International Journal of Autism

E-ISSN: 2710-3927
P-ISSN: 2710-3919
IJRSE 2022; 2(2): 01-03

www.rehabilitationjournals.com
Received: 03-04-2022
Accepted: 04-05-2022

Domina Petric
Clinical Pharmacology and Toxicology, University Hospital Center, Soltanska 1, Split, Croatia

Correspondence
Domina Petric
Clinical Pharmacology and Toxicology, University Hospital Center, Soltanska 1, Split, Croatia

The possible link between glyphosate maternal exposure and the risk of autism development in offspring

Domina Petric

Abstract
Glyphosate is a non-selective herbicide that targets the enzyme 5-enolpyruvyl-3-shikimate phosphate synthase. It has been used to effectively control perennial weed since 1974. There is some scientific evidence that supports concerns about glyphosate´s safety and potential health consequences for human health, such as eye irritation, cardiotoxicity, hepatotoxicity, nephrotoxicity, carcinogenicity, neurotoxicity, teratogenicity, mutagenicity and endocrine disruption, although there is no scientific consensus on this issue. Here, author summarized available up-to-date scientific evidence and explores the possible link between glyphosate maternal exposure and autism. Available up-to-date scientific evidence suggests that there may be a link between maternal glyphosate exposure and the increased risk for the development of autism in offspring, with possible pathophysiological mechanisms being increased levels of soluble epoxide hydrolase and *Clostridium* bacteria colonization of the intestinal tract, but more research is mandatory in order to establish the exact clinical relevance of here presented available scientific data.

Keywords: Glyphosate, autism, herbicide, toxicology

Introduction
Glyphosate is a herbicide that targets the enzyme 5-enolpyruvyl-3-shikimate phosphate synthase. It is a non-selective herbicide, effective for perennial weed control, which was commercialized in 1974, and its use has grown to dominate the herbicide market. It is mostly used on transgenic, glyphosate-resistant crops (GRCs), both of which (GRCs and glyphosate) provided the very effective and inexpensive weed management technology, although this effectiveness is in decline due to the increase in glyphosate-resistant weeds [1]. There are concerns about glyphosate´s safety and potential health consequences for human health, which have been considered to be controversial [2]. According to the acute toxicity classification used in the United States, glyphosate is classified in category IV as a practically non-toxic substance [3], but European Chemicals Agency classifies glyphosate as an eye irritant [4] as it may cause serious eye damage [2]. When it comes to chronic toxicity, studies have shown that exposure to glyphosate may be associated with QT interval prolongation and the occurrence of arrhythmias in humans [5], oxidative-stress related organ damage [6], hepatotoxic effects [7], nephrotoxicity [8], morphological changes in human erythrocytes [9], increased risk of non-Hodgkin lymphoma [10], compromised functioning of acetylcholinesterase with consequent deregulation in the transmission of nerve impulses [11], DNA damage in human leukocytes [12], teratogenic effects [13], and endocrine disruption [6], but there is no scientific consensus on whether the glyphosate should be considered as a hazardous substance or not.

Glyphosate and Autism
Results of a study showed that autism spectrum disorder (ASD)-like behavioral abnormalities were present in juvenile mice offspring after maternal exposure to high levels of formulated glyphosate. Researchers found higher levels of soluble epoxide hydrolase (sEH), for which has been shown to play a key role in the development of ASD in offspring after maternal immune activation, in the prefrontal cortex (PFC), hippocampus, and striatum of juvenile offspring, whilst oxylipin analysis showed decreased levels of epoxy-fatty aids such as 8(9)-EpETrE in the blood, PFC, hippocampus, and striatum of juvenile offspring after maternal glyphosate exposure.

Researchers also found abnormal composition of gut microbiota and short-chain fatty acids in fecal samples of juvenile offspring after maternal glyphosate exposure. Authors concluded that maternal exposure to high levels of glyphosate causes ASD-like behavioral abnormalities and abnormal composition of gut microbiota in juvenile mice offspring, and that increased activity of sEH might play an important role in the development of ASD-like behaviors in offspring after maternal glyphosate exposure [14]. Results of another study, in which water or 0.098% glyphosate was administered as drinking water from embryo at the fifth day of pregnant ddY mice (E5) to P21 (weaning), followed by behavioral tests in male offspring from P28 to P35, showed that male offspring developed ASD-like behavioral abnormalities (increasing grooming behavior, social interaction deficit) after maternal exposure to glyphosate. Authors concluded that glyphosate itself, not the other herbicides ingredients, may contribute to ASD-like behavioral abnormalities in juvenile mice offspring [15]. Results of a population based case-control study, including 2961 individuals with a diagnosis of autism spectrum disorder up to 31 December 2013, showed that risk of spectrum disorder was associated with prenatal exposure to glyphosate (odds ratio 1.16, 95% confidence interval 1.06 to 1.27), chlorpyrifos (1.13, 1.05 to 1.23), diazinon (1.11, 1.01 to 1.21), malathion (1.11, 1.01 to 1.22), avermectin (1.12, 1.04 to 1.22), and permethrin (1.10, 1.01 to 1.20). For autism spectrum disorder with intellectual disability, estimated odds ratios were higher (by about 30%) for prenatal exposure to glyphosate, chlorpyrifos, diazinon, permethrin, methyl bromide, and myclobutanil [16]. This study showed that there is a possible link between maternal exposure to pesticides containing glyphosate with the development of autism in offspring.

The results of a systematic review demonstrated an interrelation between *Clostridium* bacteria colonization of the intestinal tract and autism. Authors also hypothesized that environmental glyphosate levels may deleteriously influence the gut-brain axis by boosting the growth of *Clostridium* bacteria in autistic toddlers [17].

Conclusion

Available up-to-date scientific evidence suggests that there may be a link between maternal glyphosate exposure and the increased risk for the development of autism in offspring, with possible pathophysiological mechanisms being increased levels of soluble epoxide hydrolase and *Clostridium* bacteria colonization of the intestinal tract, but it is worth to emphasize that available toxicological studies on animals have limited significance due to limitations of data extrapolation on humans and that available evidence from human studies is scarce. Nevertheless, available data still represents safety signals worth further investigation, as well as motivation for investigation of new and safer chemicals that could be used as herbicides and pesticides in the future.

References

1. Duke SO. The history and current status of glyphosate. Pest Manag Sci. 2018;74(5):1027-1034.
2. Soares D, Silva L, Duarte S, Pena A, Pereira A. Glyphosate Use, Toxicity and Occurrence in Food. Foods. 2021;10(11):2785.
3. Williams GM, Kroes R, Munro IC. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol. 2000;31(2 Pt 1):117-165.
4. European Chemicals Agency. Proposing Harmonized Classification and Labelling at EU Level of Glyphosate, 2022 Jul 10. https://echa.europa.eu/documents/10162/2f8b5c7f-030f-5d3a-e87e-0262fb392f38.
5. Gress S, Lemoine S, Séralini GE, Puddu PE. Glyphosate-based herbicides potently affect cardiovascular system in mammals: review of the literature. Cardiovasc Toxicol. 2015;15(2):117-126.
6. Mesnage R, Defarge N, Spiroux de Vendômois J, Séralini GE. Potential toxic effects of glyphosate and its commercial formulations below regulatory limits. Food Chem Toxicol. 2015;84:133-153.
7. Mesnage R, Renney G, Séralini GE, Ward M, Antoniou MN. Multiomics reveal non-alcoholic fatty liver disease in rats following chronic exposure to an ultra-low dose of Roundup herbicide [published correction appears in Sci Rep. 2018 Aug 17;8(1):12572]. Sci Rep. 2017;7:39328.
8. Gao H, Chen J, Ding F, Chou X, Zhang X, Wan Y, *et al*. Activation of the N-methyl-d-aspartate receptor is involved in glyphosate-induced renal proximal tubule cell apoptosis. J Appl Toxicol. 2019;39(8):1096-1107.
9. Meftaul IM, Venkateswarlu K, Dharmarajan R, Annamalai P, Asaduzzaman M, Parven A, *et al*. Controversies over human health and ecological impacts of glyphosate: Is it to be banned in modern agriculture? Environ Pollut. 2020;263(Pt A):114372.
10. Zhang L, Rana I, Shaffer RM, Taioli E, Sheppard L. Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: A meta-analysis and supporting evidence. Mutat Res Rev Mutat Res. 2019;781:186-206.
11. Van Bruggen AHC, He MM, Shin K, Mai V, Jeong KC, Finckh MR, *et al*. Environmental and health effects of the herbicide glyphosate. Sci Total Environ. 2018;616-617:255-268.
12. Kwiatkowska M, Reszka E, Woźniak K, Jabłońska E, Michałowicz J, Bukowska B. DNA damage and methylation induced by glyphosate in human peripheral blood mononuclear cells (*In Vitro* study). Food Chem Toxicol. 2017;105:93-98.
13. Antoniou M, Habib MEM Howard, Fagan J. Teratogenic Effects of Glyphosate-Based Herbicides: Divergence of Regulatory Decisions from Scientific Evidence. J Environ Anal Toxicol. 2012;4:1-13.
14. Pu Y, Yang J, Chang L, Qu Y, Wang S, Zhang K, *et al*. Maternal glyphosate exposure causes autism-like behaviors in offspring through increased expression of soluble epoxide hydrolase [published correction appears in Proc Natl Acad Sci USA. 2021 Feb 2;118(5)]. Proc Natl Acad Sci USA. 2020;117(21):11753-11759.
15. Pu Y, Ma L, Shan J, Wan X, Hammock BD, Hashimoto K. Autism-like Behaviors in Male Juvenile Offspring after Maternal Glyphosate Exposure. Clin Psychopharmacology Neurosci. 2021;19(3):554-558.
16. Von Ehrenstein OS, Ling C, Cui X, Cockburn M, Park AS, Yu F, *et al*. Prenatal and infant exposure to ambient

pesticides and autism spectrum disorder in children: population based case-control study [published correction appears in BMJ. 2019 Jun 25;365:l4032]. BMJ. 2019;364:l962.
17. Argou-Cardozo I, Zeidán-Chuliá F. Clostridium Bacteria and Autism Spectrum Conditions: A Systematic Review and Hypothetical Contribution of Environmental Glyphosate Levels. Med Sci (Basel).