

REVIEW

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# Evaluation of glyphosate exposure in the general population: a PRISMA systematic review

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## Abstract

Glyphosate (GLY) is a widely used broad-spectrum herbicide that has raised increasing concern because of its environmental persistence and potential human exposure. This systematic review, conducted according to PRISMA guidelines, aims to assess the levels of indirect human exposure to GLY and its primary metabolite, aminomethylphosphonic acid (AMPA), in nonoccupationally exposed populations, with a particular focus on pregnant women and children. A comprehensive literature search was performed using PubMed, Scopus, Web of Science, and Cochrane databases for the period of 2013–2024. Fourteen eligible studies were included. GLY exposure was confirmed in the general population, with urinary concentrations ranging from 0.20 ng/mL to 7.19 ng/mL and AMPA levels ranging from 0.09 ng/mL to 10.60 ng/mL. AMPA detection, often concurrent with GLY, suggests both environmental degradation and internal metabolic transformation. Some of the included studies also explored potential correlations between exposure levels and biological or demographic parameters, although such associations are not the primary focus of this review. These findings emphasize the importance of continued biomonitoring efforts and a deeper understanding of the environmental and lifestyle factors contributing to chronic low-level exposure, particularly in vulnerable populations.

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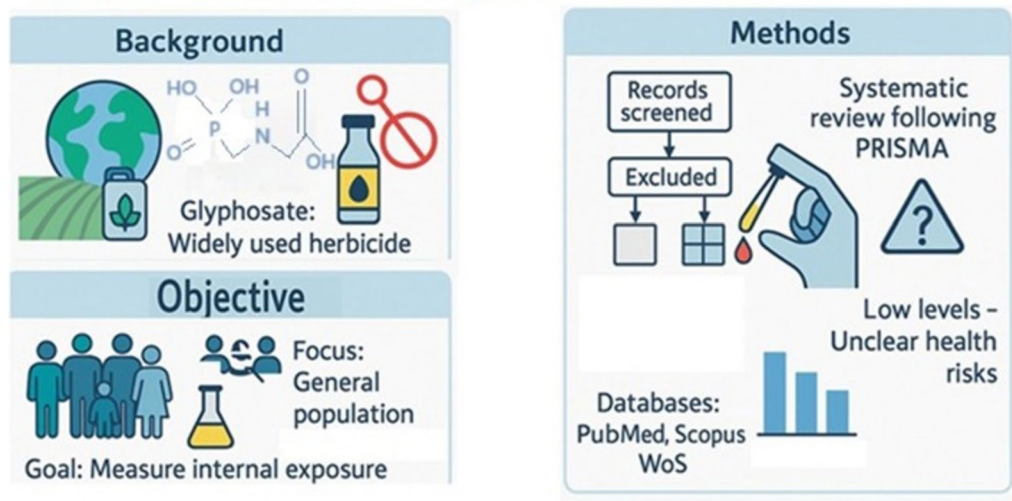
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## Graphical Abstract

## Glyphosate Exposure Evaluation in the general population: A PRISMA Systematic Review.



### Introduction

GLY is a widely used herbicide, and its main byproduct is aminomethylphosphonic acid (AMPA), according to the European Food Safety Authority [1]. Its environmental presence is primarily attributed to repeated applications over time. While GLY can form stable complexes with metals and naturally occurring minerals that may contribute to its retention in soils [2], its persistence is highly variable and strongly influenced by environmental conditions. Studies have reported half-lives in soil ranging from a few days to several months, with some cases documenting residues up to 460 days [3].

and in rare instances, up to 20 months after application. However, as noted in different studies, factors such as soil type, microbial activity, temperature, and pH can significantly shorten its half-life [4–7].

GLY is likely the most widely used herbicide in the world, with its presence recorded in more than 130 countries. By 2012, GLY production was estimated at approximately 720,000 tons per year [8]. Its applications span both agricultural and nonagricultural sectors. In agriculture, GLY is effective against numerous annual and perennial weed species, as well as broadleaf grasses [9]. The application rates typically range from ~1.5–2 kg/ha for the preharvest, postsowing, and pre-emergence phases; ~4.3 kg/ha for direct spraying in vineyards, orchards, pastures, and forestry; and ~2 kg/ha for aquatic weed control [10]. The broad-spectrum activity of this

herbicide initially restricted its use to postharvest treatments. A recent 2020 study analysed the use of GLY in 20 European countries and reported that average application rates range between 0.40 and 2.70 kg of active ingredient per hectare. For example, in Germany, GLY is applied to approximately 4.3 million hectares of agricultural land each year, with almost two-thirds of the applications focused on three main crops: oilseed rape, winter wheat, and winter barley [11]. Furthermore, in 2022, as part of the European Commission's Green Deal, a proposal was made to reduce the use and risk of chemical pesticides, including GLY, by 50% by 2030. However, importantly, in November 2023, the European Parliament rejected the proposal to reduce pesticide use, making these goals uncertain [12].

However, the development of genetically modified (GM) crops designed to resist GLY has led to its extensive use on annual crops as well [2, 8]. This application is particularly concentrated in countries such as the United States, Brazil, and Argentina, where herbicide-tolerant GM varieties are widely cultivated. Although GM crops are not cultivated in several regions, including the European Union, large quantities of GM-derived products (e.g., soybean and maize) are imported, potentially contributing to dietary exposure to GLY residues [1]. Unfortunately, the extensive and continuous application of GLY, especially in GM cropping systems, has resulted in the natural emergence of resistant weed

species, thereby reducing its agronomic effectiveness [8]. GLY is also widely used in nonagricultural contexts. In the United States, it ranks as the second most commonly used herbicide after 2,4-D [9], being employed for weed control along roadsides, under power lines [2], and even in aquatic systems or wetlands [10]. Several studies have demonstrated the ability of glyphosate to enter the human body through dermal absorption, inhalation, ingestion, and the consumption of contaminated food [13–16]. Once absorbed, GLY has been reported to distribute to various organs; however, evidence for its preferential accumulation in specific tissues remains limited. Some agronomic and regulatory documents have suggested distribution to the kidneys, liver, and colon, but these claims are not consistently supported by toxicological studies. Notably, the primary concern in human and animal studies has been the compound's ability to induce oxidative stress and mitochondrial dysfunction [16, 17]. Inhalation exposure is associated mainly with the onset of specific atopic asthma or wheezing [13]. Other documented effects include oxidative stress in hepatic tissues and cellular inflammation [18], increased nitric oxide (NO) concentrations, elevated tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels, impaired kidney function [14], and damage to adipose tissue and the liver, potentially contributing to conditions such as steatosis and nonalcoholic fatty liver disease [19].

Scientific evidence highlights the harmful effects of glyphosate on the environment and all life forms [20]. GLY has a relatively short half-life of approximately 9.05 h and breaks down quickly in the body [21, 22]. In contrast, its metabolite, AMPA, has a much longer half-life, lasting between 76 and 240 days and persisting significantly longer in the environment and in organisms [21, 23, 24]. Distinguishing between the biological and environmental half-lives of GLY is important. The biological half-life in the human body is relatively short, approximately 9.05 h, but GLY is metabolized very little and is mostly eliminated unchanged [25, 26]. On the other hand, the environmental half-life, which refers to how long GLY persists in the environment, particularly in soil, is relatively long, typically lasting several months due to substantial degradation processes [23, 24]. Its metabolite, AMPA, has an even longer half-life, persisting from 76 to 240 days in the environment. Human biomonitoring (HBM) measures chemical levels in the body, revealing exposure via several routes, including skin contact, ingestion, and inhalation [27]. Residues of GLY in food pose potential risks because they contribute to human exposure through dietary intake. Although regulatory agencies establish maximum residue limits to ensure safety, chronic consumption of contaminated food may lead to cumulative exposure [28, 29]. Currently, several studies

have assessed occupational exposure to GLY; however, data on exposure in the general population, particularly among vulnerable groups such as children and pregnant women, remain limited. Several regulatory agencies and international bodies have assessed the toxicity of GLY, sometimes reaching conflicting conclusions. The United States Environmental Protection Agency (EPA) published an overall assessment in 2020 in which it was determined that GLY is unlikely to be carcinogenic to humans based on animal and epidemiological studies. The EPA also stated that, when used as directed, GLY does not pose an unacceptable risk to human health, either to agricultural workers or to the general population [30]. However, in 2022, a U.S. court ordered the EPA to reassess the health and environmental risk of GLY, considering that the EPA had overlooked some aspects, such as the impacts on the ecosystem and protected species. The EPA responded by reserving the right to review these issues by 2026. The European Chemicals Agency (ECHA), through its Committee for Risk Assessment (RAC), confirmed in 2022 that the available evidence does not support the classification of the substance as a carcinogen, mutagen or reproductive toxin under the European Union CLP Regulation [31]. However, it was classified as a Category 1 eye irritant and as a long-term aquatic toxicant. In its 2023 assessment, the European Food Safety Authority (EFSA) concluded that, based on the available evidence, no critical areas of concern for human health, animal health or the environment exist in the context of the authorized uses of GLY [32]. However, the EFSA acknowledges that some residual uncertainties exist regarding the effects on intestinal microbes and biodiversity. Nevertheless, other authorities, such as the International Agency for Research on Cancer (IARC), have considered it appropriate to classify GLY as a carcinogen (Group 2A). The EFSA, on the other hand, has established an acceptable daily intake (ADI) for GLY of 0.5 mg/kg body weight/day [32, 33]. This ADI is intended to cover the general population, including vulnerable groups such as pregnant women and children, although no specific ADI has been separately defined for these subpopulations.

Furthermore, the conclusions of the EFSA and other regulatory bodies contrast with the assessment made by the IARC in 2015, which classified GLY as “probably carcinogenic to humans” (Group 2A). This classification was based on limited evidence of carcinogenicity in humans, primarily derived from epidemiological studies that reported an association between GLY exposure and non-Hodgkin lymphoma. In addition, the IARC identified sufficient evidence of carcinogenicity in experimental animals exposed to pure GLY. The agency also reported strong evidence of genotoxicity for both pure GLY and GLY-based formulations, suggesting the potential of

these substances to cause DNA damage. This discrepancy reflects the methodological differences between assessments oriented to danger (hazard, as in the case of the IARC) and those based on the realistic risk of exposure (risk, as for the EFSA and EPA).

Although no specific threshold exists for pregnant women, this ADI represents the exposure limit considered safe for the general population, including vulnerable groups such as pregnant women. An assessment of exposure risks, particularly for the general population, including health effects on pregnant women and children, is needed. This systematic review, conducted using the PRISMA methodology and registered in PROSPERO, aims to provide a comprehensive assessment of nonoccupational exposure to GLY in the general population, focusing on human biomonitoring studies that measured GLY levels in biological samples. Particular attention is given to vulnerable groups, such as pregnant women and children, who may experience heightened susceptibility to GLY-related health risks. By synthesizing and critically analysing the literature, this review contributes to a deeper understanding of the potential health implications of chronic GLY exposure and helps inform future risk assessments and regulatory decisions.

## Materials and methods

### Information sources and search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The systematic review project was registered in the PROSPERO (International Prospective Register of Systematic Reviews) with the code CRD42024540509, and the authors evaluated the study quality according to the PRISMA statement.

Two independent reviewers, C.F. and P.R., collected data from the specified databases. Both reviewers independently evaluated the eligibility of the records. Any discrepancies or uncertain cases were reviewed and resolved through discussion within the focus group.

### Search strategy

We utilized the keywords 'glyphosate' in combination with 'human health', 'nonfarming populations', or 'urine concentration'. We conducted our search using the following databases: PubMed (National Library of Medicine), Scopus (Elsevier), Web of Science (Clarivate), and Cochrane CENTRAL (Wiley).

The complete database search is provided in the Supplementary Files. The search was restricted to studies published between January 1, 2013, and January 1, 2025, to focus on the most recent and methodologically robust evidence. This time frame was chosen to include studies employing updated and validated biomonitoring

techniques for GLY and AMPA, ensuring greater comparability and reliability of the exposure data.

The PRISMA flow diagram (Fig. 1) illustrates the studies included and excluded, along with the reasons for exclusion. A risk of bias analysis was performed using the Newcastle–Ottawa scale to minimize study heterogeneity. Only records published in English and studies with an observational design (including longitudinal and cross-sectional studies) were included. We excluded reviews, conference proceedings, editorials, letters to the editor, articles without full-text access, articles lacking statistical data, and those published outside the specified timeframe. Additional inclusion and exclusion criteria were applied during the full-text screening process. We selected titles and abstracts, including those related to GLY and AMPA detection in human studies published as original articles. We excluded studies on occupational exposure to pesticides, studies that did not have a representative sample size, and those that did not present a statistical analysis of raw data. For each rejected item, we noted a reason. Articles with a sample size of less than 40 participants were also excluded from this review to increase the evidence force.

### Exposure assessment

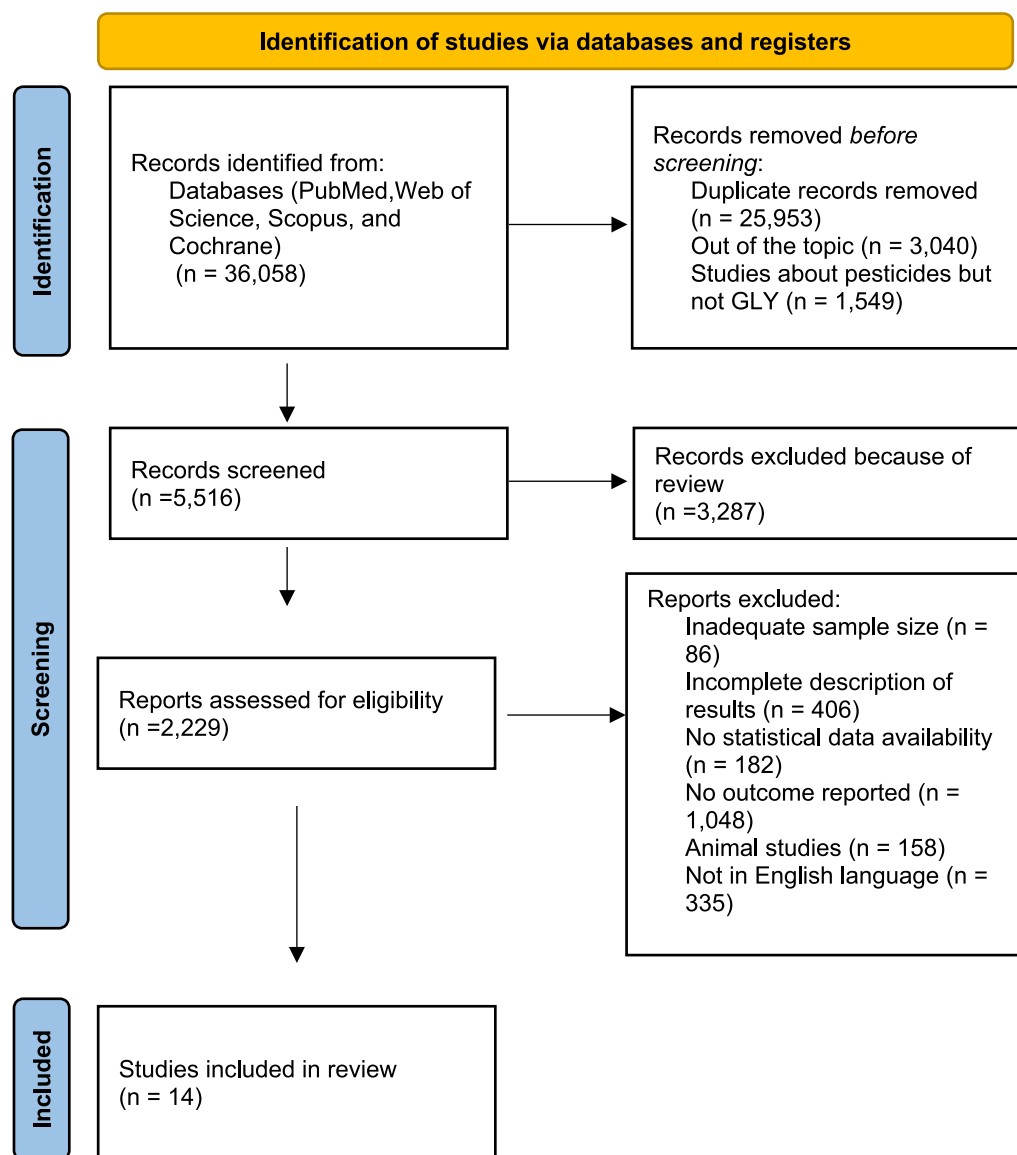
In each study, we evaluated the reported methodology with the levels of GLY and AMPA measured in urine samples. We considered studies methodologically robust if GLY and AMPA were measured using validated techniques, such as LC–MS/MS, the Abraxis Glyphosate ELISA Plate Kit®, UPLC–MS/MS, GC–MS/MS, and enzyme-linked immunosorbent assay (ELISA) kits (Table 1).

### Quality assessment and risk of bias

The methodological quality of the studies included in this review was assessed using the Newcastle–Ottawa Scale (NOS), a validated tool for evaluating the risk of bias in observational studies. The NOS evaluates three domains: selection of study groups, comparability between groups, and assessment of outcomes (for cohort studies) or exposure (for cross-sectional studies). As the scale is adapted to the study design, the maximum achievable score is 9 for cohort studies and 10 for cross-sectional studies. The quality assessment was conducted independently by two reviewers (P.R. and M.C.), and any discrepancies were resolved through discussion and consensus (Table 2).

### Screening process

Studies were screened by four reviewers (CF, PR, EP, and CS) against the set eligibility criteria. Each record required agreement on inclusion or exclusion by three



**Fig. 1** PRISMA Flow chart

of the four reviewers, who independently assessed the titles and abstracts of each record. When conflicts occurred during the screening process, the final decision was made jointly by the reviewers' focus group. Four reviewers (MC, AC, GOC, and MF) independently conducted the full-text screen of the peer-reviewed literature using the inclusion and exclusion criteria (Table 3).

In this review, we initially identified 36,058 articles and, after accurate screening (see Fig. 1), reached a final number of 13 eligible articles applying all the criteria used, and these articles were included in this systematic

review. We used Zotero as a tool for data collection to collect and manage the articles [34].

## Results

### Methodological quality of the included studies

The methodological quality of the studies included in this review, as assessed by the NOS, was generally high, with scores ranging from 8 to 9. These scores indicate a low likelihood of systematic bias that could compromise the reliability of the findings of this review. Notably, both cohort and cross-sectional studies demonstrated methodological robustness across the evaluated domains: selection, comparability, and outcome

**Table 1** Characteristics of the included studies

| Author and year     | Title of the manuscript                                                                                                                               | Target population                                                                                                                                                                                                                                           | Sampling method                                                                                                      | Study aims                                                                                                                                                                                                                                                 | Methodological techniques                                                                                                                                                                                                                                                                 | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Conrad et al., 2017 | Glyphosate in German adults; Time trend (2001 to 2015) of human exposure to a widely used herbicide                                                   | Young adults (predominantly students) aged 20 to 29 years<br>400 participants (200 males and 200 females) living in Greifswald, a city in north-eastern Germany, were recruited in the years 2001, 2003, 2005, 2007, 2009, 2011, 2012, 2013, 2014, and 2015 | 24 h-urine specimens collected in the annual sampling of the German ESB                                              | To investigate the exposure of the general German population to glyphosate and AMPA and its variation over time                                                                                                                                            | The analysis was performed using gas chromatography coupled to tandem mass spectrometry (GC–MS/MS)                                                                                                                                                                                        | -GLY $\geq 0.1$ ng/mL (LOQ) in 31.8% of patients<br>-AMPA $\geq 0.1$ ng/mL (LOQ) in 40.1% of patients<br>-GLY and AMPA > males;                                                                                                                                                                                                                                                                                                                                       |
| Parvez et al., 2018 | Glyphosate exposure in pregnancy and shortened gestational length: a prospective Indiana birth cohort study                                           | Pregnant women aged between 18 and 40 years<br>71 participants from central Indiana were recruited through referrals from midwives during routine prenatal visits (June 2015–June 2016)                                                                     | Residual urine samples from pregnant women were collected as part of routine prenatal care                           | To assess the prevalence and exposure levels of GLY in pregnant women; examine demographic, dietary, and drinking water contributions to the exposure risk; and evaluate the association between urinary GLY levels, pregnancy duration, and foetal growth | GLY measurements were obtained by liquid chromatography–tandem mass spectrometry (LC–MS/MS) using an Agilent LC 1260 system (Agilent LC 1260-AB Sciex 5500 Triple Quadrupole MS, Santa Clara, CA) with an Obelisc-N mixed-mode column (2.1 $\times$ 100 mm 5 $\mu$ m) maintained at 40 °C | -GLY > 0.1 ng/mL (LOD) in 93% of patients<br>-Max urinary GLY concentration: 7.20 ng/mL, Min concentration: 0.5 ng/mL                                                                                                                                                                                                                                                                                                                                                 |
| Soukup et al., 2020 | Glyphosate and AMPA levels in human urine samples and their correlation with food consumption: results of the cross-sectional KarMeN study in Germany | Volunteers aged between 18 and 80 years<br>301 volunteers from Karlsruhe, Germany, were recruited via telephone interviews (2012–2013)                                                                                                                      | Participants collected their urine for 24 h on the day prior to their examination, including the first morning urine | GLY exposure in a metabolically very well-characterized population                                                                                                                                                                                         | GLY and AMPA levels were quantified in the 24 h urine samples by LC–MS/MS                                                                                                                                                                                                                 | -GLY & AMPA concentrations < LODs in 65% of samples<br>-25.2% had values between the LOD and LOQ<br>- 8.3% > LOQ (LOQ = 0.2 $\mu$ g/L for GLY & AMPA)<br>-Max GLY concentration: 1.36 $\mu$ g/L, Max AMPA concentration: 1.53 $\mu$ g/L<br>Significant correlations:<br>• GLY concentration & legume consumption ( $p < 0.0001$ )<br>• GLY concentration & mushroom consumption ( $p = 0.0102$ )<br>• GLY + AMPA concentrations & legume consumption ( $p = 0.0003$ ) |

**Table 1** (continued)

| Author and year                  | Title of the manuscript                                                                                                                                | Target population                                                                                                                                                                                                       | Sampling method                                                                                                                                                              | Study aims                                                                                                                                                | Methodological techniques                                                                                                                                                                                                                                              | Results                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ferreira et al., 2021            | Urine biomonitoring of glyphosate in children: Exposure and risk assessment                                                                            | Children aged between 2 and 13 years (46.34% males, 53.7% females) 41 first-morning urine samples were collected from healthy children across Portugal (July 2018–February 2019)                                        | The 41 spot urine samples were obtained from healthy children living in different regions of Portugal                                                                        | To evaluate GLY exposure and postexposure risks in Portuguese children                                                                                    | The analytical determination was performed using the commercial GLY determination kit (Abraxis Glyphosate ELISA Plate Kit®, ABRAXIS, USA)                                                                                                                              | -GLY was detected in 95.1% of samples<br>-Mean GLY levels: $1.77 \pm 0.86 \mu\text{g/L}$<br>-Average GLY levels: $\text{♀ } 2.00 \mu\text{g/L}$ , $\text{♂ } 1.56 \mu\text{g/L}$<br>-Max GLY levels: $\text{♀ } 4.35 \mu\text{g/L}$ , $\text{♂ } 3.18 \mu\text{g/L}$<br>-Min GLY levels: $\text{♀ } 0.87 \mu\text{g/L}$ , $\text{♂ } 0.95 \mu\text{g/L}$<br>-The GLY concentration increases with age |
| Lemke et al., 2021               | Glyphosate and AMPA in urine of children and adolescents in Germany, Human biomonitoring results of the German Environmental Survey 2014–2017 (GerESV) | Children and adolescents aged 3–17 years living in Germany were recruited as part of the German Environmental Survey for Children and Adolescents 2144 early morning urine samples were collected between 2014 and 2017 | 2144 early morning urine samples were collected from German children and adolescents                                                                                         | To provide the first nationwide human biomonitoring data on exposure to glyphosate and its metabolite AMPA in children and adolescents                    | GLY and AMPA levels were quantified in urine samples by GC–MS/MS                                                                                                                                                                                                       | 52% of the GLY concentrations were above the LOQ, compared to 46% of AMPA concentrations<br>GLY: $0.107 \mu\text{g/L}$ ( $0.090 \mu\text{g/g}$ creatinine)<br>AMPA: $0.100 \mu\text{g/L}$ ( $0.085 \mu\text{g/g}$ creatinine)                                                                                                                                                                         |
| Lesseur et al., 2021             | Maternal Urinary Levels of Glyphosate during Pregnancy and Anogenital Distance in Newborns in a US Multicenter Pregnancy Cohort                        | Pregnant women aged > 18 years and their children 100 healthy pregnant women in the U.S. and 94 children (excluding preterm births) (August 2010–August 2012)                                                           | In each trimester, study participants provided urine samples and completed questionnaires that collected demographic, health, lifestyle and reproductive history information | To examine urinary GLY levels in pregnant women and explore the association between maternal GLY exposure and anogenital distance anomalies in newborns   | The urinary concentrations (ng/mL) of GLY and AMPA were measured using ultrahigh-performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS) on the Vanquish UHPLC coupled to a TSQ Altis triple quadrupole mass spectrometer (ThermoFisher, San Jose, CA) | GLY > LOQ ( $0.041 \text{ ng/mL}$ ) in 85.2% of samples<br>– Mean: $0.38 \text{ ng/mL}$<br>– Min: $0.05 \text{ ng/mL}$<br>– Max: $1.90 \text{ ng/mL}$<br>AMPA > LOQ ( $0.04 \text{ ng/mL}$ ) in 75.6% of samples<br>– Mean: $0.40 \text{ ng/mL}$<br>– Min: $0.04 \text{ ng/mL}$<br>– Max: $6.01 \text{ ng/mL}$                                                                                        |
| Buerkers et al., 2022<br>-Part A | Glyphosate and AMPA in Human Urine of HBM4EU Aligned Studies: Part A Children                                                                          | Children aged 6 to 11 years (in Germany, France, Belgium, Slovenia, and Cyprus)                                                                                                                                         | Study participants provided morning and spot urine samples and completed questionnaires that collected demographic, health, lifestyle and reproductive history information   | To evaluate exposure to glyphosate (Gly) and its metabolite AMPA in children living in various European countries through the analysis of urinary samples | Urinalysis using highly specific techniques (LC–MS/MS or GC–MS/MS)                                                                                                                                                                                                     | The highest levels of both substances were found in Cyprus ( $\text{P95} = 1.03 \mu\text{g/L}$ for Gly and $\text{P95} = 0.66 \mu\text{g/L}$ for AMPA)                                                                                                                                                                                                                                                |

**Table 1** (continued)

| Author and year               | Title of the manuscript                                                                                                           | Target population                                                                                                                                                                                                                                                            | Sampling method                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Study aims                                                                                                                          | Methodological techniques                                                                                                                   | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Buerkers et al., 2022 -Part B | Glyphosate and AMPA in Human Urine of HBM4EU-Aligned Studies: Part B Adults                                                       | Adults of the general population aged 20 to 40 (in Germany, Switzerland, Iceland, France) who were not professionally exposed                                                                                                                                                | Study participants provided morning and spot urine samples and completed questionnaires that collected demographic, health, lifestyle and reproductive history information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | To evaluate the exposure of the European adult population to glyphosate (Gly) and its main metabolite AMPA through a urine analysis | Urinalysis using highly specific techniques (LC–MS/MS)                                                                                      | The highest concentrations (µg/L) were observed for Gly in Iceland (P95 = 0.37 µg/L) and for AMPA in France (P95 = 0.42 µg/L)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Connolly et al., 2022         | A Human Biomonitoring Study Assessing Glyphosate and Aminomethylphosphonic Acid (AMPA) Exposures among Farm and Non-Farm Families | Farming and nonfarming families, adults (mother and father) and sons aged from 3 to 19 years<br>224 individuals from Ireland (54 nonfarming and 14 farming families) were recruited via invitation letters, including 92 children/adolescents (74 nonfarming and 18 farming) | Each household member provided a first morning, complete urine sample<br>Each household member on the farm provided a urine sample the morning after spraying glyphosate products<br>The direct user of the Glyph herbicide provided a urine sample<br>Each completed a questionnaire indicating the time of voiding, whether the sample was complete, storage, potential activities that led to pesticide exposure, and types of foods consumed in the 48 h prior to sample collection<br>Urine samples were initially collected from participants' homes. Subsequently, the sampling protocol had to be modified due to restrictions due to the COVID-19 pandemic | To analyse Gly and AMPA exposure among children from farming and non-farming households                                             | The analysis was performed using gas chromatography coupled to tandem mass spectrometry (GC–MS/MS) with quantification via isotope dilution | <p>-Urinary Gly and AMPA concentrations in adults corresponded to 2% and 0.2% of the EFSA ADI (0.5 mg/kg body weight/day)</p> <p>-Max Gly level: 3.21 µg/L, Max AMPA level: 7.24 µg/L</p> <p>-In nonfarming children: Gly = 3% of the ADI, AMPA = 0.4% of the ADI</p> <p>Gly: % ≥ LOQ; Range; Median</p> <p>Father: 20%; &lt; LOQ–0.17; &lt; LOQ</p> <p>Mother: 17%; &lt; LOQ–0.17; &lt; LOQ</p> <p>Children: 36%; &lt; LOQ–2.48; &lt; LOQ</p> <p>AMPA: % ≥ LOQ; Range; Median</p> <p>Father: 59%; &lt; LOQ–4.12; 0.06</p> <p>Mother: 60%; &lt; LOQ–2.86; 0.12</p> <p>Children: 60%; &lt; LOQ–7.24; 0.09</p> |

**Table 1** (continued)

| Author and year     | Title of the manuscript                                                                                                                    | Target population                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Sampling method                                                         | Study aims                                                                                                                                                                       | Methodological techniques                                                                                                                      | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Grau et al., 2022   | Quantifiable urine glyphosate levels were detected in 99% of the French population, with higher values in men, younger people, and farmers | General population from 63 French districts<br>6,848 participants were recruited by Foix French committees (June 2018–January 2020)                                                                                                                                                                                                                                                                                                                                                                   | Participants provided first-void urine samples                          | To determine the frequency and levels of GLY and explore its association with seasonal variations and exposure determinants, including lifestyle, diet, and occupational factors | Urine samples were analysed using the glyphosate enzyme-linked immunosorbent assay (ELISA) kit                                                 | -Higher GLY levels were detected in summer<br>-Lower GLY levels were detected in those who urinated 6 h before sampling (0.95 ng/mL) compared with those who did not (1.24 ng/mL)<br>-GLY levels: $\delta = 1.27$ ng/mL, $\eta = 1.13$ ng/mL; $p < 0.001$<br>-Smokers: 1.43 ng/mL, Non-smokers: 1.16 ng/mL<br>-No significant difference in GLY levels between organic and non-organic food consumers (1.19 ng/mL vs. 1.17 ng/mL), but lower GLY levels were observed in organic food consumers vs. non-consumers (1.16 ng/mL vs. 1.21 ng/mL) |
| Nomura et al., 2022 | Temporal trend and cross-sectional characterization of urinary concentrations of glyphosate in Japanese children from 2006 to 2015         | Group A = 150 children (79 boys and 71 girls), aged 4–6 years from a nursery school<br>Group B = 84 children (42 boys and 42 girls), aged 3 years from a health program in the Aichi area (Japan region)<br>150 urine samples were collected in October 2006, 2011, and 2015 to assess temporal changes in urinary Gly concentrations. Additional samples from 3-year-olds were collected in August–September 2012 (summer, n = 42) and February 2013 (winter, n = 42) to examine seasonal variations | First morning urine samples were collected from all experimental groups | To examine temporal trends (2006–2015), seasonal variations, and gender-specific differences in GLY exposure among Japanese children in nonagricultural environments             | The urinary Gly concentrations were measured using LC–MS/MS coupled with an Agilent 6430 Triple Quadrupole LC/MS System (Agilent Technologies) | -Group A: Maximum GLY level = 1.2 $\mu$ g/kg body weight/day ( $< \text{ADI} = 1$ mg/kg body weight/day)<br>GLY concentration ( $\mu$ g/L)<br>2006: 18<br>2011: 30<br>2015: 50<br>-Group B:<br>GLY concentration ( $\mu$ g/L)<br>-Summer % LOD: 60<br>-Winter % LOD: 55<br>-Male % LOD: 57<br>-Female % LOD: 56<br>-No significant correlation between GLY levels and other pesticide/insecticide biomarkers<br>-No significant associations between the child's sex and urinary GLY levels                                                   |

Table 1 (continued)

| Author and year      | Title of the manuscript                                                                  | Target population                                                                                       | Sampling method                                                                     | Study aims                                                                                                                                                                        | Methodological techniques                                                                                                                                                                                                                            | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mesnage et al., 2022 | Impacts of dietary exposure to pesticides on faecal microbiome metabolism in adult twins | 65 monozygotic twin pairs (130 individuals) from the TwinsUK Cohort (93% woman, aged 63.8 ± 10.4 years) | Urine and faecal samples; dietary intake assessed via food frequency questionnaires | To evaluate pesticide exposure in the UK population and investigate associations between urinary pesticide residues, dietary habits, and faecal microbiome composition/metabolism | GLY and AMPA were measured using liquid chromatography–tandem mass spectrometry (LC–MS/MS) after derivatization with 9-fluorenylmethyl chloroformate (FMOC–Cl) on a Shimadzu NEXERA X2 system coupled to an 8060 triple quadrupole mass spectrometer | <ul style="list-style-type: none"><li>-GLY concentration &gt; LOD (0.05 µg/L) in 53% of participants; median = 0.045 µg/L; max = 2.8 µg/L; IQR = 0.0025–0.84 µg/L</li><li>-AMPA concentration &gt; LOD (0.1 µg/L) in 5.6% of participants; most values &lt; LOD, max = 1.4 µg/L</li><li>-No significant differences in GLY/AMPA levels according to diet or geographic location; GLY was positively associated with observed species richness (p = 0.01)</li><li>-Some positive associations between GLY levels and fatty acid metabolites in fecal metabolome</li></ul> |

**Table 1** (continued)

| Author and year            | Title of the manuscript                                                                                                    | Target population                                                                                                                                                                                                                                                                                                                                                   | Sampling method                                                                      | Study aims                                                                                            | Methodological techniques                                                                                                                                                                                                            | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ashley-Martin et al., 2023 | Urinary concentrations and determinants of glyphosate and glufosinate in pregnant Canadian participants in the MIREC study | Adult women in the first trimester of pregnancy and monitored until the day of delivery. The majority of participants in this analysis were over 30 years of age<br>1,880 urine samples were collected from women in Canada (Vancouver, Edmonton, Winnipeg, Sudbury, Ottawa, Kingston, Toronto, Hamilton, Montreal, and Halifax) between June 2008 and January 2011 | At the first trimester visit (range: 6–13 weeks), women provided a spot urine sample | To measure urinary concentrations of GLY, glufosinate, and their primary metabolites, AMPA and 3-MPPA | The analytes were analysed by ultra-performance liquid chromatography (Waters Acquity) coupled to tandem mass spectrometry (Waters Xevo TQ-XS) (UPLC-MS/MS) in MRM mode using an electrospray ionization source in the positive mode | <ul style="list-style-type: none"><li>-GLY concentration &gt; the LOD in 74% of participants and AMPA concentration &gt; the LOD in 72% of participants</li><li>-GLY concentration &gt; the LOQ in 49% of participants and AMPA concentration &gt; the LOQ in 43% of participants</li><li>- Glufosinate was detected in 1% of participants and 3-MPPA in 6% of participants</li><li>-GLY levels: 0.041 µg/L, higher in Canadian-born women; no racial differences</li><li>-AMPA: 0.015 µg/L, lower in white women</li><li>-Positive correlations were observed between GLY levels, AMPA levels, pre-pregnancy BMI, and education</li><li>-No associations with maternal age, income, smoking, or newborn sex</li><li>-Strong links between high GLY levels and consumption of raw spinach, soy/rice drinks, whole grain bread, or pasta (<math>p &lt; 0.05</math>)</li><li>-All GLY results were below the LOQ (0.26 µg/L)</li></ul> |

Table 1 (continued)

| Author and year            | Title of the manuscript                                                                                                       | Target population                                                                                                                                                                                                                                                                                                                                                                               | Sampling method                                                                                 | Study aims                                                                                                                                                                                                                                      | Methodological techniques                                                                                                                                                                                                                                                           | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ashley-Martin et al., 2024 | Gestational urinary concentrations of glyphosate and aminomethylphosphonic acid in relation to preterm birth: the MIREC study | Participants were recruited from 10 Canadian cities (Vancouver, Edmonton, Winnipeg, Sudbury, Ottawa, Kingston, Toronto, Hamilton, Montreal, and Halifax) between 2008 and 2011<br>MIREC is a pregnancy cohort of 1765 participants recruited from 10 Canadian cities (Vancouver, Edmonton, Winnipeg, Sudbury, Ottawa, Kingston, Toronto, Hamilton, Montreal, and Halifax) between 2008 and 2011 | At the first trimester visit (range: 6–13 weeks), the participants provided a spot urine sample | To quantify the associations between urinary GLY and AMPA levels and preterm birth events in the pan-Canadian Maternal–Infant Research on Environmental Chemicals (MIREC) study and determine whether these associations differed by foetal sex | GLY and AMPA concentrations were quantified using ultra-performance liquid chromatography (Waters Acuity) coupled to tandem mass spectrometry (Waters Xevo TQ-XS) (UPLCMS/MS) in the multiple reaction monitoring mode using an electrospray ionization source in the positive mode | GLY levels in preterm births: 0.10 µg/L vs. term births: 0.11 µg/L; AMPA levels in preterm births: 0.16 µg/L vs. term births: 0.16 µg/L<br>GLY concentrations in MIREC (0.25 µg/L) were comparable to those observed in the TIDES study (0.25 µg/L) but half of those reported in the PROTECT study (0.47 µg/L)<br>AMPA concentrations in MIREC (0.21 µg/L) were only slightly lower than those observed in the PROTECT study (0.26 and 0.23 µg/L) and higher than those observed in TIDES (0.16 µg/L) |

GLY (glyphosate), LOD (limit of detection), LOQ (limit of quantification), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), ♀ (female), ♂ (male), ADI (acceptable daily intake), BMI (body mass index)

or exposure assessment. However, minor variations in scores, particularly within the selection domain, suggest differences in study design and execution quality. The overall quality of the included studies enhances the validity of the findings while also highlighting the need for additional prospective research with rigorous designs to further strengthen the evidence base.

#### Urinary glyphosate and AMPA exposure across populations

This systematic review included fourteen studies (Table 1): Conrad et al., 2017; Parvez et al., 2018; Ferreira et al., 2021; Soukup et al., 2020; Lemke et al., 2021; Ashley-Martin et al., 2023; Connolly et al., 2022; Grau et al., 2022; Lesseur et al., 2021; Nomura et al., 2022; Ashley-Martin et al., 2024; Buerkers et al., 2022 Part A; and Buerkers et al., 2022 Part B, Mesnage et al., 2022 (Table 4).

#### Pregnant women

Multiple studies included in this review examined urinary GLY and AMPA levels in pregnant women, reporting detectable concentrations even among women without occupational exposure. Detection frequencies and concentrations varied across regions and methodologies. Measurable concentrations of GLY and AMPA were reported, often during early or midgestation.

In one of the earliest studies, Parvez et al. (2018) analysed urine samples from 71 pregnant women in Indiana and reported GLY detection in 93% of the samples, with concentrations ranging from 0.5 to 7.20 ng/mL. Higher urinary GLY concentrations were reported among women living in rural areas and those with increased coffee consumption. Elevated GLY levels were associated with shorter gestational duration [35].

Similarly, Lesseur et al. (2021) examined 94 U.S. pregnant women and quantified GLY in 85.2% of samples (concentrations ranging from 0.05 to 1.90 ng/mL), alongside AMPA in 75.6 of samples (average concentration of 0.40 ng/mL). The study revealed a sex-specific association between prenatal exposure and newborn anogenital distance (AGD): a longer AGD-AF in female infants was linked to higher AMPA levels [36].

Ashley-Martin et al. (2023, 2024) conducted two Canadian cohort studies reporting urinary GLY and AMPA levels in pregnant women on a national scale. The 2023 study included 1,880 pregnant women and reported detectable urinary levels of GLY and AMPA in 74% and 72% of participants, respectively. The mean GLY level was 0.041 µg/L. Exposure was positively associated with BMI, education level, and the consumption of specific foods such as spinach and soy-based drinks, although no link emerged with maternal

age or smoking status [37]. The 2024 study focused on preterm birth outcomes among 1,765 participants. Sampling occurred between 6 and 13 weeks of gestation. Despite a detection rate >70%, neither GLY nor AMPA concentrations in the first trimester were associated with the gestational age or the incidence of preterm delivery [38].

#### Children and adolescents

The reviewed studies reported low-level urinary GLY and AMPA concentrations among children and adolescents in Europe, Asia, and North America.

In Portugal, Ferreira et al. (2021) conducted a biomonitoring study on healthy children aged 2–13 years. GLY was detected in 95.1% of the urine samples, with a mean concentration of approximately 1.77 µg/L. A general increase in average GLY levels was observed in children under 3 years of age up to 9 years. However, when comparing the last two age categories (older children), only a marginally statistically significant difference was detected ( $p=0.0631$ ), without clear evidence of bioaccumulation. Children consuming backyard-grown produce presented elevated urinary GLY levels, with the highest concentration (4.35 µg/L) measured in a child whose parents reported GLY use [39].

Nationwide data from Germany, presented by Lemke et al. (2021), included 2,144 urine samples from children and adolescents aged 3–17 years. GLY and AMPA were quantifiable in 52% and 46% of the samples, respectively, with mean concentrations of approximately 0.107 µg/L (GLY) and 0.100 µg/L (AMPA). No significant associations were found between urinary levels and sex, diet, or geographic residence, although children aged 11–13 years presented slightly higher concentrations than older adolescents. The study reported low-level exposure across the cohort, with limited associations with lifestyle factors. The questionnaire included a narrow set of items regarding potential exposure routes [40].

In Japan, Nomura et al. (2022) measured urinary GLY levels in 234 nonfarming children and detected higher levels during the summer months. No statistically significant differences were observed between sexes or across cohorts [41].

From a multicountry perspective, Buerkers et al. (2022–Part A) aggregated biomonitoring data from five EU nations (Germany, France, Belgium, Slovenia, and Cyprus) within the HBM4EU project. The data revealed low but widespread urinary detection, with Cyprus recording the highest concentrations among children (P95 GLY: 1.03 µg/L; AMPA: 0.66 µg/L). Results varied by country and analytical method (LC–MS/MS vs. ELISA).

**Table 2** Quality assessment of included studies using the Newcastle–Ottawa Scale (NOS)

| Author, publication year    | Study design    | Selection | Comparability | Outcome | Tot  |
|-----------------------------|-----------------|-----------|---------------|---------|------|
| Conrad, et al., 2017        | Cross-sectional | 4/5       | 2/2           | 3/3     | 9/10 |
| Parvez, et al., 2018        | Cohort study    | 3/4       | 2/2           | 3/3     | 8/9  |
| Soukup, et al., 2020        | Cross-sectional | 4/5       | 2/2           | 3/3     | 9/10 |
| Ferreira, et al., 2021      | Cross-sectional | 3/5       | 2/2           | 3/3     | 8/10 |
| Lesseur, et al., 2021       | Cohort study    | 3/4       | 2/2           | 3/3     | 8/9  |
| Lemke, et al., 2021         | Cross-sectional | 4/5       | 2/2           | 2/3     | 8/10 |
| Buerkers, et al., 2022      | Cross-sectional | 4/5       | 2/2           | 3/3     | 9/10 |
| Buerkers, et al., 2022      | Cross-sectional | 4/5       | 2/2           | 3/3     | 9/10 |
| Connolly, et al., 2022      | Cross-sectional | 4/5       | 2/2           | 3/3     | 9/10 |
| Grau, et al., 2022          | Cross-sectional | 3/5       | 2/2           | 3/3     | 8/10 |
| Nomura, et al., 2022        | Cross-sectional | 4/5       | 2/2           | 3/3     | 9/10 |
| Mesnager et al., 2022       | Cross-sectional | 4/5       | 2/2           | 3/3     | 9/10 |
| Ashley-Martin, et al., 2023 | Cross-sectional | 4/5       | 2/2           | 2/3     | 8/10 |
| Ashley-Martin, et al., 2024 | Cohort study    | 3/4       | 2/2           | 3/3     | 8/9  |

**Table 3** Study inclusion and exclusion criteria

| Category                | Inclusion                                                                                                    | Exclusion                                                                                                                                                            |
|-------------------------|--------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Population              | General population exposed to GLY and its metabolite AMPA                                                    | Population occupationally exposed (e.g., agricultural workers)                                                                                                       |
| Study design            | Observational studies (cohort, cross-sectional, case–control), clinical trials, randomized controlled trials | Conference papers, reviews, meta-analyses, book chapters, letters, notes, errata, short surveys, editorials, retracted articles, reports, incomplete data, abstracts |
| Exposure / Intervention | Exposure to GLY and AMPA not related to occupational or iatrogenic risk                                      | Occupational or iatrogenic exposure to GLY                                                                                                                           |
| Comparator / Control    | Persons not occupationally exposed to GLY                                                                    | Persons occupationally exposed to GLY                                                                                                                                |

No consistent exposure determinants were identified [42].

Connolly et al. (2022) focused on Irish families and compared farming and non-farming households. Detectable GLY and AMPA levels were observed even in non-farming households, with children showing the highest proportion of samples above the limit of quantification (36% for GLY and 60% for AMPA). Among 74 nonfarming children, GLY concentrations reached up to 3% of the EFSA's ADI and GLY levels in children exceeded those in adults from the same households [22].

Across studies, detectable urinary GLY and AMPA concentrations were reported in children in multiple regions. Some cohorts showed no consistent correlations between urinary levels and factors such as diet or geography. Biomonitoring studies in children reported limitations such as parental reporting accuracy, small sample sizes, and limited environmental metadata.

#### General adult population

In adults from the general population without occupational pesticide exposure, urinary GLY and AMPA were

detected, generally at lower concentrations than those reported in children or pregnant women. Conrad et al. (2017) conducted a historical trend analysis on German young adults (aged 20–29 years) over 15 years. No major health outcomes were reported. The frequency of GLY detection increased from 10% in 2001 to over 56% in 2012–2013, with the highest concentration reaching 2.80 µg/L. AMPA was detected in 40.1% of the samples, showing a similar temporal trend [43].

Grau et al. (2022) evaluated 6,848 adults across 63 French districts using ELISA methods and detected GLY in 99.8% of the samples, although the sensitivity and specificity of ELISA may limit quantitative precision. Higher GLY concentrations were observed in men and in smokers, as well as in samples collected during summer months. Participants consuming filtered water had lower urinary GLY levels compared with those drinking spring or tap water [44].

Buerkers et al. (2022–Part B) combined data from adults in Germany, France, Switzerland, and Iceland within the HBM4EU-aligned project. In Iceland, the GLY concentration reached the 95th percentile of 0.37 µg/L,

**Table 4** Summary of studies on urinary glyphosate levels and significant associated factors

| Author (Year)              | Population                   | Sample size | Glyphosate detected | Significant correlated factors*        | Statistical tests                                    | Notes |
|----------------------------|------------------------------|-------------|---------------------|----------------------------------------|------------------------------------------------------|-------|
| Conrad et al., 2017        | Young adults                 | 400         | ✓                   | –                                      | Pearson, Spearman                                    | –     |
| Parvez et al., 2018        | Pregnant women               | 71          | ✓                   | Shorter gestational length             | NC                                                   | –     |
| Soukup et al., 2020        | Adults (18–80 yrs)           | 301         | ✓                   | Increased mushroom consumption         | Spearman, Mann–Whitney                               | –     |
| Ferreira et al., 2021      | Children                     | 41          | ✓                   | Parental education level               | Kruskal–Wallis, Mann–Whitney                         | –     |
| Lemke, et al., 2021        | Children and adolescents     | 2144        | ✓                   | –                                      | ANOVA                                                | –     |
| Buerkers, et al., 2022     | Children                     | 971         | ✓                   | –                                      | NC                                                   | –     |
| Buerkers, et al., 2022     | Adult (20–39 yrs)            | 913         | ✓                   | –                                      | –                                                    | –     |
| Lesseur et al., 2022       | Pregnant women & new-borns   | 100 + 94    | ✓                   | –                                      | Pearson, t-test, ANOVA                               | –     |
| Connolly et al., 2022      | Families                     | 68 families | ✓                   | –                                      | Mann–Whitney                                         | –     |
| Grau et al., 2022          | French general population    | 6848        | ✓                   | Younger age, male sex, farmers         | ANOVA, Kruskal–Wallis                                | –     |
| Nomura et al., 2022        | Japanese children            | 234         | ✓                   | –                                      | Kruskal–Wallis, Dunn                                 | –     |
| Mesnage et al., 2022       | Adult monozygotic twins (UK) | 130         | ✓                   | ↑ observed bacterial species richness  | Linear mixed models, PERMANOVA, FDR-adjusted t-tests | –     |
| Ashley-Martin et al., 2023 | Pregnant women (Canada)      | 1880        | ✓                   | Water, bread, legumes, coffee, alcohol | ANOVA                                                | –     |
| Ashley-Martin et al., 2024 | Pregnant women               | 1765        | ✓                   | Preterm birth                          | –                                                    | –     |

✓: Thresholds for “> glyphosate levels” are not consistently defined

Detectable urinary glyphosate levels

\*Significant correlated factors\*: Only listed if authors reported a statistically significant correlation with higher glyphosate levels

NC: No statistically significant correlation found

“> Glyphosate levels”: Authors should clarify the threshold or reference range used to define high levels

whereas the AMPA concentration peaked in France (P95: 0.42 µg/L). Median levels often fell below the limit of quantification. Vegetarians in Iceland and high fruit/vegetable consumers in Germany had higher GLY levels. Men presented elevated concentrations compared with women. Employment status and income showed weaker associations with urinary concentrations [45].

Mesnage et al. (2022) analysed urinary GLY and AMPA levels in 130 Twins adults from UK cohort without occupational pesticide exposure. GLY was detected in 53% of participants (median 0.045 µg/L, max 2.8 µg/L), whereas AMPA was detectable in 5.6% of samples, mostly below the limit of detection. No significant associations were observed with diet or geographic location; GLY was positively associated with observed species richness and some fecal fatty acid metabolites, while AMPA showed no significant correlations [50].

In the study of Connolly et al. (2022), among adult participants from Irish families not engaged in farming, urinary concentrations of GLY and AMPA were detected in most samples and remained well below the ADI. GLY levels in children from these households often exceeded those measured in adults [22].

Across these studies, GLY and AMPA were detectable in adults, with concentrations varying by diet, season, and analytical technique. Methods ranged from high-specificity LC–MS/MS to broader immunoassays, affecting interstudy comparability.

#### Environmental and lifestyle determinants of exposure

Several of the studies included in this review assessed the environmental, dietary, and behavioural factors associated with internal exposure to GLY and its metabolite AMPA. These determinants were examined in adult, paediatric, and pregnant populations, with various methodologies and outcomes.

In the study by Soukup et al. (2020), urinary GLY was undetectable in approximately two-thirds of German adult participants, with detectable levels reaching 1.36 µg/L. GLY and AMPA concentrations were significantly positively associated with the consumption of legumes and mushrooms ( $p < 0.0001$  and  $p = 0.0102$ , respectively) [46]. Ashley-Martin et al. (2023) reported that GLY levels were higher among pregnant women who consumed foods such as raw spinach, soy/rice drinks, and

wholemeal bread or pasta, although no associations were observed with maternal age or income [37]. Ferreira et al. (2021) noted that children who consumed larger amounts of homegrown produce had elevated urinary GLY levels, with the highest level observed in a child from a household that reported using GLY in a domestic setting [39].

The water source was evaluated by Grau et al. (2022), and participants consuming tap or spring water presented higher urinary GLY levels than individuals drinking filtered water did. However, the study did not assess bottled water as a variable [44].

Geographic proximity to agricultural activity was examined in the studies by Ferreira et al. and Connolly et al. (2022). In the Portuguese cohort, 56% of children lived within 1 km of crop fields, and the parental education level showed an inverse relationship with urinary GLY concentrations [39]. Connolly et al. reported detectable GLY and AMPA levels even in nonfarming Irish families, with children exhibiting higher levels than adults in the same household [22].

Seasonal variation was considered in the studies by Nomura et al. (2022) and Grau et al. (2022). Both studies revealed slightly elevated GLY concentrations in urine samples collected during the summer months. Nomura et al. compared samples from Japanese children in different seasons and found higher GLY levels in summer than in winter [41]. Grau et al. reported similar seasonal trends across a large adult French cohort [44].

Sociodemographic factors were inconsistently associated with exposure across studies. In the study by Ashley-Martin et al. (2023), a higher urinary GLY level was observed among women with higher educational attainment [37], whereas Ferreira et al. reported higher exposure in children from families with lower education levels [39]. Buerkers et al. (2022–Part B) noted sex-based differences in adult exposure, with men showing higher GLY concentrations than women. Vegetarian diets were associated with increased GLY levels in the Icelandic cohort within the same study, although the sample size was limited [45].

Other lifestyle variables, such as smoking and pet ownership, were assessed in individual studies. Grau et al. reported higher GLY levels among smokers than among nonsmokers or former smokers [44]. Buerkers et al. (2022–Part A) examined the presence of pets in the household but did not report significant associations [42].

Across the studies, dietary intake, water source, residential proximity to agricultural zones, and season of sampling were commonly assessed. Associations of sociodemographic and behavioural factors with urinary GLY and AMPA concentrations varied across populations, study designs, and regions.

## Discussion

This systematic review synthesized the findings from fourteen studies assessing exposure to GLY and its metabolite AMPA through urinary biomonitoring in diverse populations, with a particular focus on pregnant women, children, and the general population. The results highlight widespread and persistent exposure to GLY, with detection rates above the limit of quantification in more than 70–90% of samples in many studies, confirming the ubiquity of this herbicide among the studied groups.

However, comparisons and interpretations of the findings are limited by the significant heterogeneity across the included studies. This heterogeneity is primarily due to substantial differences in urine sampling methods (e.g., spot samples, first morning urine, and 24-h collections), analytical techniques (e.g., ELISA vs. LC–MS/MS), and the limits of detection and quantification (LOD/LOQ). Additionally, variations in demographic factors, dietary habits, environmental exposures, and socioeconomic conditions among the studied populations contributed to the variability in the detected GLY levels.

In addition to methodological heterogeneity, our review identified several potential sources of bias. First, exposure measurements vary widely among studies. Although most studies have used high-specificity analytical platforms such as LC–MS/MS or GC–MS/MS, one relied on ELISA-based immunoassays, which have lower specificity and may overestimate concentrations due to cross-reactivity. Moreover, the sampling strategies differed substantially [44]. While some studies collected 24-h urine samples, many relied on single spot or first-morning collections, which may not accurately reflect chronic or episodic exposures due to the short biological half-life of glyphosate.

As reported by Mesnage et al. 2012, the absence of repeated sampling may lead to an exposure misclassification [47, 48].

Second, only a subset of studies adjusted for key confounding variables. Notably, Ashley-Martin et al. included multivariate models accounting for maternal BMI, age, education, parity, environmental tobacco smoke exposure, and employment status. The remaining studies often lacked adjustment for such variables, limiting internal validity. Additionally, while dietary intake was frequently considered, most studies did not differentiate between organic and conventional food consumption, limiting the interpretation of dietary exposure routes.

Furthermore, the reporting quality was inconsistent. Some studies omitted crucial methodological details (e.g., calibration curves, LOD definitions, or sample handling), which hindered reproducibility and comparison.

Despite these limitations, the included studies generally demonstrated acceptable methodological quality based on the Newcastle–Ottawa scale, particularly regarding the selection and outcome domains.

Moreover, studies such as that of Lesseur et al. (2021) indicate possible endocrine-disrupting effects of GLY and AMPA on neonatal sexual development parameters, with potential sex-specific differences that warrant further investigation.

While some studies, such as Thongprakaisang et al., have suggested the oestrogenic activity of GLY, other studies call these findings into question. Notably, Mesnage et al. (2017) reported no strong evidence that GLY or glyphosate-based formulations activate oestrogen receptors, indicating that any endocrine-disrupting effects are unlikely to be mediated through direct interactions with these receptors. These findings underscore the ongoing need for further investigation to clarify the potential hormonal effects of GLY [49, 50].

Furthermore, Mesnage et al., 2022, conducted a biomonitoring study in a UK twin cohort, showing that dietary habits, particularly fruit and vegetable consumption, may influence glyphosate exposure. These findings suggest a potential role of diet in modulating non-occupational pesticide exposure, highlighting the importance of considering dietary factors in human biomonitoring studies [51].

While only a limited number of biomonitoring studies have adjusted for confounders in detail, the study by Ashley-Martin et al. stands out for accounting for multiple maternal and demographic variables, enhancing the internal validity of the findings. This result highlights the need for more rigorous study designs in future human exposure assessments. A strength of this review is the inclusion of multicentre and geographically diverse studies, such as Grau et al., 2022, which underscore the extent of contamination in industrialized regions. However, the high prevalence of values below the quantification limits in certain populations and the lack of temporal consistency in data collection emphasize the need for standardized methodologies to improve comparability.

The study by Lemke et al., 2021, provides the first nationwide biomonitoring data on GLY and AMPA exposure among children and adolescents in Germany. Despite its large and representative sample, the study did not identify significant associations between urinary concentrations and variables such as sex, geographic region, dietary habits, or access to green spaces. While these findings provide valuable reference data for internal exposure levels in a non-occupational population, they also reflect a recurring limitation observed across several studies included in this review, namely, the difficulty in

identifying primary exposure sources. This limitation is partly attributable to the restricted collection of behavioural and environmental data. As with other investigations, this study reinforces the need for standardized and comprehensive methodological frameworks to better characterize GLY exposure pathways in the general population [40].

The study conducted by Buerkers et al. in 2022 within the HBM4EU project represents one of the most relevant and recent contributions to the assessment of GLY and AMPA exposure in children at the European level. Although the median urinary levels detected were generally low and below the limits of quantification (LOQs), the data confirm widespread exposure across several EU countries. Despite the broad geographic coverage and high-quality control of the data, the study showed limited associations between potential exposure determinants and urinary levels of GLY and AMPA. This finding highlights the importance of strengthening the identification of environmental sources and the urgent need to harmonize sampling and measurement protocols to improve comparability across studies [42].

The two studies published by Buerkers et al. in 2022 as part of the HBM4EU project represent some of the most extensive and coordinated efforts at the European level to assess exposure to GLY and its metabolite AMPA in the general population, distinguishing between the paediatric (Part A) and adult (Part B) populations. In both groups, the findings indicate widespread exposure across several European countries, although the median concentrations generally remained below the LOQs, indicating chronic low-level exposure.

However, a direct comparison between the two studies revealed that the 95th percentile (P95) values were consistently higher in children than in adults. This result aligns with the physiological and behavioral characteristics of childhood, such as greater intake of food and beverages per kilogram of body weight, more frequent contact with soil and surfaces, and greater time spent outdoors. These differences make children a more vulnerable subgroup to environmental contaminants such as GLY and AMPA [42, 45].

Regarding the exposure determinants, the adult study revealed clearer associations between urinary levels and behavioural or lifestyle variables, such as fruit and vegetable consumption, sex, socioeconomic status, and dietary habits (e.g., vegetarianism), especially in the German and Icelandic contexts. In contrast, a pediatric study revealed weaker or inconsistent associations between urinary levels and environmental or behavioural factors (e.g., diet, the presence of pets, and domestic herbicide use). This result may reflect the greater complexity of

reconstructing exposure pathways in children or limitations related to the availability and comparability of questionnaire data.

Finally, both studies emphasize the need to strengthen methodological harmonization in sampling, analysis, and data collection protocols to enable more accurate comparisons across age groups, countries, and determinants. Additionally, the proposal to define a group ADI for GLY and AMPA, considering their similar toxicokinetic properties, appears well-founded and consistent with the precautionary approach to risk assessments in vulnerable populations.

Another point we want to discuss is that the study by Grau et al., compared with the other studies cited, uses an immunoenzymatic method, ELISA, which has limitations in terms of specificity compared with mass spectrometry methods (LC–MS/MS) and consequently can overestimate exposure levels due to possible cross-reactivity; despite this limitation, we still decided to include it in our review because it reported the presence of this herbicide.

In terms of public health implications, although the detected GLY levels generally remain below established safety thresholds (ADIs), some studies have reported associations with potential biological effects at low doses. These observations indicate the need for further large-scale, long-term investigations to better characterize potential risks, particularly among vulnerable groups such as pregnant women and children [50, 51].

Finally, GLY exposure is only one component of overall exposure to mixtures of pesticides and environmental chemicals, whose combined effects may be more significant. This finding highlights the need for integrated biomonitoring approaches and more comprehensive environmental risk assessments.

An additional methodological limitation concerns the search strategy. To avoid the exclusion of potentially relevant studies, overly specific keywords were not used. However, the selection of a limited set of terms may have reduced the sensitivity of the search, potentially leading to the omission of some pertinent studies. Future reviews could address this limitation and enhance the comprehensiveness of the evidence by incorporating a broader range of keywords, additional synonyms, and controlled vocabulary, as well as by implementing an iterative refinement process for the search strategy.

## Conclusions

This systematic review highlights the widespread detection of GLY and its metabolite AMPA in the urine of the general population, including children and pregnant women who are not occupationally exposed. While GLY remains a widely used herbicide, the consistent

biomonitoring data raise concerns about the extent of chronic, low-level exposure among vulnerable populations.

The available evidence, although growing, remains fragmented and subject to substantial methodological heterogeneity. Differences in analytical techniques, urine sampling protocols, and confounder control limit the comparability and interpretability of the current findings. Consequently, a pressing need exists for harmonized study designs, longitudinal monitoring, and toxicological investigations to fully elucidate exposure pathways, particularly dietary intake, and the potential health effects associated with cumulative GLY and AMPA exposure.

Although the detected levels are typically below the established safety thresholds, some studies suggest possible associations with adverse developmental, endocrine, or oxidative stress-related outcomes. These observations warrant a cautious interpretation but emphasize the importance of refining current risk assessment frameworks and updating them as more high-quality evidence becomes available.

From regulatory and public health perspectives, precautionary approaches should be encouraged. Promoting sustainable alternatives to GLY, such as crop rotation, targeted biological weed control, and low-impact herbicides, can serve as long-term strategies to mitigate environmental contamination and human exposure, particularly in nonagricultural settings.

In summary, while the data reviewed do not allow definitive conclusions on long-term health outcomes, they underscore the importance of prioritizing biomonitoring studies that adopt rigorous methodologies and focus on vulnerable populations. Strengthening the scientific evidence base is essential to guide informed policymaking and support a responsible transition towards more sustainable agricultural practices.

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## Author contributions

GOC: Conceptualization, Investigation, Writing, Revision, Supervision, Validation; CF: Investigation, Writing- Reviewing and Editing, Data curation, Formal analysis; PR: Methodology, Data curation, Formal analysis; MC: Formal analysis, Data curation; Software; EP: Formal analysis, Data curation; Software; CS: Formal analysis, Visualization, Software; AC: Data curation, Visualization, Software; FM: Conceptualization, Investigation, Supervision, Validation.

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No datasets were generated or analysed during the current study.

## Declarations

## Ethics approval and consent to participate

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare no competing interests.

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