive-like behavior in adult offspring: implication of glutamate excitotoxicity and oxidative stress. Toxicology 387:67–80. https://doi.org/10.1016/j.tox.2017.06.001
31. Gallegos CE, Baier CJ, Bartos M et al (2018) Perinatal glyphosate-based herbicide exposure in rats alters brain antioxidant status, glutamate and acetylcholine metabolism and affects recognition memory. Neurotox Res 34:363–374. https://doi.org/10.1007/s12640-018-9894-2
32. Ait-Bali Y, Ba-Mhamed S, Gambarotta G et al (2020) Pre- and postnatal exposure to glyphosate-based herbicide causes behavioral and cognitive impairments in adult mice: evidence of cortical ad hippocampal dysfunction. Arch Toxicol 94:1703–1723. https://doi.org/10.1007/s00204-020-02677-7
33. Pu Y, Yang J, Chang L et al (2020) Maternal glyphosate exposure causes autism-like behaviors in offspring through increased expression of soluble epoxide hydrolase. Proc Natl Acad Sci USA 117:11753–11759. https://doi.org/10.1073/pnas.1922287117
34. Coullery R, Pacchioni AM, Rosso SB (2020) Exposure to glyphosate during pregnancy induces neurobehavioral alterations and downregulation of Wnt5a-CaMKII pathway. Reprod Toxicol 96:390–398. https://doi.org/10.1016/j.reprotox.2020.08.006
35. Luna S, Neila LP, Vena R et al (2021) Glyphosate exposure induces synaptic impairment in hippocampal neurons and cognitive deficits in developing rats. Arch Toxicol 95:2137–2150. https://doi.org/10.1007/s00204-021-03046-8
36. Pu Y, Ma L, Shan J et al (2021) Autism-like behaviors in male juvenile offspring after maternal glyphosate exposure. Clin Psychopharmacol Neurosci 19:554–558. https://doi.org/10.9758/cpn.2021.19.3.554
37. Del Castilo I, Neumann AS, Lemos FS et al (2022) Lifelong exposure to a low-dose of the glyphosate-based herbicide RoundUp® causes intestinal damage, gut dysbiosis, and behavioral changes in mice. Int J Mol Sci 23:5583. https://doi.org/10.3390/ijms23105583
38. de Oliveira MAL, Rojas VCT, de Sá JC et al (2022) Perinatal exposure to glyphosate-based herbicides induced neurodevelopmental behaviors impairments and increased oxidative stress in the prefrontal cortex and hippocampus in offspring. Int J Dev Neurosci 82:528–538. https://doi.org/10.1002/jdn.10207
39. Ricci EL, Ribeiro MO, Fukushima AR et al (2022) Perinatal exposure to an aromatase inhibitor glyphosate-base herbicide reduced male and female social behavior in juvenile age and the sexual behavior at adult female rat. Braz J Vet Res Anim Sci 59:467. https://doi.org/10.11606/issn.1678-4456.bjvras.2022.186467
40. Buchenauer L, Haange S-B, Bauer M et al (2023) Maternal exposure of mice to glyphosate induces depression- and anxiety-like behavior in the offspring via alterations of the gut-brain axis. Sci Total Environ 905:167034. https://doi.org/10.1016/j.scitotenv.2023.167034
41. de Carneiro CLCV, Chaves EMC, Neves KRT et al (2023) Behavioral and neuroinflammatory changes caused by glyphosate: Base herbicide in mice offspring. Birth Defects Res 115:488–497. https://doi.org/10.1002/bdr2.2138
42. Anarghou H, Malqui H, Ihbour S et al (2024) Impact of glyphosate-based herbicide exposure through maternal milk on offspring's antioxidant status, neurodevelopment, and behavior. Naunyn Schmiedebergs Arch Pharmacol 397:6591–6609. https://doi.org/10.1007/s00210-024-03035-5
43. El Hamzaoui A, Lamtai M, El Brouzi MY et al (2024) Melatonin attenuates affective disorders and cognitive deficits induced by perinatal exposure to a glyphosate-based herbicide via antioxidant pathway in adult male and female rats. Int J Dev Neurosci 84:745–757. https://doi.org/10.1002/jdn.10374
44. He X, Yang Y, Zhou S et al (2024) Alterations in microbiota-metabolism-circRNA crosstalk in autism spectrum disorder-like behaviours caused by maternal exposure to glyphosate-based herbicides in mice. Ecotoxicol Environ Saf 285:117060. https://doi.org/10.1016/j.ecoenv.2024.117060
45. Zhang S, Xu J, Kuang X et al (2017) Biological impacts of glyphosate on morphology, embryo biomechanics and larval behavior in zebrafish (*Danio rerio*). Chemosphere 181:270–280. https://doi.org/10.1016/j.chemosphere.2017.04.094
46. Forner-Piquer I, Faucherre A, Byram J et al (2021) Differential impact of dose-range glyphosate on locomotor behavior, neuronal activity, glio-cerebrovascular structures, and transcript regulations in zebrafish larvae. Chemosphere 267:128986. https://doi.org/10.1016/j.chemosphere.2020.128986
47. Lanzarin GAB, Venâncio CAS, Monteiro SM, Félix LM (2020) Behavioural toxicity of environmental relevant concentrations of a glyphosate commercial formulation—RoundUp® UltraMax: during zebrafish embryogenesis. Chemosphere 253:126636. https://doi.org/10.1016/j.chemosphere.2020.126636

48. Pompermaier A, Varela ACC, Mozzato MT et al (2022) Impaired initial development and behavior in zebrafish exposed to environmentally relevant concentrations of widely used pesticides. Comp Biochem Physiol C 257:109328. https://doi.org/10.1016/j.cbpc.2022.109328
49. Moraes JS, Da Costa Silva DG, Dos Santos VB et al (2023) Glyphosate is harmful to early life stages of the viviparous fish *Jenynsia multidentata*: biochemical and locomotor effects. Arch Environ Contam Toxicol 85:417–428. https://doi.org/10.1007/s00244-023-01015-z
50. Moraes JS, Ballesteros ML, Hued AC et al (2024) Glyphosate and its formulated product Roundup Transorb R® affect locomotor activity and reproductive and developmental parameters in *Jenynsia lineata* fish: an intergenerational study. Chemosphere 362:142541. https://doi.org/10.1016/j.chemosphere.2024.142541
51. Garry VF, Harkins ME, Erickson LL et al (2002) Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. Environ Health Perspect 110:441–449. https://doi.org/10.1289/ehp.02110s344
52. von Ehrenstein OS, Ling C, Cui X et al (2019) Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children: population based case-control study. BMJ. https://doi.org/10.1136/bmj.l962
53. Jenkins HM, Meeker JD, Zimmerman E et al (2024) Gestational glyphosate exposure and early childhood neurodevelopment in a Puerto Rico birth cohort. Environ Res 246:118114. https://doi.org/10.1016/j.envres.2024.118114
54. Connolly A, Leahy M, Jones K et al (2018) Glyphosate in Irish adults: a pilot study in 2017. Environ Res 165:235–236. https://doi.org/10.1016/j.envres.2018.04.025
55. Pires NL, Passos CJS, Morgado MGA et al (2020) Determination of glyphosate, AMPA and glufosinate by high performance liquid chromatography with fluorescence detection in waters of the Santarém Plateau, Brazilian Amazon. J Environ Sci Health B 55:794–802. https://doi.org/10.1080/03601234.2020.1784668
56. De Melo KG, Ferreira Jacobucci SR, Garlipp CR et al (2020) Determination of glyphosate in human urine from farmers in Mato Grosso-BR. IAJMH. https://doi.org/10.31005/iajmh.v3i0.124
57. Bienvenu J-F, Bélanger P, Gaudreau É et al (2021) Determination of glyphosate, glufosinate and their major metabolites in urine by the UPLC-MS/MS method applicable to biomonitoring and epidemiological studies. Anal Bioanal Chem. https://doi.org/10.1007/s00216-021-03194-x
58. Ashley-Martin J, Huang R, MacPherson S et al (2023) Urinary concentrations and determinants of glyphosate and glufosinate in pregnant Canadian participants in the MIREC study. Environ Res 217:114842. https://doi.org/10.1016/j.envres.2022.114842
59. OECD (2018) Test no. 414: prenatal developmental toxicity study. Guideline for testing of chemicals. OECD Publishing, Paris. https://doi.org/10.1787/9789264070820-en
60. Ojiro R, Ozawa S, Zou X et al (2024) Similar toxicity potential of glyphosate and glyphosate-based herbicide on cerebellar development after maternal exposure in rats. Environ Toxicol 39:3040–3054. https://doi.org/10.1002/tox.24163
61. Sánchez JAA, Barros DM, De Los Angeles-Bistoni M et al (2021) Glyphosate-based herbicides affect behavioural patterns of the livebearer *Jenynsia multidentata*. Environ Sci Pollut Res 28:29958–29970. https://doi.org/10.1007/s11356-020-11958-8
62. Román P, Ruiz-González C, Rueda-Ruzafa L et al (2024) Exposure to environmental pesticides and the risk of autism spectrum disorders: a population-based case-control study. Medicina 60:479. https://doi.org/10.3390/medicina60030479
63. Funke T, Han H, Healy-Fried ML et al (2006) Molecular basis for the herbicide resistance of Roundup Ready crops. Proc Natl Acad Sci USA 103:13010–13015. https://doi.org/10.1073/pnas.0603638103
64. Anadón A, Martínez-Larrañaga MR, Martínez MA et al (2009) Toxicokinetics of glyphosate and its metabolite aminomethyl phosphonic acid in rats. Toxicol Lett 190:91–95. https://doi.org/10.1016/j.toxlet.2009.07.008
65. Chávez-Reyes J, Gutiérrez-Reyes CD, Hernández-Cuellar E, Marichal-Cancino BA (2024) Neurotoxicity of glyphosate: Focus on molecular mechanisms probably associated with alterations in cognition and behavior. Environ Toxicol Pharmacol 106:104381. https://doi.org/10.1016/j.etap.2024.104381
66. Costas-Ferreira C, Durán R, Faro LRF (2022) Toxic effects of glyphosate on the nervous system: a systematic review. IJMS 23:4605. https://doi.org/10.3390/ijms23094605
67. Mose T, Kjaerstad MB, Mathiesen L et al (2008) Placental passage of benzoic acid, caffeine, and glyphosate in an ex vivo human perfusion system. J Toxicol Environ Health A 71:984–991. https://doi.org/10.1080/01932690801934513
68. Richard S, Moslemi S, Sipahutar H et al (2005) Differential effects of glyphosate and roundup on human placental cells and aromatase. Environ Health Perspect 113:716–720. https://doi.org/10.1289/ehp.7728
69. Bano F, Ahmed A, Parveen T, Haider S (2014) Anxiolytic and hyperlocomotive effects of aqueous extract of *Nigella sativa* L. seeds in rats. Pak J Pharm Sci 27:1547–1552. PMID: 25176249
70. Gallo EF, Salling MC, Feng B et al (2015) Upregulation of dopamine D2 receptors in the nucleus accumbens indirect pathway increases locomotion but does not reduce alcohol consumption. Neuropsychopharmacology 40:1609–1618. https://doi.org/10.1038/npp.2015.11
71. Blaylock RL, Strunecka A (2009) Immune-glutamatergic dysfunction as a central mechanism of the autism spectrum disorders. Curr Med Chem 16:157–170. https://doi.org/10.2174/092986709787002745
72. Verma M, Lizama BN, Chu CT (2022) Excitotoxicity, calcium and mitochondria: a triad in synaptic neurodegeneration. Transl Neurodegener 11:3. https://doi.org/10.1186/s40035-021-00278-7
73. Subashini C, Dhanesh SB, Chen C-M et al (2017) Wnt5a is a crucial regulator of neurogenesis during cerebellum development. Sci Rep 7:42523. https://doi.org/10.1038/srep42523
74. Bathina S, Das UN (2015) Brain-derived neurotrophic factor and its clinical implications. Arch Med Sci 11:1164–1178. https://doi.org/10.5114/aoms.2015.56342
75. Shih R-H, Wang C-Y, Yang C-M (2015) NF-kappaB signaling pathways in neurological inflammation: a mini review. Front Mol Neurosci 8:77. https://doi.org/10.3389/fnmol.2015.00077
76. Estes ML, McAllister AK (2016) Maternal immune activation: Implications for neuropsychiatric disorders. Science 353:772–777. https://doi.org/10.1126/science.aag3194
77. Ma M, Ren Q, Yang J et al (2019) Key role of soluble epoxide hydrolase in the neurodevelopmental disorders of offspring after maternal immune activation. Proc Natl Acad Sci 116:7083–7088. https://doi.org/10.1073/pnas.1819234116
78. Pallàs M, Vázquez S, Sanfeliu C et al (2020) Soluble epoxide hydrolase inhibition to face neuroinflammation in parkinson's disease: a new therapeutic strategy. Biomolecules 10:703. https://doi.org/10.3390/biom10050703