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Review

# Review of Glyphosate-Based Herbicide and Aminomethylphosphonic Acid (AMPA): Environmental and Health Impacts

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**Abstract:** The use of synthetic molecules to achieve specific goals is steadily increasing in the environment, and these molecules adversely impact human health and ecosystem services. Considering the adverse effects, a better understanding of how these molecules behave in the environment and their associated risks is necessary to keep their use acceptably limited. To meet the demands of farmers and combat weed problems, woodlands and farmlands are sprayed with agrochemicals, primarily glyphosate-based herbicides. Farmers increasingly embrace these herbicides containing glyphosate. Glyphosate and aminomethylphosphonic acid (AMPA), a key metabolite of glyphosate, have been reported as toxicological concerns when they become more prevalent in the food chain. The chemical glyphosate has been linked to various health issues in humans and other living organisms, including endocrine disruption, reproductive issues, tumours, non-Hodgkin lymphomas, and liver, heart, and blood problems. Therefore, the current review aims to compile data on glyphosate-based herbicide use in the environment, potential risks to human and ecological health, and various maximum residual limits for crops as suggested by international organizations. As a result, regulatory agencies can advise glyphosate users on safe usage practices and synthesize herbicides more efficiently.

**Keywords:** glyphosate-based herbicide; AMPA; toxicological effect; ecological risk; regulations

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## 1. Introduction

Increasing numbers of synthetic molecules are being released into the environment to achieve specific outcomes [1]. Those molecules may adversely affect human health and ecosystem services [1,2]. An in-depth understanding of how those molecules behave in the natural world combined with an estimate of their complexity can help regulate their use and enable users to take precautionary measures to protect human health [3]. Although regulations have set the highest points for known pollutants found in water supplies or drinking water [4], and food [5], there are none for soil residue [3]. Indeed, the United Nations' Food and Agriculture Organization recently released a report that exposes the unseen truth of soil degradation [6]. Agrochemicals, primarily herbicides, are used on agricultural lands to suit farmers' demands and overcome weed resistance [7]. Formulation, approval, use, and monitoring of these herbicides, especially glyphosate-based herbicides (GBHs) involve numerous stakeholders [3].

Following World War II, food scarcity was a problem around the world. As a result, today farmers across the globe use several herbicides that are synthetic to manage pests and weeds. However, the formulation of glyphosate has been considered as the most important herbicide in that area [8]. Glyphosate-based herbicides (GBHs) come in a variety of commercial formulations, including broad-spectrum, non-selective, post-emergent, and synthetic herbicides [9]. The first glyphosate was developed in 1950, and its herbicidal properties were only discovered in 1970 when GBHs were resynthesized and tested [10]. The herbicide Roundup contains 'GLY' as an active component, which was introduced and commercialized by Monsanto Corporation in 1974 [11]. Agricultural weed control with glyphosate quickly became popular with farmers, who gained the ability to eliminate weeds without causing crop damage [8]. According to Zhang et al. [12], the glyphosate hinders the synthesis of amino acids including tyrosine, phenylalanine, and tryptophan, thereby killing weeds without destroying the agricultural crops. Its use has progressively increased in non-agricultural and agricultural settings, and it is now the most common herbicide worldwide [13,14]. In addition, many agrochemical companies market GLY formulations in various strengths and with various adjuvants, because they have already been reviewed and registered by regulatory organizations [11,15]. It was decided by the European Union Council on 27 November 2017 that glyphosate would be permitted to be used for five more years with the majority of 18 member nations voting in favor of allowing the use [16]. As a result, GLY can be used as a component of plant protection products (PPPs) through the end of 2022 [17]. Agencies in Europe, such as the European Food Safety Authority and the European Chemicals Agency, conducted a thorough assessment of GLY in recent years based on concerns over its environmental and human health consequences [18]. Based on current scientific data, the European Chemicals Agency (ECHA) concluded that glyphosate does not meet the criteria for a carcinogenicity hazard classification, and cannot be categorized as a carcinogen, reproductively harmful substance or mutagen [16,19]. As part of EFSA's risk-assessment process, the scientific committee has been asked to create guidelines on how to describe, record, and justify uncertainty [20]. In order to continue the renewal as an element in PPPs, GLY must not have a negative impact on the environment or human or animal health, according to European laws [21].

Glyphosate's widespread use stems from its effectiveness in weed control at a reasonable price, its presumed low toxicity, fast uptake by plants, and gradual weed resistance development to glyphosate [22]. Due to the accumulation of residues in the food chain, glyphosate and aminomethylphosphonic acid (AMPA), one of its main metabolites, are reported to be toxicologically problematic [23]. Several environmental conditions can affect the degradation of glyphosate, depending on its structural affinity with certain transformations [24]. Despite AMPA's longer half-life in soil, with 23–958 days compared to glyphosate's (1–197 days), most studies examined only glyphosate [25–28]. In the long term, contaminants with a long half-life and slow degradation can damage the environment [29]. This occurs most frequently in agricultural and forestry settings where repeated applications are common. Due to its extremely low vapour pressure, it cannot be volatilized significantly even if it undergoes mineralization, immobilization, or leaching once applied [29,30]. As a result of glyphosate mineralization, AMPA, methyl phosphonic acid, sarcosine and glycine are produced [30,31]. After that, AMPA is mineralized to methylamine and phosphate, which when decomposed to produce carbon dioxide and ammonium [29,32]. In research, the presence of glyphosate in the environment was established. As a result, potential health risks associated with glyphosate must be assessed.

The present review is therefore aimed at consolidating information on glyphosate-based herbicides in the environment, the potential threat this type of herbicide poses to ecological and human health, and various maximum residual limits (MRLs) proposed by international agencies on agricultural crops. Consequently, regulatory organizations and other authorities can provide glyphosate users with the necessary precautions and guidelines for future usage and to more effectively formulate herbicides by using safer surfactants.

## 2. Factors Affecting the Degradation Mechanisms of Glyphosate Pollution

Factors and mechanisms of degrading glyphosate pollution in soil include mineralization, immobilization and leaching having physical and chemical properties that influence the mechanism.

### 2.1. Mineralization

In some circumstances, biochemical properties of a soil can result in glyphosate and AMPA mineralization occurring very quickly [30]. Increased phosphate content, soil pH, and low Fe and Cu content accelerate glyphosate mineralization, driven primarily by increased microbial mineralization [30,33,34]. Adsorption of glyphosate to organic carbon (C) may provide environmental benefits such as delaying leaching, promoting soil degradation, and slowing the release of the herbicide. If the glyphosate use continues, the organic C system may eventually become saturated. Thus, soil biochemical properties, microbial diversity and activities are all factors in glyphosate degradation [23].

### 2.2. Immobilization and Leaching

The high adsorption of glyphosate results in its rapid immobilization in most natural situations after application [26,35]. Influential factors in the immobilization of glyphosate include minerals, soil organic matter, and clay. It has also been reported by Shushkova et al. [36] that adsorption to soil occurs within 3 h of the application when about 20% of glyphosate quantity is initially applied. High levels of clay, organic matter, iron, and aluminium are required for high adsorption, soils with low pH and phosphate concentrations, and high levels of clay [35–38]. Contrarily, soils with high levels of phosphate, high pH, and low levels of organic matter, Fe, and Al are more prone to glyphosate and AMPA losses because of a reduced capacity for adsorption and a larger propensity for leaching [36,38]. According to Bai and Ogbourne [23], the leaching of glyphosate and resulting contamination of water sources is increasingly due to the recurrent finding of glyphosate and AMPA residues in the water.

## 3. Environmental Hazards Posed by Glyphosate and AMPA Residues

A wide range of environmental risks has been created due to the relatively persistence of GLY and AMPA in the environment. There is not much information regarding the toxicity, health, or safety of glyphosate and AMPA on frequent and prolonged exposure, so it is difficult to predict their consequence and magnitude. Several issues surround these compounds' ecotoxicological and toxicological assessments, which may contribute heavily to the toxicological properties of formulated herbicides [39,40]. Because it is extremely difficult to assess safe, marketable products (as these products have properties that are only known to their manufacturers and are partially unknowable to regulatory agencies and research scientists), it can be suggested that all herbicide formulation ingredients must be declared and regulated. As a result, this review focuses on the existence of glyphosate and AMPA residues in soil and water bodies and the risks to human and animal health.

Roundup formulations are among the most extensively utilized GBH products that consist of other surfactants and chemical adjuvants. The active ingredients in Roundup are IPA-salt, polyethoxylated tallow amine (POEA) and other constituents [41]. These adjuvants can sometimes be even more toxic than glyphosate [42,43]. A thorough examination of surfactant co-formulants in glyphosate-based herbicides is urgently needed. There are several classes of POEA molecules with common structural characteristics [44]. Over many decades, ethoxylated amines, also known as POEA, have been the most common surfactants used in GBH formulations [45]. For instance, according to Guilherme et al. [46], in a study on the Roundup Ultra formulation, POEA was detected at a concentration of 16%.

Nonetheless, the labeled Roundup Ultra in Portugal (MON 52276) contains neither POEA nor propoxylated quaternary ammonium surfactants [47]. There are many instances in which authors cite the brand without citing the source country of the formulation. The co-formulants found in a formulation called Roundup Ultra vary depending on the country of sale. For example, Roundup Ultra is sold under the MON 76473 label in Ireland, whereas it has the MON 52256 label in Germany, the MON 79351 label in Greece, and the MON 77360 label in the United States [47]. It is not surprising that the same assay used to test the same GBH brand yields different results in different laboratories worldwide because it is difficult to identify substances across studies.

Mesnage et al. [48] confirmed that formulated herbicides are possibly more hazardous than the active substances alone, as evidenced by studies using glyphosate-based herbicides including a variety of other active components. It has become apparent that glyphosate has a wide range of harmful consequences [49], and co-formulants in Roundup have endocrine-disrupting effects in human cells [50]. As a result of these impacts, agrochemicals like GBHs will affect agricultural products and the environment, notably as chemical residues in goods produced by agriculture and as adverse effects on nontarget organisms [51]. Various studies on glyphosate and AMPA in several countries is described by Gillezeau et al. [52] in Table 1 given below. Even though the values of GLY and AMPA (in the table) may or may not be harmful, accumulating them over time will result in various health problems.

**Table 1.** Description of glyphosate and AMPA studies in several countries.

| Country | Subjects | Type of Sample | Year of Sampling | Lab Methods | Glyphosate LOD | Effects of Glyphosate | AMPA LOD | Effects of AMPA | References |
|---|---|---|---|---|---|---|---|---|---|
| ***EXPOSURE IN THE WORKPLACE*** | | | | | | | | | |
| United States (South Carolina, Minnesota) | Forty-eight farm families (farmers and wives, with 79 children aged between 4 and 18) on the day of application and three days later. | Urine | Unreported | HPLC | 1 µg per litre | On application day, farmers' geometric mean ± SD: 3.2 ± 6.4 µg/L (range < 1–233); while on day 3, 1.0 ± 3.6 (<1–68) µg per litre. Less than 25% of the wives or kids displayed values that could be identified. | Unreported | Unreported | [53] |
| Finland | Five forest workers sprayed 8% Roundup solution 6 h a day for one week | Urine | 1988 | GC with a 63 Ni-electron capture detector | 100 µg per litre | Samples of urine remained below LOD for glyphosate. A subsequent quantified urine sample contained 85 µg per litre of glyphosate. | 50 µg per litre | For AMPA, urine samples remained below the limit of detection | [54] |
| France | Herbicides based on glyphosate are used by a farmer and his family (5 in the household) | Urine | Unreported | LC-MS | 1 µg per litre | A 9.5 µg per litre concentration was found on the farmer following spraying and about 2 µg per litre after 2 days; After 2 days, 2 µg per litre was also measured in one child. No measurable levels were present in the mother or the other two kids. | Unreported | Unreported | [55] |
| Ireland | Amenity horticulturalists (17 males and 1 female), prior to and following spraying. | Urine | 2015 | LC MS-MS | 0.5 µg per litre | Prior to spraying, mean ± SD: 0.71 ± 0.92. After spraying: 1.35 ± 2.18 µg per litre | Unreported | Unreported | [56] |
| Mexico | 76 farmers | Urine | Unreported | ELISA | 0.05 µg per litre (in water) | In farming areas (Mean ± SD): 0.26 ± 0.23 µg per litre, (median: 0.28) | Unreported | Unreported | [57] |
| Sri Lanka | Ten farmers in good health from regions where chronic renal disorders are endemic | Urine | Unreported | ELISA | 0.6 µg per litre | Ranged between 40.2–>80 µg per litre, (Median: 73.5) | Unreported | Unreported | [58] |

**Table 1.** *Cont.*

| Country | Subjects | Type of Sample | Year of Sampling | Lab Methods | Glyphosate LOD | Effects of Glyphosate | AMPA LOD | Effects of AMPA | References |
|---|---|---|---|---|---|---|---|---|---|
| ***GENERAL POPULATION WITHOUT DIRECT CONTACT*** | | | | | | | | | |
| Sri Lanka | Ten healthy non-farmers from regions without a long-standing endemic kidney illness. | Urine | Unreported | ELISA | 0.6 µg per litre | Ranged between 1.2–5.5 µg per litre, (Median: 3.3) | Unreported | Unreported | [58] |
| US (Iowa) | Households who do not farm (23 fathers, 24 mothers, 51 children) | Urine | 2001 | FCMIA | 0.9 µg per litre | For the non-farm fathers, djusted geometric mean was 1.5 µg per litre | Unreported | Unreported | [59] |
| US (Washington and Idaho) | A total of 41 lactating women of greater than 18 years old | Milk (41), Urine (40) | 2014–2015 | LC-MS | 1 µg per litre in Milk; 0.02 µg per litre in Urine | For milk, glyphosate is below LOD. For urine, the glyphosate mean is 0.28 ± 0.38 µg per litre. Glyphosate detectable in 37/40 of the urine samples. There are no statistically significant differences between consuming conventional or organic food or living in an urban or suburban region. | In milk: 1 µg per litre; while 0.03 µg per litre was detected in Urine | In milk, AMPA is below the LOD. In urine: AMPA mean is 0.30 ± 0.33 µg per litre | [60] |
| Canada | Similar in age and BMI of pregnant (30) and non-pregnant women (39), and 30 umbilical cords | Maternal and umbilical cord serum | unreported | GC-MS | 15 µg per litre | No glyphosate found in the umbilical cord or in pregnant women. Mean of glyphosate found in non-pregnant women is 73.6 ± 28.2 µg per litre | 10 µg per litre | In none of the samples was AMPA found. | [61] |
| US (Indiana) | Pregnant women (71) between the ages of 18 and 39 | Urine and drinking water | 2015-2016 | LC MS-MS | In urine: 0.1 µg per litre; while in water: 0.2 µg per litre. | Glyphosate found in the urine: mean (SD) 3.40 (±1.24) µg per litre. No glyphosate was found in the drinking water. | Unreported | Unreported | [62] |
| Ireland | Fifty Irish persons over the age of 18 who do not have any special dietary preferences, with no pesticide usage in their line of works | Urine | 2017 | LC-MS-MS | 0.5 µg per litre. | A total of 47 samples were examined, and their urinary creatinine levels ranged from 3.0 to 30 nmol/L. 20% of the samples had Glyphosate levels above LOD. Glyphosate levels in samples with medians above the LOD (Range): 0.87 (0.80–1.35) µg per litre. | Unreported | Unreported | [63] |

**Table 1.** *Cont.*

| Country | Subjects | Type of Sample | Year of Sampling | Lab Methods | Glyphosate LOD | Effects of Glyphosate | AMPA LOD | Effects of AMPA | References |
|---|---|---|---|---|---|---|---|---|---|
| ***GENERAL POPULATION WITHOUT DIRECT CONTACT*** | | | | | | | | | |
| Denmark | A total of 13 mothers and 14 children (6–11 years old) in rural and urban communities | Urine | 2011-2012 | ELISA | 2.5 ppb | For children, the mean was 1.96 (range: 0.85–3.31) µg per litre. For mothers, the mean was 1.28 (range: 0.49–3.22) µg per litre | Unreported | Unreported | [64] |
| Germany | 399 individuals aged 20–29 years | Urine | 2001-2015 | GC-MS-MS | LOQ: 0.1 µg per litre | A total of 31.8% of the samples (127 samples) were found to have glyphosate level above LOD. The highest levels were found in males. | LOQ: 0.1 µg per litre | AMPA: 160 (40.1%) > LOD. | [65] |
| 18 European countries | 182 volunteers | Urine | 2013 | GC-MS-MS | LOQ: 0.15 µg per litre | 44% of the samples (of about 80 samples) were found to have glyphosate level above LOQ; Latvia had the highest glyphosate concentration, which is 1.8 µg per litre. | LOQ: 0.15 µg per litre | 36% > LOQ AMPA;) highest AMPA concentration: 2.6 µg per litre (Croatia) | [66] |
| Colombia | A total of 112 people who live in locations where glyphosate was applied aerially | Urine | 2006 | GC with a detector for electron micro-capture | 0.5 µg per litre | For the glyphosate (mean ± SD): 7.6 ± 18.6 µg per litre, ranged from 0–130 µg per litre. There were quantifiable AMPA levels in 4/42 participants with quantifiable glyphosate levels: Mean glyphosate: 58.8 µg per litre (range: 28–130 µg per litre). | 1.0 µg per litre | AMPA: 1.6 to 8.4 µg per litre (range: 0–56 µg per litre) | [67] |
| Thailand | A total of 82 expectant women, aged 19 to 35, who gave birth in a participating hospital | Umbilical cord and maternal serum | 2011 | HPLC | 0.4 µg per litre | Median for maternal serum: 17.5 µg per litre (range 0.2–189.1), while for the umbilical cord serum: 0.2 µg per litre (range 0.2–94.9). 50.7% of the umbilical cord serum samples are below LOD, 46.3% maternal serum samples are below LOD. | UUnreported | Unreported | [68] |

Note: AMPA, aminomethylphosphonic acid; ELISA, enzyme-linked immunosorbent assay; FCMIA, fluorescence covalent microbead immunoassay; GC, gas chromatography; HPLC, high-performance liquid chromatography; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantification; MS, mass spectrometry; MS/ MS tandem, mass spectrometry.

### *3.1. Soil with Glyphosate*

Given the widespread usage of glyphosate, understanding how it interacts with the soil ecosystem is critical for environmental safety assessment and practical application. Despite not being sprayed directly on the ground, glyphosate-based herbicides can contaminate the soil in and surrounding treated areas due to spray drift during application and leaf surfaces that have been washed away by rain. Mineralization, degradation, immobilization, and leaching are all factors in glyphosate's fate in soil. Several kinds of research have been published in recent years, attempting to discover and comprehend the processes that determine how chemicals behave in the environment and produce pollution, particularly in soil and water [12]. Mesnage et al. [69] analyzed the most prevalent surfactants used as co-formulants in glyphosate-based herbicides. They looked at how adding surfactants (such as Triton CG-110) would impact the soil's glyphosate adsorption, mineralization and leaching processes.

Soil composition, physicochemical factors, biological properties, chemical properties of the individual pesticide, and timing of precipitation and pesticide application all influence the fate of glyphosate [25,26,70–72]. Total organic carbon, pH, and temperature fluctuations in German soil were recently discovered to affect glyphosate mineralization kinetics, level of bio-NER formation, and the amount of recoverable glyphosate over time [73].

In most soils, glyphosate degrades quite quickly, with an estimated half-life of 7 to 130 days on-site [74]. Because glyphosate degrades relatively quickly, it has a low impact on the environment, particularly water and soil resources. On the other hand, its metabolites, AMPA and/or sarcosine, may boost the pollution risk. According to Grandcoin et al. [14], the herbicide molecule can be degraded in two ways (Figure 1). The first technique relies on the dissolution of the carbon-nitrogen bond, which forms AMPA (glyphosate's main metabolite) via the enzyme glyphosate oxidoreductase, which is broken down to carbon dioxide. In contrast, the second process relies on the broken carbon–phosphorus (C–P) bond, which is accomplished through the C–P lyase enzyme and results in the synthesis of glycine and sarcosine [75–77]. However, as an aminopolyphosphonate photodegradation product in water, AMPA can also be found in the natural world [78].

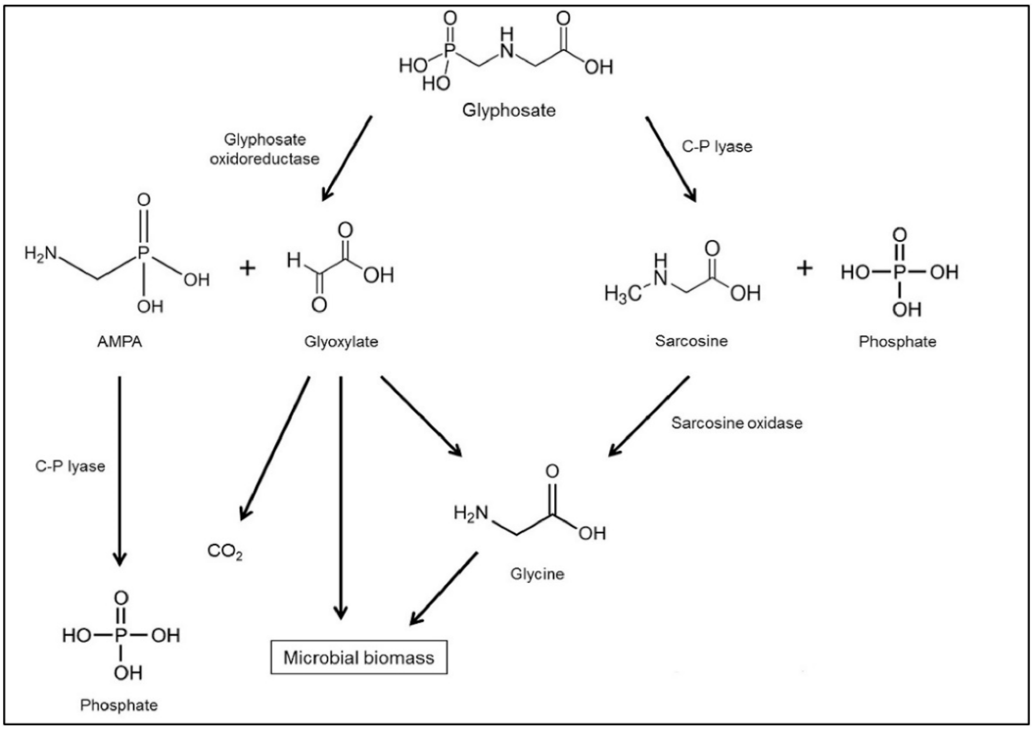


**Figure 1.** Biodegradation pathways of glyphosate in the environment [14].

Glyphosate is a three-polar functional group amphoteric chemical (amine, carboxymethyl, and phosphonomethyl) in its structure, linearly arranged. It is an ionic compound that is highly polar and soluble in water (10.5 g L1 at 20 °C) due to the existence in its structure of those groups [79]. Even when glyphosate dissolves in water, it can sometimes attach to soil particles, especially in clays. It has been found in several laboratory experiments that the molecule has a high absorption constant in soil, ranging between 8 and 377 $dm^3/kg$. The characteristics of the soil, temperature, and soil moisture all influence glyphosate adsorption and subsequent release from the soil. As a result, it may wash away rapidly in clay-rich soils for more than a year or in sandy soils. Even when attached to soil particles, in the presence of phosphates, in some cases, it can be broken down into soil water. Additionally, glyphosate can form compounds with metal ions, which could alter the soil's nutritional availability [3]. Because glyphosate adsorbs to soil particles suspended in the runoff, it risks surface water contamination due to erosion [80,81].

Concerns regarding the existence of environmental levels of GLY and AMPA have grown as the use of herbicides containing glyphosate has grown. Argentina [82–85], Canada [86], the United States [87], Mexico [88], and Portugal [89], as well as Spain [90], New Zealand [91], Austria [92], and France [93], have received a lot of attention.

Even though GLY is the most widely used herbicide, an investigation into the presence and amounts of glyphosate residues in soils and analytical methods for this purpose is relatively limited, especially given the scale of its use [94–96]. Furthermore, some polluted soils were found in locations prone to water and wind erosion [97]. Therefore, it is necessary to establish soil residue threshold values to identify potential risks to soil health, as well as off-site consequences from wind and water erosion [3].

Studies on soil microbial diversity and composition do not necessarily support the notion that glyphosate and AMPA are non-toxic to soil microorganisms [98,99]. For example, studies indicated earthworms as an essential biomarker for soil health, and following glyphosate application to the soils, the soils' biomass was reduced [100,101]. According to García-Pérez et al. [101], soil earthworm biomass was considerably lower in coffee plantations subjected to continuous glyphosate spraying for 22 years compared to those not treated in the previous seven years. Other research found that glyphosate had no direct effect on earthworms [102–104]. In contrast, others found that although earthworms may survive after glyphosate treatment, it can disrupt cocoon hatching, resulting in lower earthworm numbers in the soil [105,106]. According to another study, sub-lethal glyphosate spraying can alter soil chemistry, affecting water quality and other soil dwellers [107]. Moreover, due to glyphosate application, a change in the makeup of the soil community was seen, altering the availability of soil nutrients and nutrient balance [108]. However, there have been studies that disagree on whether or not applying glyphosate or glyphosate resistance species can cause nutritional imbalances [109].

### *3.2. Water with Glyphosate*

A metabolite of glyphosate, AMPA, and its residues are increasingly discovered in water sources, with runoff being one source of water contamination [110]. Glyphosate concentrations of more than 400 g/L harm some aquatic animals, including amphibians and fish [111,112]. According to Mercurio et al. [113], glyphosate has been reported in the marine ecosystem, and its persistence in saltwater is now being investigated. Table 2 showed the occurrence and concentrations of glyphosate in various water bodies across several countries in America and Europe. Although, they proved to be safe according to their respective guidelines, persistent exposure to glyphosate can pose a health threat.

Regarding risks posed to human health, the maximum concentration level (MCL) of glyphosate in the United States of America [23] and Australia is 700 $\mu g\ L^{-1}$ and 1000 $\mu g\ L^{-1}$ respectively. In Europe, glyphosate concentrations in drinking water are permitted to be less than 0.1 g/L, but 77 g/L are considered tolerable, according to reports by Horth and Blackmore [114]. According to European criteria, glyphosate residue in human drinking water must be reduced; however, glyphosate water treatment is expensive. Although these remedies have little influence on the presence of glyphosate in the water supply, the long-term impacts of glyphosate remain a worry [23]. Saunders and Pezeshki [81] urged that correct management measures, such as lower application rates and vegetation buffers, be used to limit glyphosate's eco-toxicity hazards.

### 3.3. Glyphosate in Nontarget Plant Species

In spite of the specified waiting period in harvested crops, glyphosate and AMPA residues are observed in unintended plant species after weed spraying [23]. Glyphosate residues in tree foliage that are unusually high (e.g., 1000 mg/kg) may be attributable to direct absorption into tree leaves due to airborne herbicide drift contamination [115]. In addition to the possible health problems associated with food contamination, glyphosate exposure can have phytotoxic effects. Reduced absorption of vital nutrients is one way phytotoxicity affects plant performance [116], nutritional imbalances, reduced yield, and poor food quality [117,118]. Various studies have reported that about 50% of plant biomass being reduced following glyphosate contamination in some nontarget plant species [116,119]. Following the application of GBH to crops, residual GLY and AMPA may remain in harvested crops and processed foods [120]. According to testing conducted by the UK Food Standard Agency, 27 out of 109 samples of bread had glyphosate residues of at least 0.2 mg/kg. The US Department of Agriculture Tests in 2011 revealed that 90.3% of 300 samples of soybeans contained glyphosate and 95.7% of which included AMPA with concentrations of 1.9 and 2.3 ppm, respectively [120].

Consumers are exposed to more glyphosate residues through their food, so this exposure should also be considered [51]. By drifting, leaching, and surface runoff, biologically active herbicide interacts with biomass and is absorbed by soil and water [121]. Among other places, glyphosate contamination is found in human urine, animal urine, ground water, and human milk and meat from farm animals [32,122–125]. Therefore, interactions with other stressors should be investigated in a more realistic situation when interacting with biological systems or the environment [126,127].

**Table 2.** Investigation of the presence and levels of glyphosate in surface and ground water samples collected from several countries in Europe, South America, and North America.

| Country | Year | Presence of Glyphosate/Concentration | References |
|---|---|---|---|
| United State | | | |
| *(Midwest)* | 2002 | Of the sampled streams, 36% were positive/about 8.7 g/L. | [128] |
| *(Midwest)* | 2013 | Of the sampled streams, 44% were positive/about 27.8 µg/L. | [129] |
| *(Washington, Maryland, Iowa, Wyoming)* | 2005–2006 | Positive outcomes in all of the sampled streams/about 328 µg/L. | [130] |
| *(Iowa, Indiana, Mississippi)* | 2004–2008 | Positive results for most of the sampled rivers/about 430 µg/L after a storm. | [131] |
| Spain | 2007–2010 | Of the groundwater samples, 41% were positive/about 2.5 µg/L. | [90] |
| Canada | 2002 | Of the samples, 22% were positive/about 6.07 µg/L. | [132] |
| Argentina | 2012 | Of the surface water samples, 35% were positive/0.1–7.6 µg/L. | [133] |
| Switzerland | 2016 | Positive results for most of the stream samples/about 2.1 µg/L. | [134] |
| France | 2003–2004 | Positive results from 91% of stream samples/up to 165 µg/L. | [135] |
| Hungary | 2010–2011 | Positive results for most rivers and groundwater samples/about 0.001 µg/L. | [136] |
| Denmark | 1999–2009 | Of the surface water samples, 25% were positive/about 31 µg/L.<br>Of the groundwater samples, 4% were positive/up to 0.67 µg/L. | [137] |
| Mexico | 2015 | The groundwater samples were all positive/about 1.42 µg/L. | [57] |
| Germany | 1998 | Only a few positive samples in two tributaries of the Ruhr River/with concentrations up to 0.59 µg/L. | [138] |

## 4. Toxicological Effects of Glyphosate and AMPA

Glyphosate inhibits the route of shikimic acid in weeds by blocking the synthase of enolpyruvylshikimic phosphate (EPSP), which prevents aromatic amino acid production, including tryptophan, tyrosine, and phenylalanine [139]. Herbicide exposure results in green colouration disappearance, leaf wrinkling or deformation, stunted growth, and tissue damage and the plant will eventually die after 7–21 days [81,139]. Plants, fungi, and some microorganisms are the only species that synthesize aromatic amino acids through shikimic acid [81]. Animals do not synthesize shikimic acid, so it is required to supplement their diet with aromatic amino acids. As a result, the low toxicity of glyphosate in animals is due to the absence of this pathway. Despite this, some adverse effects are associated with exposure to high doses for extended periods [32,81,139,140]. Due to its minimal acute toxicity, glyphosate appears to have little or no impact on microorganism populations and processes [98,141]. However, as shown in Table 3 below, the harmful effects of glyphosate-based formulations on aquatic and terrestrial nontarget creatures were found to be distinct [42,142–145]. The observed toxicity of Roundup formulations can be attributed to surfactants, including POEA [31,139,145–147]. Acute toxicity could not be as serious as reproductive, chronic, and sub-chronic harm, according to new findings on glyphosate contamination in the environment [23]. Figure 2 illustrates various pathways of glyphosate formulations used in agricultural or non-agricultural settings, liable for causing potential environmental and human health risks.

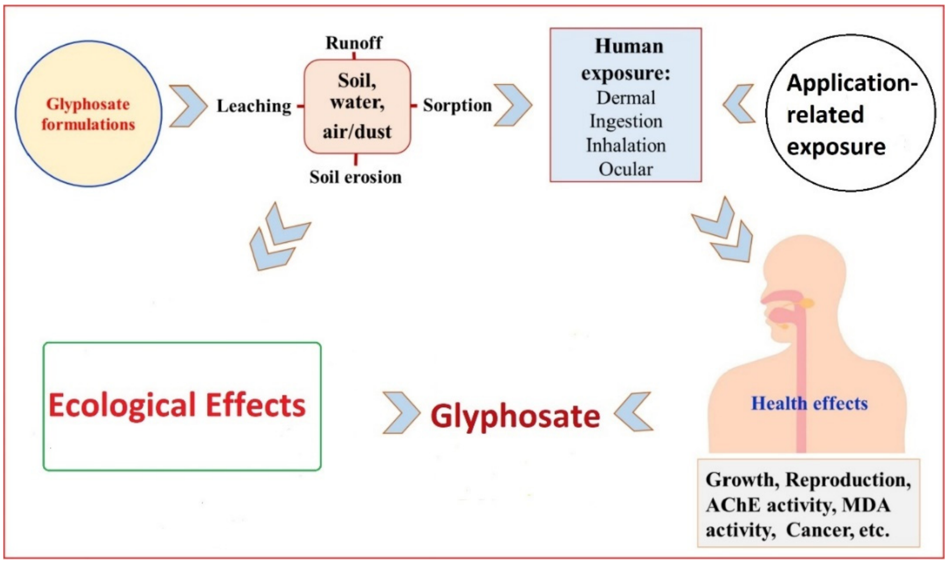


**Figure 2.** Pathways of glyphosate-based formulations in human health and the environment [148].

### 4.1. Acute Toxicity

In spite of the most severe cases of glyphosate poisoning (125 μg $kg^{-1}$ $day^{-1}$) and AMPA poisoning (5 μg $kg^{-1}$ $day^{-1}$) documented in adult humans, it was concluded that these substances do not pose a risk to humans [149]. Approximately 3.2% of patients died of acute poisoning, and the pathophysiology of these deaths remains unclear. This happened after evolving cardiorespiratory toxicity over a period of many hours and no proof that increased accessibility to intensive care units or laboratory services would have made a difference in these outcomes [150]. The use of various glyphosate formulations could lead to variations in reported cases. Surfactants are typically used in commercial glyphosate formulations to help the active component penetrate more easily and effectively. It is worth noting that neat glyphosate exhibits the lowest in vitro toxicity (approx. 2 g $L^{-1}$) while Roundup 450 and 400 exhibit the highest levels (approx. 0.001 g $L^{-1}$) [151].

### 4.2. Toxicity, Both Chronic and Subchronic

A dose of 560 mg $kg^{-1}$ $day^{-1}$ is recommended as the highest dose for male rats and 671 mg $kg^{-1}$ $day^{-1}$ for female rats, that do not lead to chronic toxicity [152]. Bai and Ogbourne [23] found that even relatively low amounts of glyphosate are enough to alter cell activities and produce cytotoxicity. Sub-agricultural concentrations of glyphosate and Roundup 400 in living organisms can impact the endocrine system at 0.5 ppm, estrogen receptor transcriptional activity at 2 ppm, and cytotoxicity at 10 ppm [151].

### 4.3. Genotoxicity

Several studies have questioned and mostly rejected claims that glyphosate is genotoxic [149,152]. Most previous DNA damage studies used excessive glyphosate doses [23]. Human cells have experienced DNA damage in other experiments utilizing sub-agricultural levels of glyphosate and Roundup [151,153,154]. According to Koller et al. [154], evidence of DNA damage was recorded after exposure of buccal epithelial cells to Roundup and glyphosate at quantities of 10 to 20 mg/L lower than recommended agricultural rates. In addition, DNA of caiman embryos was also damaged when exposed to Roundup at various sub-lethal doses [155]. However, Kier and Kirkland [156] reported that DNA damage from glyphosate is due to cytotoxicity, rather than genotoxicity. Then Bai and Ogbourne [23] concluded that, regardless of the cause, DNA damage can still happen at relatively low glyphosate levels.

### 4.4. Toxicity of Reproductive System

Glyphosate is unlikely to be toxic to reproductive systems [149] with no-observed-adverse-effect-level (NOAEL) between 300 mg/kg/day and 50 mg/kg/day [152]. Other studies reported that exposure to NOAEL concentrations of glyphosate may affect reproductive function in offspring [157,158]. Rates between 50 mg/kg and 450 mg/kg of Roundup were applied to rats during pregnancy without adverse effects; however, male offspring were affected [157]. These results highlight the need for more research to be carried out in order to fully comprehend the impacts of glyphosate-based herbicide use.

### 4.5. Carcinogenicity

When exposure is within the allowable NOAEL, studies have shown that glyphosate is not carcinogenic [23]. According to George et al. [159] and Thongprakaisang et al. [160], They reported glyphosate could promote tumour growth in skin cells (in vivo mouse) and breast cell proliferation (in vitro human models). In Thongprakaisang's [160] study, glyphosate residue concentration in drinking water as low as $10^{-12}$ M stimulated hormone-induced breast cancer. The International Agency for Research on Cancer recently determined that glyphosate is most likely human carcinogenic [161]. It has been reported that non-Hodgkin lymphoma (NHL), cancer derived from lymphocytes of the regular human immune system, is caused by GBH [162]. Different subtypes of NHL exist depending on where the cell originates, for example, in T and B cells, or natural killer cells. The distinct stages of lymphocyte development are related to the different NHL subtypes. Typically, lymph nodes and the spleen are enlarged, as well as other tissues such as the blood and bone marrow are affected [162]. A variety of infection agents, chemical agents, and deficiencies in the immune system are among the causes of NHL [162]. Zhang et al. [163] discovered that being exposed to GBH raises the risk of NHL among workers that are highly exposed to glyphosate. In 2020, NHL accounted for approximately 77,000 new cases and caused almost 20,000 deaths in the United States alone [164]. There were many lawsuits in court by the time Bayer bought Monsanto in 2018, alleging that Roundup is linked to NHL [165–167]. Researchers from the University of Washington found that Roundup exposure increases NHL risk by 41%, a clear link between the herbicide and cancer [166].

Even though glyphosate and glyphosate-based herbicides are valuable and significant weed-management tools for agricultural and forestry practices, long-term appropriate procedures and control of glyphosate usage are still needed to ensure efficacy, minimize pollution, and avoid adverse human health effects.

**Table 3.** The toxicity of glyphosate-based herbicide formulations to a variety of living organisms.

| Living Organisms | GLY Concentration | Toxic Effects | References |
|---|---|---|---|
| Human | 0.5–10 mg $L^{-1}$ | Endocrine disruption | [151] |
| | >20 mg/L to >80 mg $L^{-1}$ | DNA damage | [154] |
| | <1000 mg $L^{-1}$ | Effects on oxidative balance | [168] |
| | 4000 mg $L^{-1}$ | Neurological disorder | [169,170] |
| | 85–1690 mg $L^{-1}$ | Blood disorder | [171] |
| | 1–3 mg $L^{-1}$ | Human cell toxicity | [147] |
| | 36–178 mg $L^{-1}$ | Effects on cell physiology | [172] |
| Earthworm | 1–10 mg $L^{-1}$ | Growth and reproductive defects | [106,173] |
| Snails | 0.1–10 mg $L^{-1}$ | Body growth | [174–176] |
| Wasps | 960 g $ha^{-1}$ | Parasite eggs are harmed when exposed to this substance | [177] |
| Honeybee | 2.5–10 mg $L^{-1}$ | Adaptation in agricultural environments | [175,177–179] |
| Amphibians | 1.5–684 mg $L^{-1}$ | Chronic toxicity | [41,42,180–184] |
| Daphnia | 1.4–250 mg $L^{-1}$ | Chronic toxicity | [39,185] |
| Zebrafish | 10 mg $L^{-1}$ | Toxicity in the reproductive system | [186] |
| Birds | Wetland with glyphosate aerial spray coverage of 50–90 percent | Reduced natural habitats and bird populations, as well as affected male genital organs | [187–189] |
| Goldfish | 32 µg $L^{-1}$ | Effects on acetylcholinesterase (AChE), malondialdehyde (MDA), and OH in the liver | [183] |
| Reptiles | 144 mg $L^{-1}$ | Increase in heterophils and total protein content DNA damaged, physiological stress, decrease in WBC | [145,190,191] |
| Tilapia fish | 108–540 mg $L^{-1}$ | Toxic to the point of death | [192] |
| Wistar rat | 14.4–375 mg $kg^{-1}$ | Consequences for physiology and reproduction | [193,194] |
| Silver catfish | 0–5 mg $L^{-1}$ | Enzymatic activity, leukocytes, vacuolization, melanomacrophages and cytoplasm all show changes | [195] |
| Pig | 41% of IPAG and 15% surfactant | Effects on the cardiovascular system | [196] |

## 5. Health and Immunological Impacts of GBH

Microorganisms break down glyphosate into its most active metabolite, AMPA, and methyl phosphonic acid, once it reaches the environment [149]. They are found in water, soil, plants, and food, among other places [11,197,198]. Human urine, blood, and breast milk have all been shown to contain glyphosate. The urine levels in exposed workers ranged from 0.26 to 73.5 g/L, whereas those in the general population ranged from 0.16 to 7.6 g/L [199]. Most likely, the skin, mouth, and through the lungs are where glyphosate is absorbed [149,200]. Although skin absorption is the most widely mentioned route of ingestion in affected farmers, it only accounts for about 2% of total absorption [201]. According to Williams et al. [149], glyphosate appears to build up in the small intestine, liver, kidneys, and colon before excreting in the urine and faeces within two days. Nonetheless, an increasing body of knowledge exists about the human health impacts of GBHs and glyphosate [202].

Glyphosate has been evaluated by the International Agency for Research on Cancer (IARC) as "probably carcinogenic" in humans after more than 40 years of widespread usage [165]. Other bodies, such as Health Canada [203] and the European Commission [204] have renewed their authorizations for glyphosate use based on scientific findings as of 2017. However, with the "Monsanto Papers" revelation in 2017, the validity of several studies was called into question [205]. Monsanto is accused of interfering with the disclosure of important glyphosate toxicity data and ghostwriting studies confirming the safety of the herbicide [205]. Consequently, according to Peilex and Pelletier [206], it seems appropriate to provide a summary of the observed impacts of glyphosate and GBHs on humans' immune systems and cellular to systemic animal health consequences. Animal data is valuable in and of itself, not simply due to glyphosate contamination affecting a wide range of species in the environment, which might be transferred down the food chain. Given that numerous animals are common laboratory models and share largely conserved immunological systems and defensive processes with humans, they can provide essential knowledge when human data is restricted [207].

## 6. Health Effects and Toxicity of GLY and GBHs

### *6.1. Cellular Impact*

In a rat cardiac cell model, no substantial harm was seen at glyphosate doses that are significant to the environment. However, toxicity was found to be dose-dependent with increasing doses of TN20 surfactant at a constant glyphosate dosage [208], indicating that GBH components, including glyphosate, may be harmful. Additionally, this study discovered that this combination of glyphosate and TN20 induced the proliferation of tumour cells. Apoptosis and necrosis caused their deaths equally; however, when TN20 levels were increased, apoptosis was the predominant mode of cell death [208]. Rats exposed to a mixture of 12 chemicals, including glyphosate, for 18 months showed some cytotoxic effects in testis and kidney cells [209]. However, determining glyphosate's role in this cytotoxicity is difficult [206].

On the one hand, investigations of glyphosate alone on human cells, both fibrosarcoma and healthy cells, found no substantial cytotoxicity at environmentally relevant amounts [210] whereby GBHs show toxicity that is dose-dependent, even when producing at the sub-agricultural level. Roundup, like another GBH product called glyphogan, killed human Sertoli cells, with glyphogan causing the most substantial harm [211]. The necessity of investigating GBHs rather than glyphosate alone is highly required.

The glyphosate appeared to be highly genotoxic in Nile tilapia erythrocytes [209], but only affects both fibrosarcoma and healthy human cells at high doses [210]. These findings show that GLY and GBHs have the potential to be genotoxic, cytotoxic, or both and that the effects vary depending on the cell type.

### *6.2. Impacts on Reproduction, Hormones, and Teratogenicity*

It has been demonstrated that glyphosate and GBHs interfere with the human estrogen pathway [206]. Roundup inhibits the production of estrogen by the aromatase enzyme in the placental and embryonic cell lines of humans [212,213]. For glyphosate, it has been proposed that the enzyme be inhibited competitively, an effect facilitated by adjuvants that increase glyphosate solubilization and activity in herbicide formulations [214].

Mesnage et al. [215] discovered the impact of GLY on estrogen receptors (ER) in breast cancer cell lines, most likely through an indirect mechanism because it is structurally incapable of binding $ER_{\alpha}$. Because ER antagonists impede the glyphosate effect, Thongprakaisang et al. [160] theorized that glyphosate has estrogen-like properties interacting with the $ER_{\alpha}$ and $ER_{\beta}$. Furthermore, glyphosate may trigger up to 50% of the estrogen response and cause breast cancer cell proliferation. Upon exposure, both ERs were expressed after 6 h and just $ER_{\alpha}$ after 24 h. In addition, endogenous estrogen had an antagonistic effect when it was present. As a result, GLY could disrupt estrogen pathways and cause endocrine disruption [206].

Male offspring of rats that were given glyphosate exposure in an acceptable amount have lower testosterone production [158]. This endocrine imbalance influenced reproductive behaviour, resulting in changes in sexual choice and a long period in the females' first mount starting to reproduce [158]. Young et al. [216] reported that Roundup has been shown to suppress progesterone synthesis in human placental cells effectively, but only at greater doses compared to those that kill cells, implying that the progesterone impact is most likely due to cytotoxicity. GBHs also had an effect on human pregnancies, as shown by the association between GBH exposure and an increase in the frequency of premature births and miscarriages [217]. Several studies theorized that glyphosate cytotoxicity may be responsible for this behavior in light of its effects on embryonic, placental, and human cell lines [160,218].

GBHs have also been demonstrated to cause teratogenicity in fish (primarily in the form of heart abnormalities), mice, chickens, and rats, with brain and bone deformities [219–221]. According to Campana et al. [222], GBH exposure before a child's birth has been associated with a higher prevalence of malformations such as Down's syndrome and cleft lip in humans. Then Peillex and Pelletier [206] concluded that based on the evidence shown above, glyphosate and GBHs appear to have the ability to disrupt the system of reproduction at several stages, such as teratogenicity and hormonal pathway disruption.

### 6.3. Neurological Impact

As seen by acute poisoning instances resulting in neurological changes, some components of GBH can penetrate the blood–brain barrier. For example, aseptic meningitis with measurable glyphosate levels was found in cerebrospinal fluid of a 58-year-old woman who attempted suicide by consuming a significant dose of the glyphosate surfactant herbicide [223]. Vasculitic neuropathy struck a 70-year-old man after a month following a large-scale Roundup application with no protection, which was linked to the herbicide [224]. As a result, acute GBH poisoning or long-term exposure could hasten the onset of neurological illness.

When pregnant rats were given various doses of Roundup in their drinking water, their progeny had impaired movement [225]. Several studies have also indicated that in Parkinson's disease, cerebral functions (both movement and learning ability) are both hindered. Therefore, it's not surprising that increasing cases imply a link between GBH exposure and the start of Parkinson's disease [226–229].

### 6.4. Digestive Impact

The shikimate pathway that glyphosate targets in plants is also found in microorganisms exposed to GBHs in their guts whether accidentally or not, through oral ingestion. When rumen of cattle was subjected to various doses of glyphosate, specific phyla of microorganisms decreased in favour of others, and the dysbiosis benefited pathogens [230]. The glyphosate prevents the growth of *Enterococcus* spp., which can reduce *Clostridium botulinum* in cattle rumens [124]. Compared with cattle not exposed to glyphosate, mycobiota in the rumen of dairy cows exposed to glyphosate differed [231].

There is considerable concern about glyphosate and the effects of GBHs on liver, an essential organ in detoxifying xenobiotics [206]. When rainbow trout were exposed to higher concentrations of GBH, they developed various liver pathologies, such as fibrosis and mild changes [232]. Pandey et al. [233] also detected mild changes and fibrosis in rats that exhibited accumulation of collagen plus increased liver weights and varying glycogen levels following oral administration of Roundup. A hepatic progenitor cell line from a human showed that glyphosate on its own had a negligible impact on the metabolome, as well as a decrease in polyunsaturated and long-chain fatty acids [234]. Only the lowest glyphosate concentration examined resulted in a substantial reduction, demonstrating a concentration-independent impact [206].

Other digestive system components appear unaffected by Roundup in weaned piglets [235], nor was there a substantial connection between GBH exposure and diabetes in GBH applicators [236]. There was no indication of kidney damage among children, despite glyphosate presence in their urine [237]. Overall, these findings show GBH causes damage to the liver at the cellular and histological level; however, they do not show any effects on the rest of the digestive organs [206].

### 6.5. Cardiovascular Impact

Numerous GBHs and glyphosate effects on cardiovascular system have been observed. After consumption of glyphosate-contaminated drinking water for 72 weeks, mice hemoglobin levels were significantly lower, causing non-significant anemia [238]. The aortic rings of rats treated with 1% glyphosate displayed an insignificant vasorelaxation, corresponding to 20% of a standard response. The atria of a rat heart in isolation were stimulated like controls, but they failed to undergo spasmodic spontaneous contractions when 1% glyphosate was added [239]. In human cases of acute poisoning, it was reported that four out of ten poisoned subjects developed heart arrhythmias [240]. Therefore, glyphosate alone appears to affect the cardiovascular system, and GBHs may have similar impacts, at the very least in situations of severe poisoning [206].

### 6.6. Impact on Carcinogenesis

The carcinogenic potential of glyphosate is still being discussed. George et al. [159] found mice treated topically with glyphosate not to develop tumors, but did experience tumor-propagating effects in a skin cancer test.

## 7. Regulations Currently in Effect

According to the EPA's glyphosate Interim Registration Review Decision Case number 0178 of January 2020, glyphosate exposure poses no harm to human health. Although projected to be limited to the application area or nearby areas, the agency acknowledged potential ecological concerns for birds and mammals. In line with glyphosate's usage as an herbicide, the EPA identified a possible risk from off-site spray drift to terrestrial and aquatic vegetation. When glyphosate is used according to label directions, the EPA believes the benefits outweigh the potential environmental concerns [241]. However, because glyphosate is a component of several GBHs, there are concerns about the GBHs' regulation and management. Xu et al. [242] reported that the EPA regularly reviews the maximum allowable quantities in retail GBHs, including the permission granted to farmers using them for a specific reason for feed and food purposes. The Food and Drug Administration is therefore in charge of ensuring that imported and domestic goods sold in stores do not violate the EPA's standards. The EPA issued glyphosate residue tolerances and determined the maximum allowable residue for all group 15 cereals at 30 mg/kg, except maize and rice, which are 5 mg/kg and 0.1 mg/kg, respectively; likewise, all oilseeds in group 20 to be 40 mg/kg, apart from canola, which is 20 mg/kg [243]. In Table 4, you can find a summary of the details of the glyphosate maximum residue limits (MRLs) set by different agencies for common cereals and grains

Furthermore, in July 2017, the California Office of Environmental Health Hazard Assessment (OEHHA) listed glyphosate as a known carcinogen under Proposition 65 Law and Regulations [166]. This law ensures that California is informed about substances that could cause congenital disabilities, reproductive harm, or cancer. Meanwhile, the OEHHA claims that glyphosate exposure below 1100 µg/day has no significant risk level for cancer [244].

Glyphosate residues in drinking water are regulated differently in different countries. In the United States, for example, glyphosate has a maximum contamination limit (MCL) of 700 µg/L [245] and 1000 µg/L in Australia [246].

The use of GBHs was recently extended by the European Commission (EC) until 2022 when it will be reviewed. Based on EFSA [247], the EC established the MRL for sunflower seed, barley, sorghum, soybean, and oat at 20 mg/kg; 10 mg/kg for wheat, rye, mustard seed, linseed, lentils, peas, lupin, cotton seed and rapeseed; 1.0 mg/kg for corn; 2.0 mg/kg for beans, and 0.1 mg/kg for unnamed grains and cereals.

Health Canada regulates herbicide and pesticide maximum residue limits (MRLs) [242]. It establishes a maximum allowable residue of 20 mg/kg for soybean and rapeseeds, 5 mg/kg for wheat, 15 mg/kg for oats, 10 mg/kg for barley, and maize at 3 mg/kg for glyphosate-treated crops.

Globally, the World Trade Organization (WTO) plays a significant role in regulating GLY through its Agreement on the Application of Sanitary and Phytosanitary Measures, which all of the nations that make up the organization have in common. The Codex Alimentarius (18-3485), which outlines worldwide recognized accepted standards and recommendations, is updated by the WTO and FAO and reviews GBHs.

**Table 4.** Maximum permissible glyphosate residue (mg/kg) in grains placed by different agencies.

| Food Sources | European Commission | Health Canada | USEPA | WHO/FAO |
|---|---|---|---|---|
| ***Cereals*** | | | | |
| Barley | 20 | 10 | 30 | 30 |
| Corn | 1 | 3 | 5 | 5 |
| | Not Available | Not Available | 0.1 (popcorn) and 3.5 (Sweet corn) | 3 (Sweet corn) |
| | Not Available | Not Available | | |
| Millet | 0.1 | Not Available | 30 | 30 |
| Oat | 20 | 15 | 30 | 30 |
| Rice | 0.1 | Not Available | 0.1 | NA |
| Rye | 10 | Not Available | 30 | 30 |
| Sorghum | 20 | Not Available | 30 | 30 |
| Teff | Not Available | Not Available | 5 | 30 |
| Wheat | 10 | 5 | 30 | 30 |
| | | | | 20 (bran) |
| ***Oilseeds*** | | | | |
| Cotton seeds | 10 | 40 | 40 | 40 |
| Hemp seeds | 0.1 | Not Available | 40 | Not Available |
| Linseed | 10 | 3 | 40 | Not Available |
| Mustard seeds | 10 | 10 | 40 | Not Available |
| Peanuts | 0.1 | Not Available | 0.1 | Not Available |
| Pumpkin seeds | 0.1 | Not Available | 40 | Not Available |
| Rapeseeds | 10 | 20 | 20 | 30 |
| Safflower seeds | 0.1 | Not Available | 40 | Not Available |
| Sesame seeds | 0.1 | 10 | 40 | Not Available |
| Soybeans | 20 | 20 | 20 | 20 |
| Sunflower seeds | 20 | Not Available | 40 | 7 |
| ***Pseudocereals*** | | | | |
| Buckwheat | 0.1 | Not Available | 30 | 30 |
| Quinoa | Not Available | Not Available | 5 | 30 |
| ***Pulses*** | | | | |
| Beans | 2 | 4 | 5 | 2 |
| Lentils | 10 | 4 | 5 | 5 |
| Lupins | 10 | Not Available | 5 | Not Available |
| Peas | 10 | 5 | 8 | 5 |

Sources: [74,241,247,248].

## 8. Conclusions

With respect to the literature that focuses on the effects of GBHs and the current reality in agriculture and the environment, it is clear that GBHs, with their weed-controlling effect are becoming more commonly used. Glyphosate will likely continue to be used, regardless of all the damage it can do to the environment. However, glyphosate's accumulation in soil, water, and indirectly in the humans and animals that consume agricultural products should not be disregarded. The majority of agricultural production today relies heavily on herbicides, and there are no environmentally friendly or commercially viable alternatives. Even though glyphosate is mineralized, under certain conditions, glyphosate and its metabolites have long half-lives. In some circumstances, plants, soil, and water may still contain glyphosate and AMPA residues. Studies have shown that water, soil, and a variety of foods are contaminated at rates that could endanger the environment. Regardless, according to most scientific studies, the contamination rate does not prove harmful to most organisms and poses no risks to the environment provided recommended application rates are adhered to, and reapplications are avoided. However, a health concern can arise from the long-term buildup of these compounds in humans, animals, and the environment as glyphosate affects the body in an insidious way, slowly and over time.

In agricultural practices and home gardeners, glyphosate is an important weed control tool. Nevertheless, new research indicates that it is imperative to determine the most environmentally and toxicologically sensitive scenarios to guide glyphosate use in the future for it to continue to be useful, thereby assuring minimum contamination of the environment and no negative health consequences. Therefore, further interdisciplinary research regarding prolonged herbicide exposure at low levels, microbial community alterations, growth of antibiotic resistance, and increase in disease outbreaks in humans, plants, and animals is recommended. Considering all possible health risks, independent studies are required to revisit glyphosate residue tolerance criteria in food, animal feed, soil, and water.

Based on literature findings, around 30% of global cropland was contaminated with glyphosate at low levels, while 93% of worldwide cropland was contaminated with AMPA. Much information is lacking about the ecotoxic effects of AMPA, the most persistent and recalcitrant metabolite, i.e., complex for soil microbes to degrade. Therefore, to better assess the risk of contamination by AMPA, it is necessary to elucidate the ecotoxicity of this metabolite, as well as its biodegradation pathways and kinetics. Research like this could lead to the standardization of glyphosate rules among organizations and provide a definitive answer to glyphosate toxicity among regulators.

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