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Glyphosate: Human Exposure and Health Impacts — A Literature Review

Authors:

Aleksandra Słojewska

Independent Public Voivodeship Integrated Hospital in Szczecin, ul. Arkońska 4 71-455
Szczecin

o.slojewska@gmail.com

<https://orcid.org/0009-0007-7532-0948>

Mikołaj Łabuda

Independent Public Voivodeship Integrated Hospital in Szczecin, ul. Arkońska 4 71-455
Szczecin

labuda.mikolaj@gmail.com

<https://orcid.org/0009-0002-4137-4319>

Klaudia Królikowska

University Clinical Hospital no. 2 PMU in Szczecin, Powstańców Wielkopolskich 72 St 70-111 Szczecin

klaudia.1799@wp.pl

<https://orcid.org/0009-0007-7984-4642>

Adrianna Bogucka

Independent Public Voivodeship Integrated Hospital in Szczecin, ul. Arkońska 4 71-455
Szczecin

adrianna.bogucka@icloud.com

<https://orcid.org/0009-0001-8870-0495>

Teresa Sowińska
University Clinical Hospital no. 2 PMU in Szczecin, Powstańców Wielkopolskich 72 St 70-111 Szczecin
tsowinska@icloud.com
<https://orcid.org/0009-0003-0061-212X>

Oliwia Mentel
University Clinical Hospital no. 2 PMU in Szczecin, Powstańców Wielkopolskich 72 St 70-111 Szczecin
oliwiamentel@gmail.com
<https://orcid.org/0009-0004-4739-0621>

Jakub Sikora
Profi-Med Medical Center Goleniów Marii Konopnickiej 10A 72-100 Goleniów
esiak10play@gmail.com
<https://orcid.org/0009-0007-9637-0709>

Karolina Knychalska
University Clinical Hospital no. 2 PMU in Szczecin, Powstańców Wielkopolskich 72 St 70-111 Szczecin
karolinaknychalska@gmail.com <https://orcid.org/0009-0003-3736-0579>

Agata Kotkowiak
Family Medicine Clinic "Podgórna", Podgórna 22 St. 70-205 Szczecin Poland
akotkowiak@gmail.com
<https://orcid.org/0009-0004-4797-6980>

Agnieszka Szema
University Clinical Hospital no. 2 PMU in Szczecin, Powstańców Wielkopolskich 72 St 70-111 Szczecin
aga.szema@gmail.com
<https://orcid.org/0009-0000-5017-3426>

Abstract

Introduction and Purpose: Glyphosate is the most widely used herbicide globally, primarily due to its effectiveness and compatibility with genetically modified (GM) crops. Its non-selective action on the shikimate pathway makes it suitable for widespread use in agriculture, urban areas, and water management. However, growing concerns have emerged over its potential health effects, particularly following its classification by IARC in 2015 as "probably carcinogenic to humans." This review aims to examine current knowledge on glyphosate exposure, its environmental prevalence, human biomonitoring data, and associated health risks.

Brief Description of the State of Knowledge: Extensive global use of glyphosate has led to its detection in air, soil, water, and food. Urinary biomonitoring studies in the U.S. and Europe show high detection rates, with levels varying by region, age, and occupation. Although glyphosate alone exhibits low mammalian toxicity, commercial formulations (GBHs) often contain adjuvants that enhance toxicity. Health concerns include reproductive toxicity, carcinogenicity, gut microbiome disruption, and interference with embryonic development. Glyphosate's action on gut bacteria and cytochrome P450 enzymes may contribute to conditions such as autism, autoimmune diseases, and developmental abnormalities.

Conclusions: Widespread human exposure to glyphosate is now well-documented. Given its environmental persistence and health concerns, continued biomonitoring and independent research are critical. Future regulatory decisions should assess full GBH formulations, not just glyphosate alone, and consider cumulative effects. Enhancing reporting transparency, and improving public access to pesticide data are essential for protecting environmental and public health.

Key words: glyphosate; AMPA; environmental exposure; biological monitoring; dysbiosis

Introduction

Glyphosate is currently the most widely used herbicide in the world. It is applied in the form of dozens of different commercially available formulations, the most well-known of which is Roundup, produced by Monsanto. Chemically, it is N-phosphonomethyl glycine, a derivative of phosphonic acid, classified as a phosphonate herbicide [1]. One of the mechanisms by which glyphosate affects plant organisms is the inhibition of the key enzyme in the shikimate pathway, 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which is responsible for the synthesis of essential aromatic amino acids required for plant growth. This pathway is present in all plants, making glyphosate-based products non-selective. They are used not only to eliminate unwanted vegetation in agricultural fields but also to prevent the overgrowth of water reservoirs, railway tracks, pavements, and even ordinary garden hedges. Plants typically wither within three to four weeks after application [1].

Another use of this pesticide is desiccation, which involves drying crops before harvest by disrupting the photosynthesis mechanism. Glyphosate causes the closure of stomata, thereby limiting respiration and reducing water uptake into plant tissues [2]. This procedure is also performed using other desiccants to synchronize plant maturation and facilitate harvesting [3].

The use of this herbicide has increased significantly following the development of genetically modified (GM) crops resistant to its effects. The area of transgenic crop cultivation expanded rapidly, from 1.7 million hectares in 1996 to 206.3 million hectares in 2023, which is more than a 121-fold increase in total planting area [4,5]. As of 2023, the United States accounts for the largest share of these crops (74.4 million ha), followed by Brazil (66.9 million ha) and Argentina (23.1 million ha). The most commonly cultivated transgenic plants include soybeans, maize, cotton, canola and alfalfa [5].

The tolerance towards glyphosate was achieved by introducing a gene for the EPSP synthase, derived from the bacterium *Agrobacterium tumefaciens*, or a gene encoding glyphosate oxidoreductase (GOX), which accelerates its degradation [6]. Thanks to additional features, the growth of GMO plants is not disrupted, even when entire crops are sprayed. This convenience has made glyphosate formulations increasingly popular, driving sustained interest in their agricultural applications [2].

A great deal of controversy surrounding glyphosate emerged with the 2015 publication of the International Agency for Research on Cancer (IARC) opinion, which stated that glyphosate is probably carcinogenic to humans (Group 2A). This conclusion was based on the increased occurrence of rare liver and kidney tumors observed in chronic animal feeding studies, epidemiological data linking exposure to non-Hodgkin lymphoma, and evidence showing both genotoxicity and the potential to induce oxidative stress. Earlier, governmental organisations such as the United States Environmental Protection Agency (U.S. EPA) and the European Commission assured that the proper use of glyphosate does not pose such a risk [7,8]. Later that year, the European Food Safety Authority (EFSA) released a risk assessment, stating that glyphosate is unlikely to pose a carcinogenic hazard to humans. The discrepancies in study results were attributed to the IARC evaluating both glyphosate and its formulations as a single group of compounds, whereas European studies focused on the active substance only. This means that while glyphosate's safety profile was assessed, the potential combined effects of the adjuvants present in commercial formulations were not directly tested as part of this renewal process [9]. Nevertheless, in response to the EFSA's opinion, the European Commission has twice extended glyphosate's authorisation in the EU, allowing its use until 15

December, 2033 [10]. The new regulation, however, provides several important safeguards: it prohibits glyphosate use for pre-harvest crop desiccation, reduces maximum application rates to 1.44 kg active ingredient per hectare per year in agriculture, and implements additional requirements to protect environmental quality and biodiversity [11].

Unfortunately, in agricultural practice, glyphosate-based herbicides (GBHs) are used, and they exhibit greater toxicity than glyphosate itself, which, when used alone, has relatively low toxicity for animals, including mammals [12]. The enhanced effect of GBHs is associated with the presence of so-called adjuvants, which increase the herbicide's efficacy. Among these are surfactants—surface-active agents that facilitate the absorption of the active substance through the cuticle—and water conditioners, which bind calcium and magnesium cations, preventing the formation of insoluble glyphosate salts that would otherwise reduce its absorption by plant tissues [13].

This review aims to examine current knowledge on glyphosate, focusing on its widespread use, environmental persistence, and human exposure routes. It presents biomonitoring data and outlines potential health risks, particularly gut microbiota disruption and developmental effects. The review emphasizes the need for more transparent reporting of glyphosate use, comprehensive toxicological studies on complete formulations, and long-term biomonitoring to better protect human and environmental health.

Description of the State of Knowledge

Glyphosate and Environmental Exposure

As the cultivation of genetically modified (GM) crops expanded—most of which were engineered for glyphosate resistance—the total amount of glyphosate applied naturally increased as well [5,14]. In addition, growing reliance on glyphosate has contributed to the spread of tolerant and resistant weed species in both the U.S. and globally. In response to declining weed sensitivity, farmers often increase application rates and spray more frequently [14]. The United States is the leading user of glyphosate, and the latest survey data from 2012 to 2016 indicate that an average of approximately 281 million pounds are applied annually in agriculture, with an additional average of 24 million pounds used in non-agricultural sites, primarily in the homeowner market, on turf, in forestry, and on roadways [15]. In Europe, glyphosate remains widely used, despite the fact that glyphosate-resistant GM crops are not currently cultivated within the EU. Although it represents Europe's most extensively utilized

and controversial pesticide active ingredient, comprehensive public statistics and data regarding its sales volumes and usage patterns are not readily available [11].

Due to the growing diversity of applications and dramatic increases in volumes applied, glyphosate and its primary environmental biodegradation product, aminomethylphosphonic acid (AMPA), have been detected in air, soil, and water [14]. Research tracing pesticide residues shows that glyphosate and AMPA are among the most frequently detected compounds in soil, water, and sediment samples throughout Europe [16,17].

The excessive agricultural use of glyphosate may increase its concentration in water and sediment through leaching, which explains the high detection frequency of both substances. AMPA persists in sediments longer than glyphosate itself because it is more resistant to degradation and has a higher sorption affinity to sediments. Consequently, even after the parent glyphosate has broken down, AMPA can remain in sediments for extended periods [17].

Farmers are particularly exposed to glyphosate. They may encounter high doses of herbicides not only during spraying but also when preparing solutions or through contact with unwashed equipment. Glyphosate can enter the body via the skin, the gastrointestinal tract, and the respiratory system. To ensure safety, air measurements are taken during such activities to confirm that glyphosate concentrations do not exceed the maximum allowable limit of 10 mg/m³ [2, 18]. Additionally, individuals living near agricultural fields are also at risk of exposure, with glyphosate detected in farmers' homes and in the urine of their family members [19,20].

For non-occupational exposure, the primary route of glyphosate intake is through food. Pesticide residues may remain on cultivated plants, which is why maximum residue levels (MRLs) considered safe for health are established. In the European Union, a default MRL of 0.01 mg/kg applies to pesticides not specifically mentioned in the MRL legislation, including glyphosate [21]. In Europe, the highest glyphosate levels in food have been reported in pulses, particularly lentils and peas, as well as cereals, buckwheat, and other pseudo-cereals [22, 23]. Despite its hydrophilic nature, glyphosate can accumulate in leaves, grains, or fruits. It cannot be removed by washing or cooking, and its residues can persist in food for more than 12 months, even after freezing, drying, or processing [24].

Pharmacokinetics of Glyphosate

It has been shown that glyphosate is only minimally absorbed from the gastrointestinal tract. When administered to rats as a single dose of 10 mg/kg of body weight, approximately 30–36% was absorbed, whereas in a 14-day daily administration at a concentration not exceeding 100 ppm, the absorption level was 15%. Similar results were obtained in studies involving rabbits, goats, and chickens. A small amount of glyphosate (about 2%) undergoes hydrolysis in the gastrointestinal tract to form aminomethylphosphonic acid (AMPA), which exhibits greater stability and toxicity than the parent compound, although its mode of action is not yet fully understood [25,26].

The highest level of glyphosate in the bloodstream was observed 2 hours after a single oral administration. A significant concentration of this compound was detected in the small intestine, colon, kidneys, and bones. Over 90% of the absorbed dose was excreted in the urine within 72 hours. With prolonged administration (doses at the level of 100 ppm), the highest concentrations were detected in the kidneys, spleen, adipose tissue, and liver, which stabilised after approximately 6 days. Nevertheless, glyphosate did not bioaccumulate, and once it was removed from the diet, its concentration in the tissues declined rapidly, ranging from 0.067 to 0.12 mg/kg of body weight after 10 days. This can be attributed to its polar structure, which renders it insoluble in fats [1, 26].

Glyphosate undergoes virtually no biotransformation in the body. The vast majority (approximately 97.5% of the dose) is excreted unchanged, and less than 0.3% of the dose is excreted as CO₂ in exhaled air. Due to its low absorption, the main route of excretion is via the faeces (62–69% of the dose), with the remainder of the substance absorbed into the bloodstream being filtered by the kidneys and eliminated in the urine [26].

Human studies suggest that 1–6 % of orally ingested glyphosate is eliminated as the unchanged compound in urine with reported elimination half-life ranges of 5.5–10 h. Therefore, concentrations of glyphosate in urine can serve as a useful biomarker for recent exposure to glyphosate [27,28].

Human Exposure to Glyphosate

Biomonitoring studies across multiple countries provide compelling evidence of widespread human exposure to glyphosate. In the United States, initial national assessments

from approximately a decade ago detected glyphosate in urine samples from over 80% of individuals aged six and older [28]. This high prevalence has been confirmed in subsequent research, with detection rates between 70.0% and 81.7% across age groups, including children as young as three years, indicating pervasive environmental presence [29].

European investigations reveal similar patterns of exposure. In France, a comprehensive study of 6,848 participants found glyphosate in 99.8% of urine samples (mean concentration: 1.19 ng/mL), with higher levels in males, children, and agricultural workers [30]. A Danish cohort study reported glyphosate in all of the analyzed samples from mothers and their children, with children showing slightly elevated concentrations compared to adults (approximately 1 ng/mL), suggesting age-specific exposure pathways [31]. Portuguese biomonitoring demonstrated temporal variation in glyphosate presence, with detection rates increasing from 28% (median: 0.25 µg/L) to 73% (median: 0.13 µg/L) between two sampling periods [32]. The German KarMeN study found glyphosate in 8.3% of 24-hour urine samples from 301 healthy adults, with concentrations reaching up to 2.80 µg/L [33]. An Irish pilot study detected glyphosate in 20% of participants (range: 0.80-1.35 µg/L) [34], further confirming exposure in European populations, even in regions without widespread cultivation of glyphosate-resistant crops.

Glyphosate health outcomes

Studies reporting the negative effects of glyphosate and its formulations on animal organisms were published as early as the 1990s. A three-month feeding of glyphosate to rats resulted in reduced weight gain, diarrhoea, and damage to the salivary glands. Lifetime feeding of animals caused hypertrophy and death of hepatocytes, cataract and lens degeneration, as well as an increased incidence of tumours in the thyroid, pancreas, and liver. Glyphosate also reduced sperm count in males, prolonged the oestrous cycle in females, and increased the risk of miscarriages [35]. Numerous studies from that time confirm these findings and also indicate an association between glyphosate and the development of conditions such as autism, neurodegenerative diseases, inflammatory bowel disease, coeliac disease, cancers, kidney diseases, and even obesity [36, 37, 38, 39].

Glyphosate's impact on gut dysbiosis

One reason why some consider glyphosate harmless to humans is that the shikimate pathway is absent in mammals. However, it is present in gut bacteria, which play an important

role in the synthesis of vitamins and the metabolism of aromatic amino acid derivatives (for example, serotonin), in the detoxification of xenobiotics, and in maintaining the integrity of the intestinal barrier [25]. Moreover, it has been shown that beneficial bacteria such as *Enterococcus*, *Bacillus*, or *Lactobacillus* are more sensitive to glyphosate than pathogenic strains of *Clostridium* or *Salmonella* [40]. This leads to the overgrowth of undesirable flora and results in dysbiosis. Pathogens, by activating the signalling molecule zonulin, disrupt the tight junctions between the cells of the intestinal mucosa, leading to the so-called 'leaky gut syndrome'. This is, in turn, associated with the occurrence of inflammatory bowel diseases and autoimmune conditions, such as coeliac disease, type 1 diabetes, asthma, or ankylosing spondylitis [41].

Dysbiosis is also considered one of the factors contributing to the development of autism spectrum disorders (ASD) [42, 43]. Some researchers have noted a correlation between the increased use of glyphosate and the rising number of autism diagnoses in the United States [44]. Additional evidence supporting this relationship is the fact that autism is associated with a deficiency of phenol sulphotransferase (PST) and impaired oxidation of sulphur compounds, excessive production of nitrogen oxides, and an overgrowth of bacteria that produce phenolic compounds in the gut, leading to increased levels of toxic p-cresol in the urine. All these symptoms may be explained by the action of glyphosate in the bloodstream and gastrointestinal tract on the bacterial flora [25, 45, 46].

Glyphosate's impact on embryonic development

Further studies have shown that glyphosate inhibits certain cytochrome P450 (CYP) enzymes, which are the primary enzymes involved in the metabolism of a wide range of both endogenous compounds and xenobiotics. One of those enzymes is aromatase (CYP19A1), which is responsible for converting androgen precursors into oestrogen, as well as an enzyme involved in the breakdown of retinoic acid (CYP26A1) [25]. Retinoic acid is of great importance in embryonic development, and even small changes in its concentrations can disrupt specific stages of development. Prompted by reports concerning neurological disorders and craniofacial deformities in newborns in regions where glyphosate-based herbicides were used, Paganelli et al. [47] conducted a study on the effects of small doses of glyphosate on the development of chicken and frog embryos. The frog embryos developed into tadpoles with significant skull deformities, while microcephaly was observed in chicken embryos. These malformations were linked to increased retinoic acid activity, and it was

confirmed that the simultaneous use of its antagonists protected against developmental disturbances.

Conclusion

Global biomonitoring studies conclusively demonstrate widespread human exposure to glyphosate, with detection in urine samples across diverse populations—even in regions without glyphosate-resistant crop cultivation. While glyphosate alone exhibits relatively low acute toxicity, evidence indicates that commercial formulations (GBHs), containing adjuvants and surfactants, present significantly greater health concerns. Animal and epidemiological studies suggest associations between exposure to glyphosate and adverse health effects, which include endocrine disruption, carcinogenicity, reproductive toxicity, gut microbiome disturbances, and developmental abnormalities.

Exposure levels vary across countries due to differences in agricultural practices, dietary habits, and regulations. Regulatory focus should shift from isolated glyphosate assessment to evaluating complete commercial formulations. With inconsistent global assessments and growing evidence of harm, continued monitoring of vulnerable populations—especially children and agricultural workers—is critical. Future research should focus on long-term studies of cumulative exposure risks and interaction effects between formulation components. Better reporting transparency and public access to pesticide data are essential for protecting environmental and public health.

Disclosure

Author's contribution

- Conceptualization: Aleksandra Słojewska, Agnieszka Szema
- Methodology: Klaudia Królikowska, Jakub Sikora, Oliwia Mentel
- Software: Teresa Sowińska, Karolina Knychalska, Agnieszka Szema
- Check: Oliwia Mentel, Klaudia Królikowska, Jakub Sikora
- Formal analysis: Aleksandra Słojewska, Agata Kotkowiak, Teresa Sowińska
- Investigation: Agata Kotkowiak, Karolina Knychalska
- Data curation: Adrianna Bogucka, Agnieszka Szema
- Writing - rough preparation: Aleksandra Słojewska, Klaudia Królikowska
- Writing - review and editing: Aleksandra Słojewska, Mikołaj Łabuda
- Visualization: Adrianna Bogucka, Jakub Sikora

- Supervision: Mikołaj Łabuda, Adrianna Bogucka
- Project administration: Aleksandra Słojewska, Mikołaj Łabuda, Teresa Sowińska, Oliwia Mentel
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