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Review paper

GLYPHOSATE TOXICITY: A REVIEW OF ITS PROPERTIES, EXPOSURE AND RISKS TO HUMAN HEALTH

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Abstract

Glyphosate (N-(phosphonomethyl) glycine) is the most widely used herbicide globally, with applications exceeding 125 million kilograms annually across more than 160 countries. Its broad-spectrum efficacy and cost-effectiveness, especially in genetically modified glyphosate-tolerant crops, have made it indispensable in modern agriculture. However, its extensive use has raised concerns regarding environmental persistence and potential health effects. Although it binds strongly to soil particles, glyphosate and its main metabolite, aminomethylphosphonic acid, are frequently detected in soil, water, and, to a lesser extent, air and food. Human exposure occurs primarily through diet, environmental contact, or occupational activities. Biomonitoring studies confirm widespread low-level exposure, with glyphosate and AMPA detected in human urine samples worldwide. Toxicological and epidemiological data remain inconsistent. While the International Agency for Research on Cancer classified glyphosate as "probably carcinogenic to humans," other agencies, including EFSA and the U.S. EPA, found no evidence of carcinogenicity. Evidence linking glyphosate exposure to non-Hodgkin lymphoma and other cancers remains inconclusive. Environmental studies highlight adverse effects on soil microorganisms, aquatic systems, and non-target species, prompting regulatory reassessment in the EU and beyond. Future research should prioritize formulation-specific toxicity, long-term biomonitoring, and mechanistic studies addressing endocrine, metabolic, and microbiome effects. Integrating toxicological, epidemiological, and environmental data will be essential for refining risk assessment, guiding sustainable weed management, and balancing glyphosate's agricultural benefits against its potential ecological and health risks.

Key words: *N-(phosphonomethyl)glycine, herbicide toxicity, aminomethylphosphonic acid, Roundup.*

INTRODUCTION

Glyphosate (N - (phosphonomethyl) glycine) (GLY) is a synthetic, broad-spectrum herbicide that has become one of the most widely used agrochemicals in the world since its introduction in 1974. Initially synthesized in 1950 by Swiss chemist Henry Martin, glyphosate's herbicidal properties were not recognized until it was resynthesized and tested in 1970 by the Monsanto Corporation (Duke 2018). The commercial formulation Roundup, which contains glyphosate as an active ingredient, quickly gained popularity due to its ability to effectively control a wide range of weeds without harming most of the crops (Dill et al., 2010). Since its commercial launch, glyphosate's usage has grown steadily. In 1974, the global application was estimated at 0.6 million kilograms, while in 2014, that number had increased to over 125 million kilograms (Benbrook, 2016). As of 2021, glyphosate is used in more than 160 countries, in both agricultural and non-agricultural settings. The glyphosate global market report for 2024 has estimated the glyphosate market size at US$10.92 billion, which makes it the most widely used herbicide globally (The Business Research Company, 2025). The Asia–Pacific region, followed by North America, represents the largest market for glyphosate. Its widespread use is largely attributed to the introduction and continued cultivation of genetically modified (GM) crops resistant to glyphosate, the rising global demand for food, and its cost-effectiveness. Despite that, glyphosate has been at the center of ongoing controversy regarding its environmental and health impacts. Growing evidence has raised concerns about its potential toxicity to human health, animals, and ecosystems. Studies have linked glyphosate exposure to various adverse health effects, including cancer, endocrine disruption, reproductive toxicity, and developmental toxicity (Ingaramo et al., 2020; Muñozet al., 2021). In 2015, the International Agency for Research on Cancer (IARC 2015) classified glyphosate as "probably carcinogenic to humans" (Group 2A) based on the evidence from epidemiological studies and animal research. This classification has led to increased scrutiny from regulatory agencies worldwide and a series of legal actions against manufacturers. GLY's toxicity is not limited to human health. Its detrimental effects have been shown on soil health, aquatic ecosystems, and biodiversity, raising concerns about long-term environmental contamination (Borggaard and Gimsing, 2008). Studies have also documented the impact of glyphosate on non-target organisms, including pollinators, aquatic life, and soil microorganisms, which play critical roles in ecosystem functioning (Tan et al., 2022; Ferreira et al., 2023). The European Union (EU) has been particularly active in reviewing glyphosate's safety, with the European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA) conducting comprehensive risk assessments. Glyphosate's most recent approval in the EU was renewed in October 2023, with an expiration date set for December 2033. This decision was made after intense scientific debate, with some Member States advocating for stricter regulations or a ban, while others supported its continued use. In the United States, the Environmental Protection Agency (US EPA) has maintained that glyphosate is not likely to pose a significant risk to human health when used according to label instructions (US EPA 2023). However, the EPA's position has been challenged by independent researchers and advocacy groups, leading to calls for more rigorous testing and reassessment (Gillam 2022; Novotný et al., 2022). Despite its ongoing approval in many countries, the debate over glyphosate's safety continues to evolve. The approval process for glyphosate in the EU has become a model for regulatory scrutiny of agrochemicals globally. Regulatory authorities are increasingly under pressure to reconcile the benefits of glyphosate in agriculture with the mounting concerns about its potential long-term effects on human and environmental health. As a result, understanding the full scope of glyphosate's toxicity has become a key issue in both scientific and policy circles.

This paper aims to provide a comprehensive review of the current literature on glyphosate's toxicity, examining both the direct and indirect effects of exposure on human health, animals, and the environment. By synthesizing the most recent findings, this work seeks to contribute to the ongoing discussion about the safety of glyphosate and inform future regulatory and agricultural practices.

PHYSICOCHEMICAL PROPERTIES AND FORMULATION COMPONENTS OF GLYPHOSATE-BASED PRODUCTS

Glyphosate exhibits high chemical stability across a wide pH range (3–9) and is relatively resistant to photodegradation under environmental conditions (EFSA, 2023). In field settings, glyphosate does not readily undergo hydrolysis or oxidation (EPA, 2020). When heated, it decomposes to produce toxic fumes, including nitrogen and phosphorus oxides (WHO, 1994). The solubility of glyphosate acid in water is moderate (approximately 11.6 g/L at 25 °C), whereas its amine and alkali-metal salts are highly soluble in water and many common organic solvents such as ethanol and acetone (FAO, 2021). To enhance the solubility of technical-grade glyphosate, it is typically formulated as salts of isopropylamine, monoammonium, potassium, sodium, or trimesium. The isopropylamine salt remains the most widely used, appearing in agriculture formulations as liquid concentrates (5–62% active ingredient), ready-to-use liquids (0.5–20%), pressurized liquids (0.75–0.96%), solids (76–94%), or tablets and pellets (60–83%) (EPA, 2020). Globally, more than 750 glyphosate-containing products are registered for agricultural use. These formulations usually contain non-ionic surfactants, such as polyethoxylated tallow amine (POEA), to enhance plant uptake (Mesnage et al., 2019). Some products also include additional herbicidal active ingredients, such as 2,4-D, to improve weed-control efficacy and mitigate resistance development (FAO/WHO, 2021). Formulated products may also contain acids (such as sulfuric or phosphoric acid) and typical impurities found in technical-grade glyphosate, such as formaldehyde (up to 1.3 g/kg), N-nitrosoglyphosate (maximum 1 mg/kg), and N-nitroso-N-phosphonomethylglycine (EFSA, 2023). The composition and concentration of these coformulants vary by the formulation type (EPA, 2020). Its herbicidal activity is attributed to the interference with the production of essential aromatic amino acids, inhibiting the activity of enolpyruvylshikimate phosphate synthase in plants (EPA 1993).

GLYPHOSATE USAGE

Glyphosate is a broad-spectrum, non-selective, post-emergent systemic herbicide that effectively suppresses or eliminates a wide range of plant species, including annual and perennial grasses, vines, shrubs, and trees. It is considered that it controls over 100 annual broadleaf and grass weed species, as well as more than 60 perennial weed species (Dill et al., 2010). At sublethal or lower application rates, it also acts as a plant growth regulator and desiccant. Due to its efficacy and versatility, glyphosate is extensively applied in agricultural, industrial, and urban environments across the world. Field-application rates vary depending on use. Approximately 1.5–2 kg/ha are applied for pre-harvest, post-planting, and pre-emergency treatments, around 4.3 kg/ha for directed sprays in vineyards, orchards, pastures, forestry, and industrial weed management, and about 2 kg/ha when used as an aquatic herbicide (Tomlin, 2000). Initially, glyphosate's agricultural use was mainly restricted to post-harvest and inter-row weed control in perennial crops due to its non-selective nature. However, the widespread adoption of no-till and conservation-till systems, which reduce soil erosion and labour/fuel costs while relying on effective chemical weed management combined with the introduction of genetically modified crop varieties engineered for glyphosate tolerance, transformed glyphosate into a post-emergent herbicide in many annual crops (Duke & Powles, 2009; Dill et al., 2010). By 2012, cultivation of glyphosate-tolerant crops accounted for nearly half of global glyphosate demand (Transparency Market Research, 2014). In Europe and other regions where genetically modified crops remain largely restricted, glyphosate continues to be applied primarily as a post-harvest or pre-sowing treatment (Glyphosate Task Force, 2014). Nevertheless, intensive and repeated use has contributed to the evolution of glyphosate-resistant weed populations, which now challenge its long-term effectiveness and demand integrated weed-management strategies (Powles, 2021). Glyphosate was first introduced for the control of perennial weeds along roadsides, ditch banks, and beneath power-line corridors, where its broad-spectrum efficacy and residual soil stability made it well-suited for vegetation management in non-crop areas (Benbrook, 2018; EFSA, 2023). It is also widely used to suppress invasive plant species in wetlands and aquatic systems, including emergent macrophytes such as Phragmites australis and Hydrilla verticillata (Wagner et al., 2024). In the United States, forestry applications account for approximately 1–2% of total glyphosate use, primarily during site preparation, conifer release, and invasive vegetation control operations (NCASI, 2021). Beyond agricultural and silvicultural contexts, glyphosate has been employed in aerial herbicide-spraying programs targeting illicit crop production. For example, in 2000, large-scale aerial applications were implemented in Colombia to eradicate coca (Erythroxylum coca) plantations (Solomon et al., 2007; Sánchez et al., 2020). Similar operations were conducted in parts of Mexico and South America to reduce marijuana cultivation, though these efforts have been controversial due to environmental and public health concerns (Székács & Darvas, 2018). According to the European Commission regulation OJ L, 2023/2660, 29.11.2023, GLY should not be used more than 1.44 kg per hectare per year in agricultural land and not more than 3.6 kg per hectare per year for non-agricultural land. Its maximum usage should be 1.8 kg per hectare for the control of invasive species in agricultural and non-agricultural areas.

GLYPHOSATE PERSISTENCE AND FATE IN THE ENVIRONMENT

Glyphosate is a systemic herbicide absorbed by the plants through the leaf tissue. Therefore, it is applied mostly by foliar application, most often using a backpack sprayer or a tractor-mounted sprayer. Absorbed GLY molecules translocate through the phloem down to the roots and to the growing points of the plant, where they disrupt the plant's metabolism and kill it. During application, GLY may end up in soil and non-target sites by washing off from the leaves by rain or simply by drift. It is also noticed that the release of glyphosate in soil may even occur from exudates from undamaged roots of glyphosate-tolerant plants (Mamy et al.,2016). Once it is found in soil, GLY fate and behavior will be determined by soil physicochemical and biological properties, composition, and climatic conditions. GLY in soil degrades rapidly. Its half-life is estimated from 7 to 60 days, depending on soil properties and environmental conditions. Its half-life in soil can be prolonged due to the formation of metal complexes with highly chelating cations such as Cu+2 and Fe+2, which can significantly reduce the availability of microbial community to decompose GLY (Tsui et al., 2005). The mineralization kinetics of glyphosate and the amount of extractable glyphosate in soil is influenced mostly by temperature, pH, and total organic carbon content in the soil (Muskus et al., 2019). Degradation may also appear due to the microbial-mediated processes with aminomethylphosphonic acid (AMPA) and sarcosine as key metabolites (Topp et al., 2013). Glyphosate's soil adsorption coefficient (Koc) ranged from 8 000 – 24 000 ml/g or higher, depending on the soil type (Areal & Rodrigues, 2003). This means that it has a strong affinity to adsorb to the clay particles and organic matter in the soil, which should limit its mobility and leaching into the groundwater. But since its solubility in water is estimated to be 12 g/L at 25°C, it is not surprising that it is found to leach with drainage water (Kjaer et al., 2003) and together with AMPA is found in groundwater and surface water bodies (US EPA, 2009). The presence of phosphates in soil can reduce GLY sorption to soil particles, making it more prone to leaching. AMPA is the primary, most abundant, and least toxic metabolite of glyphosate. It is also subject to microbial degradation, but it typically persists longer than glyphosate, which can degrade relatively quickly (Topp et al., 2013). Due to its solubility in water, AMPA can also leach into groundwater, especially in highly permeable soils or areas with heavy rainfall. Studies show that microorganisms are not able to utilize GLY as a source of carbon, and it is biodegraded co-metabolically (Dick and Quinn, 1995). This suggests that glyphosate degradation and general microbial activity in the soil are correlated. Strong adsorption capacity of the soil may prevent microbial access. GLY and AMPA in soil are detected worldwide such as USA, Canada, Argentina, France, Austria, New Zealand, Portugal, Spain, Mexico, etc. (Tzanetou & Karasali, 2020). Silva et al. (2018) assessed the distribution of both glyphosate and AMPA in agricultural topsoils across the European Union. Out of 317 soil samples analyzed, 21% contained glyphosate and 42% contained AMPA. The highest concentrations of both compounds in soil were found to be around 2 mg/kg. The authors also notice that northern European soils exhibited higher frequencies of glyphosate and AMPA contamination, whereas soils from eastern and southern regions generally showed lower contamination levels, often with concentrations below 0.05 mg/kg· Additionally, some areas prone to water and wind erosion displayed higher levels of contamination. These findings highlight the urgent needs of establishment residue threshold values for GLY and AMPA in soils, to help assess potential risks to soil health and the off-site transport of contaminants via erosion processes.

As it was mention before GLY from soil may leach into the groundwater and rich surface water bodies. Its half-life in surface water typically ranges from a few days to a few weeks, depending on environmental factors like temperature, pH, and microbial activity. In groundwater, it tends to degrade more slowly than in surface waters, since there is less microbial activity. Battaglin et al., (2005) investigated 154 water samples collected from 51 agricultural areas in the USA during the pre- and post-emergence application and during the harvest season. GLY and AMPA were identified in 36% and 69% of investigated samples, with maximum concentrations of 5.1 µg/L and 3.67 µg/L, respectively. In another study conducted in Denmark from 2010 to 2012 were investigated 450 water samples from which 23% showed the presence of GLY while 25% were contaminated with AMPA. The concentrations were in the range of 0.1 – 31 µg/L (Bruch et al. 2013). In the period from 1999 to 2022, the Danish pesticide assessment leaching programme found 43% and 81% of samples contaminated with GLY and AMPA, respectively, out of 250 samples tested. In the same study, only 2 out of 223 groundwater samples tested were found to be positive on AMPA (Badawi et al., 2023). In its last evaluation of GLY, the European Commission (EC) noted that groundwater modelling showed no risk of contamination from glyphosate or its metabolite AMPA, with predicted concentrations below 0.001 µg/L. Over 99% of EU monitoring samples contained levels below 0.1 µg/L. However, EFSA noted that in certain hydrological areas, such as river systems and catchments where groundwater and surface water are connected, additional data are needed to better assess potential exposure. Non-agricultural uses of glyphosate on sealed or highly permeable surfaces (e.g., sand or gravel) may increase the risk of leaching into groundwater. Therefore, Member States should take extra measures to protect groundwater in vulnerable areas and carefully evaluate such uses for both professional and non-professional applications (OJ L, 2023/2660, 29.11.2023).

Although GLY vapor pressure is negligible and estimated at 1.31 × 10–2 mPa at 25 ^{0}C (Tomlin, 2000), there are studies showing that GLY and AMPA are present in the air and rainwater. In the study of Chang et al., (2011) conducted in the agricultural areas in Indiana, Mississippi and Iowa during two growing seasons, GLY was detected in 100% and 60% of rain and air samples. The maximum concentration found in rain water samples was 2.5 µg/L, and in air samples was 9.1 ng/m3.

GLYPHOSATE RESIDUES IN FOOD

EFSA tested 16,283 samples from 26 countries in 2023 for glyphosate residues across various food and feed products, from which 674 samples were from animal feed, 18 were from fish, while the remaining 15,591 were food samples. In the food category, 97.9% (15,256 samples) contained no quantifiable residues of glyphosate. 296 samples (1.9%) showed detectable residues below the Maximum Residue Level (MRL), and 39 samples (0.2%) exceeded this limit. After accounting for analytical uncertainty, 23 samples (0.1%) were classified as non-compliant. These were mainly associated with dry beans, honey and other apicultural products, buckwheat, and other pseudo-cereals. The non-compliance rate was slightly lower than in 2022 (0.3%) (EFSA 2024). Glyphosate residues were also analyzed in 399 samples of food intended for infants and young children, and all were below the limit of quantification (LOQ). EFSA is currently carrying out an updated review of glyphosate MRLs, as required under the latest approval renewal provisions. Analysis of glyphosate metabolites covered several compounds, including AMPA (8,308 samples), AMPA-N-acetyl (949 samples), N-acetyl-glyphosate (5,967 samples), and trimethylsulfonium cation (6,309 samples). Among these, AMPA was detected in 14 samples (0.2%), primarily in soybeans. No quantifiable residues were found for AMPA-N-acetyl or N-acetyl-glyphosate, which are relevant mainly to genetically modified crops. In samples from crops used exclusively for animal feed, where no specific MRLs are established, residues related to glyphosate were found as follows: AMPA-N-acetyl in 7 of 13 samples (54%), glyphosate in 181 of 674 samples (27%), and AMPA in 49 of 243 samples (20%). None of the samples showed residues of N-acetyl-glyphosate or trimethylsulfonium cation above the LOQ (EFSA, 2025). According to EFSA's 2019 MRL review, glyphosate is approved for use on grass and other feed crops, often at relatively high application rates. However, under the newer approval conditions, residue concentrations in feed are expected to decline. Analysis of trimethylsulfonium cation, a glyphosate-related compound, by eight Member States showed quantifiable levels in 44 samples (0.7%), mainly in cultivated mushrooms, citrus fruits, and tea (EFSA 2025).

In the USA, the GLY application is limited to the pre-sowing or pre-planting period. And since its absorption through roots is neglected, the US Department of Agriculture (USDA), considers GLY as not likely to be found in food commodities so it is not included in the annual monitoring programs, and there is no official information about the presence of GLY in food commodities in the annual summary report of USDA on pesticide residues in food. While glyphosate is not investigated by USDA it is investigated and documented in the U.S. Food & Drug Administration (FDA) dataset. The FDA report for 2022 highlighted that GLY was detected in 54 samples out of 757 tested samples, placing it as the 31st most-frequently detected chemical in that sampling year. Anyway, it should be noted that the FDA report does not provide detailed breakout data for each commodity or specify the number of samples of each food type in which glyphosate was detected.

HUMAN EXPOSURE AND REGULATORY EVALUATION

In 2015, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) classified glyphosate (GLY) as "probably carcinogenic to humans" (Group 2A) (IARC, 2015). In contrast, that same year, the European Food Safety Authority (EFSA) concluded that glyphosate is not carcinogenic (EFSA, 2015). Based on urinary excretion within 48 hours and comparative kinetic data from oral and intravenous studies, EFSA reported that, following oral administration, glyphosate is rapidly but only partially absorbed, and approximately 20% of the administered dose is taken up. The compound is largely excreted unchanged in feces. Once absorbed, glyphosate undergoes minimal metabolism, is widely distributed throughout the body, does not undergo enterohepatic recirculation, and is rapidly eliminated unchanged in urine, indicating a low potential for bioaccumulation (EFSA, 2015). The following year, the U.S. Environmental Protection Agency (US EPA, 2016) reached a similar conclusion, classifying glyphosate as non-carcinogenic. In 2017, the European Chemicals Agency (ECHA) extended this assessment, classifying glyphosate as neither carcinogenic, mutagenic, nor reprotoxic, based on the scientific reviews from eight institutions: EFSA, US EPA, the Canadian Pest Management Regulatory Agency (PMRA), the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Japanese Food Safety Commission, New Zealand's Environmental Protection Authority, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), and the German Federal Institute for Risk Assessment (BfR).

Despite these assessments, numerous studies have detected glyphosate in human urine, demonstrating that it is absorbed by the body to some extent and excreted primarily via urine. Such findings have been reported among individuals living in agricultural areas, occupationally exposed workers, and even the general population, likely due to indirect exposure through food or environmental contamination. Humans are also exposed to glyphosate's primary metabolite, aminomethylphosphonic acid (AMPA). Both glyphosate and AMPA have been consistently detected in human urine, indicating widespread exposure. However, despite the long-term and extensive use of glyphosate-based herbicides (GBHs), human biomonitoring (HBM) data remain limited.

Reported urinary concentrations in the U.S. are generally higher than those observed in Europe (Buekers et al., 2022). Mills et al. (2017) documented a marked increase in urinary glyphosate and AMPA levels among adults in California between 1993 and 2016. To better understand exposure patterns, the German Environment Agency analyzed morning urine samples collected in the German Environmental Survey for Children and Adolescents (GerES, 2014–2017) for both glyphosate and AMPA. The study included 2144 urine samples from children and adolescents aged 3-17 years. GLY and AMPA were found above the limit of quantification (LOQ ~0.1 µg/L) in 52% and 46% of samples, respectively (Lemke et al., 2021). Similarly, Connolly et al. (2018) observed elevated urinary glyphosate levels among horticultural workers in Ireland, with peak concentrations detected up to three hours after glyphosate-based herbicide application. In another study, Connolly et al. (2020) provided a comprehensive overview of human glyphosate exposure based on the data provided in 21 scientific papers examining GLY and AMPA in human urine and concluded that human exposure to these compounds may be substantially higher than previously reported. Although some urinary AMPA may result from glyphosate metabolism, they assumed that most urinary AMPA in HBM studies originates from direct AMPA exposure rather than from glyphosate itself. Therefore, simultaneous measurement of both glyphosate and AMPA in urine is essential to resolve discrepancies in their concentrations, which may indicate different exposure sources or pathways. This finding aligns with the Joint FAO/WHO recommendation that GLY, AMPA, and other degradation products should be considered as residues of toxicological relevance (JMPR, 2005). In 2011, the JMPR established the acceptable daily intake (ADI) of 1 mg/kg body weight for the sum of glyphosate, including AMPA, N-acetyl-glyphosate, and N-acetyl-AMPA (JMPR, 2011). Consequently, including AMPA and other GLY metabolites in HBM-based exposure assessments is crucial for understanding combined glyphosate/AMPA human exposure from environmental sources. More recently, Wu et al. (2025) analyzed 1,532 human urine samples from participants aged 6–80 years and detected glyphosate in approximately 81% of samples and AMPA in 77% of them. Higher concentrations were observed in females and individuals over 60 years of age. Interestingly, participants with lower body mass index (BMI) showed higher glyphosate levels than those with higher BMI. The study also found an association between higher glyphosate concentrations and lower levels of several sex hormones, suggesting potential endocrine-related effects.

The final renewal report on GLY was made by the European Commission Directorate in October 2023. According to this report, the health-based referenced values ADI and AOEL remain the same (0.5 mg/kg bw per day and 0.1 mg/kg bw per day, respectively), the ARfD has increased to 1.5 mg/kg bw, and the AAOEL was set for the first time (0.3 mg/kg bw). As a part of this evaluation, the residue definition for risk assessment in different commodities, including plant and animal raw and processed products, honey, and other bee products, and rotational crops, has not changed and includes the sum of glyphosate and AMPA, expressed as glyphosate. But the residue definition for genetically modified crops tolerant to glyphosate (crops with CP4-EPSPS, with GOX, and with GAT modifications) is different and includes the sum of glyphosate, AMPA, N-acetyl glyphosate, and N-acetyl AMPA, expressed as glyphosate.

GLYPHOSATE TOXICITY

In mammals, glyphosate is not metabolized efficiently and is mainly excreted unchanged into the urine. However, it has been suggested that glyphosate can undergo gut microbial metabolism in humans and rodents (Brewster et al., 1991; Motojyuku et al., 2008). The epidemiological studies of human GLY exposure have not demonstrated a clear association with cancer. The IRAC has declared GLY as probably cancerogenic with emphasis on NHL, due to the mechanistic and other data, which support the "probable" carcinogen conclusion by providing strong evidence for genotoxicity and oxidative stress, mechanisms of action that are relevant to humans. Most of the studies were considered inadequate due to limited information provided, by a small group of animals included in the study, or poor histopathological description (IRAC, 2017). Thus, GLY has been extensively examined for non-Hodgkin lymphoma (NHL) and other lymphatic and hematopoietic cancers. Although some small and individual studies in the literature have linked GLY with non-Hodgkin lymphoma (NHL), multiple myeloma, and leukemia (McDuffie et al., 2001; De Roos et al., 2005; Eriksson et al., 2008; Cocco et al., 2013; Andreotti et al., 2018), large meta-analyses and pooled projects revealed that there is not sufficient evidence to link GLY with NHL. In a meta-analysis study conducted in 2021, which considered findings from 15 relevant scientific publications investigating human exposure to GLY and NHL, the outcome revealed no strong overall confirmation of increased risk for all NHL, but some indication of elevated risk for the DLBCL subtype was identified to exist (Boffetta et al., 2021). Findings from the North American Pooled Project suggest that there is limited evidence for an association between GLY and NHL, but that associations with small lymphocytic lymphoma (SLL) deserve additional attention (Pahwa et al., 2019). The results of an Italian multicenter case-control study revealed no association with NHL overall, B-cell lymphoma, or other major subtypes except the follicular lymphoma (FL), for which an elevated risk was observed among higher exposure groups (Meloni et al., 2021). A systematic review and meta-analysis performed by Chang & Delzell (2016) on 19 relevant scientific articles on the relationship between glyphosate exposure and risk of lymphohematopoietic cancer (LHC), including NHL, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia found no relationship between GLY exposure and the risk of NHL, HL, MM, leukemia, or any other subtype of LHC.

FUTURE PERSPECTIVES

Although numerous studies have addressed glyphosate (GLY) toxicity, many suffer from methodological limitations, bias, or poor design. To overcome these shortcomings, establishing multidisciplinary and international collaborations, along with standardized protocols for data comparability and exposure assessment, should be a priority. Future research should employ highly sensitive analytical techniques with lower detection limits to enhance exposure quantification and provide more accurate data on internal exposure levels across different populations, including children, pregnant women, and occupationally exposed workers (Connolly et al., 2020). Advances in omics technologies such as transcriptomics, metabolomics, and proteomics should be integrated into long-term exposure studies to identify reliable biomarkers of glyphosate exposure and toxicity. Conventional toxicity assessments typically focus on pure glyphosate; however, glyphosate-based herbicides (GBHs) often contain surfactants (e.g., POEA) and other additives that can increase overall toxicity. Because biomonitoring data on POEA and other co-formulants remain scarce, future assessments should require formulation-specific toxicity data rather than extrapolations from glyphosate alone (Mesnage et al., 2022). Moreover, future toxicological evaluations should consider the cumulative effects of pesticide mixtures and interactions with food components. Increasing evidence suggests that chronic, low-level exposure to glyphosate may induce subtle biological effects not captured by standard toxicity testing. Research should therefore focus on potential impacts on the gut microbiota, metabolic and immune disorders, and developmental and reproductive endpoints. Long-term, multigenerational studies are particularly needed. Current research trends emphasize mechanistic investigations into endocrine-disrupting potential, epigenetic alterations, oxidative stress pathways, mitochondrial dysfunction, and neurotoxicity. There is also a growing demand for transparency in industry-funded studies and the inclusion of independent, peer-reviewed data. Integrating epidemiological, mechanistic, and exposure data into comprehensive risk assessments, along with the development of safer alternatives and sustainable weed management strategies, will be essential to reduce reliance on glyphosate in the future.

CONCLUSION

Humans can be exposed to GLY through multiple environmental pathways, including air, soil, water, and food. When GLY-based products are applied to plants, exposure may occur via inhalation, contact with unprotected skin or eyes, or by entering recently treated areas. Individuals may also come into contact with glyphosate by walking through or touching contaminated soil after spraying. Young children can be particularly vulnerable when playing in areas recently treated with glyphosate-containing products. Investigations showed that only trace amounts of glyphosate typically enter the body through food consumption. In general, glyphosate does not readily reach groundwater or surface water unless it is directly applied to water bodies. Once in the environment, glyphosate binds strongly to soil particles and undergoes microbial degradation in soil, aquatic sediments, and water. Its main metabolite, AMPA, also degrades within several weeks. Glyphosate bound to soil particles is generally not absorbed by plant roots. Epidemiological evidence regarding the carcinogenic potential of glyphosate remains inconsistent. Although several case–control studies have investigated associations between glyphosate exposure and cancers such as non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, and leukemia, the results have been inconclusive. Limitations such as small sample sizes, exposure misclassification, and potential confounding factors reduced the strength of these findings. Considering the overall body of evidence, no causal relationship has been established between glyphosate exposure and the risk of NHL, HL, MM, leukemia, or any lymphohematopoietic cancer subtype.

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ТОКСИЧНОСТ НА ГЛИФОСАТОТ: ПРЕГЛЕД НА НЕГОВИТЕ СВОЈСТВА, ИЗЛОЖЕНОСТ И РИЗИЦИ ЗА ЧОВЕЧКОТО ЗДРАВЈЕ

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Резиме

Глифосат (N-(фосфонометил) глицин) е најшироко употребуваниот хербицид во светот, со примена што надминува 125 милиони килограми годишно во повеќе од 160 земји. Неговиот широк спектар на ефикасност и економичност, особено кај генетски модифицираните култури отпорни на глифосат, го направија незаменлив во современото земјоделско производство. Сепак, неговата широка употреба предизвикува загриженост во врска со неговата перзистентност во животната средина и потенцијалните здравствени последици. Иако силно се врзува за честичките од почвата, глифосатот и неговиот главен метаболит, аминометилфосфонската киселина, често се детектираат во почвата, водата, а во помала мера и во воздухот и храната. Изложеноста на човекот најчесто се случува преку исхраната, контакт со загадена средина или при професионални активности. Биомониторингот потврдува широка распространетост и ниско ниво на изложеност. Глифосат и AMPA се откриени во примероци на човечка урина ширум светот. Токсиколошките и епидемиолошките податоци остануваат неусогласени. Додека Меѓународната агенција за истражување на ракот (IARC) го класифицираше глифосатот како „веројатно канцероген за луѓето", други агенции, вклучувајќи ја EFSA и Американската EPA, не пронајдоа докази за канцерогеност. Доказите што ја поврзуваат изложеноста на глифосат со не-Хочкинов лимфом и други видови рак остануваат неубедливи. Еколошките истражувања укажуваат на штетни ефекти врз почвените микроорганизми, водните екосистеми и нецелните видови, што доведе до регулаторна преоценка во ЕУ и пошироко. Идните истражувања треба да се фокусираат на токсичноста на специфичните формулации, долгорочниот биомониторинг и студии за влијанието врз ендокриниот, метаболичкиот и микробиомскиот систем. Интеграцијата на токсиколошките, епидемиолошките и еколошките податоци ќе биде клучна за подобрување на проценката на ризикот, развојот на одржливото управување со плевелите и постигнување рамнотежа помеѓу земјоделските придобивки од глифосатот и неговите потенцијални еколошки и здравствени ризици.

Клучни зборови: *N-(фосфонометил) глицин, токсичност на хербициди, аминометилфосфонска киселина, рандап.*