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REVIEW

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Herbicide-related health risks: key mechanisms and a guide to mitigation strategies

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Abstract

Background Herbicides are a group of substances used to control undesired vegetation in both agricultural and non-agricultural settings. They are recorded as the most consumed class among other pesticides, reaching nearly two million tons worldwide. Despite their effectiveness in weed control, the extensive utilization of herbicides has raised concerns regarding adverse effects on human health. However, comprehensive reviews addressing herbicide-related human health risks remain limited. This work aims to compile scientific evidence and possible underlying mechanisms to emphasize the hazards that need to be acknowledged, as well as to explore novel strategies for minimizing the impact on human health.

Method Scientific data on herbicide-related human health risks, including human-related data and non-human experimental research, were retrieved from databases such as PubMed, Scopus, and Google Scholar. Pre-determined eligibility criteria were applied to select the final studies.

Result A narrative summary of evidence-based human incidence and laboratory experiments is presented to organize and highlight key findings. This indicates the life-threatening nature of herbicide exposure in humans, ranging from acute toxicity to the development of chronic diseases at any stage of life.

Conclusion Herbicidal chemicals can harm individuals through various pathways, especially by inducing oxidative stress or directly disrupting molecular and cellular processes. Despite some conflicting findings, effective mitigation strategies are urgently needed to promote a safer society and protect human well-being.

Keywords Herbicide, Human health, Toxicity, Pathology, Management strategies

Introduction

As the global population is forecasted to surpass 9 billion by 2050 with the subsequent high food demands, it is essential to maximize productivity to ensure food security and cater to the needs of the growing population [1]. Herbicide, a subset of pesticides depending on their pest management, are defined as any natural or chemical compounds used to eradicate or reduce unwanted weeds that interfere with crop growth by competing for nutrients, water, and light [2]. The concept of weed management began in the late 1890s and was further introduced for general agricultural

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purposes in the early 1940s. The first two discovered herbicides were 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) [3]. Currently, herbicide use is not only limited to agricultural but also extend to non-agricultural applications, including aquatic weed management, wildland ecosystem, and urban areas maintenance [4–6]. Globally, herbicide exhibited the highest consumption among other pesticides due to their various advantages, such as cost-effectiveness, time and human labor savings, and high weed control efficacy [7].

However, the widespread use of these substances has raised concerns regarding their potential adverse effects on human health. Certain residues are non-biodegradable ability and persist in natural resources such as water surfaces, soil particles, and the atmosphere [8]. Herbicide-associated health problems can manifest as either acute or chronic toxicity, depending on the amount and duration of exposure. These adverse effects can occur at any age or gender. Hence, occupational, accidental, or purposeful exposures to these chemicals, whether by skin contact, ingestion, or inhalation via contaminated commodities, water, or airborne pollutants, poses a risk. Several studies have also demonstrated health implications after contact with herbicide residues, including cytotoxicity, neurotoxicity, infertility, metabolism, and endocrine disruption through various signaling pathways [9]. In addition, herbicide poisoning is related to high morbidity and mortality, which is exacerbated by the absence of specific treatments to mitigate the effects [10, 11]. Therefore, addressing human health problems related to herbicide exposure is crucial for several reasons. Understanding the potential health risks can advocate individuals to self-guard against the likelihood of residues exposure. It will also encourage workers, communities, organizations, and governments to improve environmental and social responsibility by adopting best practices and creating legislation to prevent unacceptable residue pollution. Furthermore, these insights provide a proactive basis for research and development, leading to the advancement of safer alternatives and management strategies.

Although the widespread use of herbicides and their life-threatening matter have recently been a major concern, comprehensive reviews on their potential health risks remain limited. This review aims to compile the human health problems caused by herbicide exposure. Evidence-based epidemiology studies, case reports, and laboratory experiments exploring the possible underlying mechanisms that contribute to pathological diseases are provided to emphasize the hazard that needs to be concerned. In addition, evidence-based strategies and management approaches to alleviate their adverse effects on human health are also discussed.

Methods of literature search

Database search and keyword selection

A comprehensive search for relevant articles was conducted across several academic databases, including PubMed, Scopus, and Google Scholar. To ensure a thorough capture of pertinent literature, the following keywords were employed, either alone or in any combination: "herbicide" OR "herbicides" OR "glyphosate" OR "paraquat" OR "atrazine" OR "2,4-D" OR "2,4-dichlorophenoxyacetic acid" with "consumption" OR "utilization" OR "exposure" OR "toxicity" "side effects" OR "human health" OR "health effects" OR "epidemiology" OR "toxicological impact" OR "mitigation strategies" OR "implementation". The search was limited to articles published in English, with no restriction on the publication year.

Article selection criteria

The primary focus was on studies investigating the adverse effects of herbicide exposure on both the general population and herbicide applicators. Articles related to human incidence and herbicide exposure, including systematic reviews, meta-analyses, case reports, cohort studies, and case-control studies, were selected regardless of whether the outcomes were statistically significant. Additionally, non-human studies providing valuable insights into potential human health complications were also selected. Experiments conducted with non-human subjects were included if they demonstrated mechanisms or biomarkers that could be replicated in humans. Additionally, studies that ensured the observed toxicity was attributed to the pure chemical herbicide itself, rather than to any co-adjuvants, were considered.

Overview of herbicide application

In 2021, herbicide consumption was estimated to have exceeded 1.7 million tons globally, outpacing all other types of pesticides used for agricultural purposes (Fig. 1) [7]. In addition, its applications beyond agriculture for aquatic weed management, public wildland management, and urban area maintenance [4–6]. The top three continents showing the highest herbicide consumption were the Americas, Asia, and Europe, accounting for more than 1 million, 300 thousand, and 190 thousand tons, respectively [12]. Brazil, one of the world's prominent producers of major commodities including soybeans, coffee, and corn [13], applied approximately 400 thousand tons, which almost doubled in the past decade [12]. During this period, herbicides also remained the most used class, accounting more than 50% of total pesticides, as the global trend. The top active ingredients were

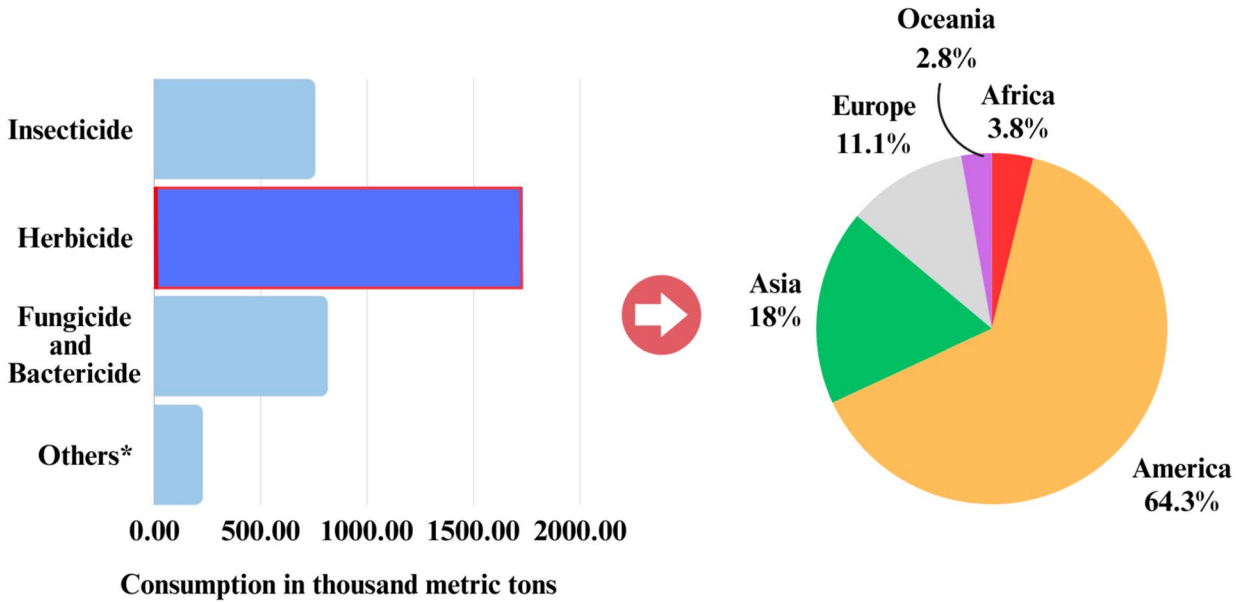

*Figure was calculated by Statista based on the values provided by the source. Includes plant growth regulators and rodenticide, among others.

Fig. 1 Global pesticides consumption with particular herbicide usage across different continents as recorded in 2021 (Data obtained from Statista [7] ; FAOSTAT [12])

glyphosate (GLY), 2,4-D, atrazine (ATZ), and paraquat (PQ), accounting for 36%, 7.4%, 4.6%, and 1.5%, respectively [14]. The United States of America was the leader of herbicide utilization at approximately 300 thousand tons in 2021 [12]. GLY was most widely used in the country, with approximately 140 thousand tons applied annually [15], followed by ATZ, 2,4-D, and PQ at nearly 43, 25, and 6 thousand tons, respectively [16–18].

Among Asian countries, China had the highest herbicide consumption at almost 100 thousand tons, due to 10% crop yield loss and a 60 million tons reduction in grain output were caused by weed damage. There were more than thousands of product registrations in 2021, in which the highest registered active ingredients were GLY (1,805 products), ATZ (1,401 products), and acetochlor (1,238 products) [19]. Almost half of the herbicide consumption in Asia was contributed by the Southeastern region, especially Thailand, Vietnam, and Malaysia [12, 20]. Since the agricultural sector is fundamental to the national and regional economy, herbicide is the common weed control used to meet global demands. In Thailand, yearly pesticides imports were comprised of herbicide accounting for 80%. Notably, 79% of the total were GLY (40–50%), PQ (15–20%), and 2,4-D (11–18%), as recorded in 2021 [21]. On the other hand, herbicide utilization in Europe is less significant. The percentage value shared in the market was 34% herbicide, which was second only to fungicide and bactericide holding 44% [22]. As illustrated, Africa and Oceania were the two continents with the smallest herbicide consumption with 3.8% and 2.8% respectively.

Herbicide exposure and impacts on human health

The widespread utilization of herbicides allows their residues to enter environmental resources through transfer processes, including adsorption, runoff, or volatilization, resulting in bioaccumulation where specific residues remain persistent in nature [23]. Thus, exposure to residues can occur through various transmission routes, including skin contact, inhalation, ingestion, and in various situations, such as self-harm, accidental exposure, contaminated food consumption, or occupational contact (i.e., agriculture, horticulture, and industrial production). The primary route through which humans come into contact with herbicides is skin exposure, which often occurs during the preparation, application, and even cleanup of contaminated utensils and protective clothing. The ability of chemicals to penetrate the skin depends on their formulations. For instance, oil- or solvent-based liquid formulations are more easily absorbed compared to water-soluble wettable powders, dusts, and granular formulations. In addition, the area of skin contact, duration of exposure, and chemical intensity also influence the severity of dermal exposure [24]. Ocular exposure poses a significant risk, as the eyes are highly absorbent tissue that can easily

allow chemicals to enter the bloodstream, causing irritation or blindness in severe conditions. Exposure can occur through airborne particles, splashes during application, or by rubbing the eyes with contaminated hands or gloves. Inhalation of vapors, powders, or aerosols particles can result from burning containers, pouring, spraying herbicide, or using methods that generate smaller droplets such as high pressure, ultra-low volume, or foggy equipment [25]. Ingestion of herbicide typically occurs accidentally or as a result of suicidal attempt. Activities such as unplugging the nozzle with mouth, smoking, eating with unwashed hands after application, as well as consuming the commodities containing residues above regulation levels allow the particles to enter the body. Moreover, children are frequently the victims of unintentionally intake of improperly stored products, and unlabeled bottles or food containers [24]. These exposures drive the off-target consequences, which negatively affect humans. The herbicides, notably GLY, PQ, 2,4-D, and ATZ, which are consistently prevalent in most countries and possess several threats to human health causing high morbidity and mortality, will be the focus of this review. This included major evidence supporting their potential adverse effects on human health both in terms of acute toxicity and the development of chronic diseases (Fig. 2).

Acute toxicity

Acute toxicity is defined as adverse effects that occur within a short time, typically observed within 14 days after exposure to a single dose or multiple doses of a substance lasting less than 24 h [26]. According to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) classification, acute toxicity is categorized into five levels, with class 1 representing the most severe hazard. These categories are based on animal testing via oral, dermal, and inhalational routes [27]. GLY, ATZ, and 2,4-D are categorized into class 4 for an acute oral toxicity with the observed lethal doses between 300 and 2,000 mg/kg [28–30]. Meanwhile, PQ is placed into class 3 due to its higher oral acute toxicity, with observed lethal doses between 50 and 300 mg/kg [31]. Moreover, most of the herbicides are classified as Category 1 for acute dermal toxicity, indicating severe skin and eye irritation [28–31]. In particular, PQ can cause severe poisoning even through damaged skin or prolonged skin exposure [32].

Indeed, the impact of acute toxicity in real-life scenarios can be represented through suicidal attempts or occupational exposure. Approximately 20% of suicidal cases are specifically attributed to pesticides self-poisoning [33]. Herbicides are the most commonly used group among individuals, with PQ being the leading chemical, followed by GLY [34]. As detailed in Table 1, the initial

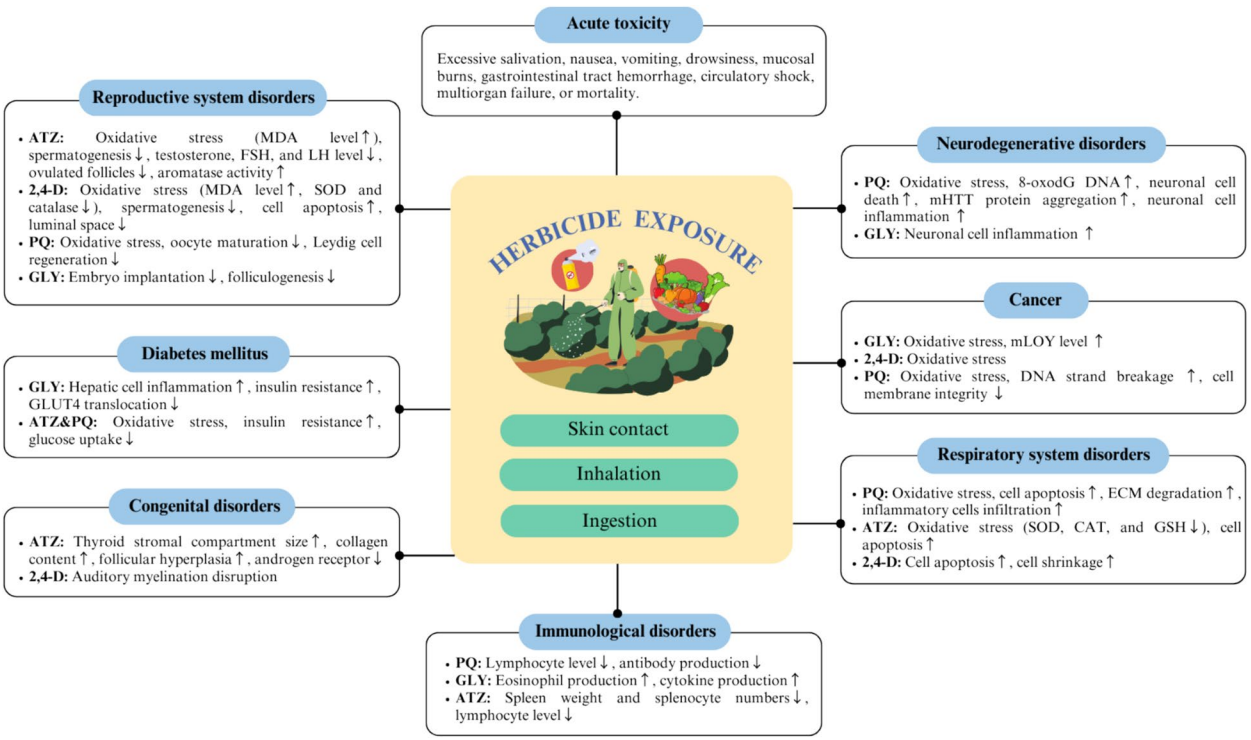

Fig. 2 Herbicide exposure and possible health impacts (By author)

Table 1 Herbicide-associated acute toxicity

Herbicide	Subjects	Dose Exposure	Main findings	Ref.
GLY	Case report	200 mL of 30–36% GLY	Respiratory distress, hypotension, metabolic acidosis, and hyperkalemia were noted during hospitalization, but was successfully resuscitated.	Mutkule, Venkategowda, and Mahendrakar [35]
		400 mL of 41% GLY	Metabolic acidosis, respiratory failure and shock were noted during hospitalization, ultimately leading to a fatal outcome.	C.-B. Chang and Chang [36]
		200 mL of 36% GLY	Metabolic acidosis, cardiorespiratory deterioration, erosive lesions of digestive tract, acute renal failure, and circulatory shock were noted during hospitalization, but was successfully resuscitated.	Picetti et al. [37]
		500 mL of 41% GLY	Respiratory distress, hypotension, metabolic acidosis, and pulmonary consolidation were noted during hospitalization, but was successfully resuscitated.	Kunapareddy and Kalisetty [38]
		75 mL of 41% GLY	Epigastric tenderness, respiratory distress, metabolic acidosis, and acute pulmonary edema were noted during hospitalization, but was successfully resuscitated.	Khot et al. [39]
PQ	Case report	10 mL of 24% PQ	Oral ulcers, hypokalemia, and renal failure were noted during hospitalization, but was successfully resuscitated.	Janeela et al. [40]
		Unknown quantity of 24% PQ	Congested and edematous oral mucosa, tachycardia, respiratory alkalosis, erosive lesions of digestive tract, blood-mixed bronchoalveolar lavage fluid, and renal failure were noted during hospitalization, but was successfully resuscitated.	Ghosh et al. [41]
		10 mL of 20% PQ	Oral ulcers, metabolic acidosis, and acute kidney and liver injury were noted during hospitalization, but was successfully resuscitated.	Sigdel et al. [42]
		> 100 mL of 20% PQ	Oral ulcers, and severe lung, liver, and kidney damage were noted during hospitalization, but was successfully resuscitated.	Yu et al. [43]
		20% w/v PQ	Erythema, blister, and severe haemorrhaging diathesis on exposed skin, with dyspnea in some cases.	Zhou et al. [44]
2,4-D	Case report	30 mL of 58% 2,4-D	Oral secretion, tachycardia, poor muscle response, renal failure, and circulatory collapse were noted during hospitalization, and ultimately leading to a fatal outcome.	Demissie et al. [45]
		70 mL of 58% 2,4-D	Tachycardia, metabolic acidosis, and diffuse cerebral edema were noted during hospitalization, but was successfully resuscitated.	Hiran and Kumar [46]

clinical features of herbicide poisoning are non-specific, such as excessive salivation, nausea, vomiting, drowsiness or mucosal burns. Several GLY-poisoning cases presented rapid onset of multiorgan failure following the ingestion of large quantities approximately 75–500 mL of 30–41% GLY solution [35–39]. Symptoms of GLY poisoning commonly include electrolyte abnormality, circulatory shock, gastrointestinal tract hemorrhage, respiratory failure, renal failure, cardiac arrest and ultimately death in severe cases [35–39].

Similarly, individuals who consumed nearly 10–100 mL of a 20–24% PQ solution presented signs of multiorgan failure encompassing renal, hepatic, respiratory, and cardiac dysfunction [40–43]. Particularly, the preceded diffuse alveolitis and subsequent pulmonary fibrosis are the hallmarks of PQ poisoning [41, 47]. In addition to suicidal attempted cases, the workers who sprayed a concentrated formulation of 20% weight per volume (%w/v) of PQ for approximately 3 h a day, without any protection, exhibited erythema, blister, and severe haemorrhaging diathesis on their skin [44]. Moreover, some cases of PQ poisoning through skin contact exhibited dyspnea as an atypical complication, accompanied by abnormal breath sounds [44]. These conditions suggest that PQ can be absorbed through the skin and spread throughout the body, causing life-threatening effects in humans. In addition, severe cases who ingested between 30 and 70 mL of 58% 2,4-D progressed into comatose state by developing circulatory collapse, poor muscle response, or ultimately death despite receiving several supportive cares [45, 46].

Unfortunately, the specific antidote for pesticides poisoning is only available for carbamate and organophosphate poisoning [48]. Therefore, in all of the herbicide-poisoning cases, the mainstay of management includes decontamination, symptomatic and supportive care. The individual prognosis then relies on dose dependence, promptness of medical intervention and effectiveness of immediate resuscitation [46].

Collectively, despite being considered of low acute toxicity in humans, exposure to concentrated solutions can result in severe toxicity or even mortality. The adverse effects may not be confined to the specific body part of exposure, but can extend to other systems throughout the body, highlighting the potential for life-threatening consequences.

Chronic toxicity

Chronic toxicity refers to the sublethal effects, as well as lethal effects in some cases, that a substance can have on living organisms when they are repeatedly exposed over a period of time, usually at lower or less toxic concentrations compared to acute toxicity tests [49]. Major herbicide-related sublethal effects include neurodegenerative disorders, cancer, reproductive system disorders, congenital disorders, respiratory system disorders, and immunological disorders. This section describes the principal effects contributing to pathological diseases and highlights the primary toxic herbicide affecting each body system, as established by human incidence and experimental studies.

Neurodegenerative disorders

Although the etiology of neurodegenerative disorders such as Parkinson's (PD), Alzheimer's (AD), and Huntington's disease (HD) remains multifaceted, neurotoxic agents like herbicide, which disrupt the function or alter the chemical levels of the nervous system, are significant contributors, as evidenced in Table 2 [50, 51]. Specifically, a study reported that occupational uses of pesticides increased the risk of PD by 29 to 89%, doubling for those who used them for more than 10 years. Among the 360 participants diagnosed with PD, 11.4% were associated with herbicide exposure, including 2,4-D, GLY, and PQ [52]. While most studies on human incidences found a positive correlation between AD development and pesticide exposure, they were also acknowledged for having small number of cases. For instance, one study reported that 344 out of 3,084 participants developed AD following pesticide exposure [53]. Moreover, the explorations did not thoroughly investigate specific types of pesticides, leading to the ambiguous toxicity of herbicide-induced AD [54, 55]. Furthermore, there is a lack of epidemiological evidence connecting between herbicide exposure to HD development, necessitating future research in this area.

However, PQ is a well-known neurotoxin, particularly associated with PD development, due to its structural similarity to dopaminergic neurotoxin like 1-methyl-4-phenylpyridinium (MPP^+). In addition to oxidative stress induction and mitochondrial damage [62], PQ-treated mice showed the disruption of lipid metabolism in the midbrain, leading to motor dysfunction and

Table 2 Herbicide-associated neurodegenerative disorders

Herbicide	Subjects	Dose Exposure	Main findings	Ref
PQ	C57BL/6J mice	10 mg/kg	- Reduced motor control through dopaminergic neuron loss, lipid profile alteration, inflammation activation, and PD-related gene malfunction. - Induced DNA 8-oxodG in the brain, heart, and small intestine.	De Luca et al. [56] and Tong et al. [57]
	Human osteosarcoma cells	30 µM	Induced the aggregation of Huntington protein and cell death through disruption of protein degradation pathways.	Pinho et al. [58]
GLY	C57BL/6J mice	125 to 500 mg/kg/day	Induced neuroinflammation through the upregulation of TNF-α cytokine.	Winstone et al. [59]
	APP/PS1 pups primary cortical neurons	10 to 40 µg/mL	Induced the expression of soluble $A\beta_{40-42}$ and decreased cell viability.	
	Induced pluripotent stem cells (iPSCs)	0.1 to 1000 µM	Altered metabolic activity and enhanced permeability of the blood-brain barrier through the disruption of occludin and claudin-5 proteins.	Martinez and Al-Ahmad [60]
Triazine group	In silico study	-	Disrupted cell cycling and cellular senescence processes through targeting EGFR, FN1, and TYMS proteins.	Li et al. [61]

increased levels of inflammatory cytokines (i.e., interleukins (IL-6 and IL-1β), which significantly correlated with PQ-poisoning cases in humans [57]. Furthermore, this herbicide has also been implicated in HD development. De Luca et al. [56] demonstrated that PQ-treated mice exhibited the formation of oxidized purine 8-oxo-7,8-dihydroguanine (8-oxodG), a biomarker of DNA oxidation commonly found in post-mortem brains of HD patients. Additionally, Pinho et al. [58] found that PQ-conjugated mitochondria increased mutant huntingtin (mHTT) aggregation and cell death in human osteosarcoma cells. These findings suggest that mitochondria-derived reactive oxygen species (ROS) may impair protein degradation pathways, contributing to mHTT aggregation and HD development.

Conversely, GLY and triazine herbicide have been possibly linked to AD development. Studies have demonstrated that GLY can penetrate the blood-brain barrier, by impairing tight junction proteins like occluding and claudin-5, and inducing inflammatory responses in both mice and human neurons [59, 60]. This inflammation is also associated with alterations in AD-related pathological markers, such as β-amyloid (Aβ) levels and cell viability. Together, Li et al. [61] identified triazine herbicide, including ATZ, simazine (SIM), and propazine (PRO), as potential contributors to AD through in silico analysis. Disruption of cell cycle regulation and cellular senescence by targeting thymidylate synthase (TYMS), fibronectin 1 (FN1), and epidermal growth factor receptor (EGFR), leading to abnormal development and cell death of neuronal cells, were proposed as underlying mechanisms. Although these findings are preliminary, they lend support to the hypothesis that herbicide exposure could contribute to AD development.

Cancer

Extensive research has been conducted for decades on the correlation between pesticide exposure in agriculture, horticulture, forestry, pesticide manufacturing, and cancer development [63]. Table 3 provides various types of cancer that have been linked to herbicide exposure, including gastric (odds ratio (OR) = 1.66, 95% confidence interval (CI): 1.08–2.55), thyroid (OR = 3.00, 95% CI: 1.38–6.54), bladder (rate ratios (RR) = 1.54, 95% CI: 1.05–2.26), lung (RR = 1.74, 95% CI: 1.07–2.84), colorectal (RR = 1.75, 95% CI: 1.08–2.83), endometrial (OR = 5.25, 95% CI: 1.84–17.67), and brain tumors (effect sizes (ES) = 2.38, 95% CI: 1.31–4.33) [64–69].

Despite ongoing debates regarding the carcinogenicity of GLY [80, 81], the International Agency for Research on Cancer (IARC) has classified it as probably carcinogenic to humans (Group 2 A) [82]. Study has linked GLY exposure to a significantly elevated risk of non-Hodgkin lymphoma (NHL) (OR = 2.02, 95% CI: 1.10–3.71) [70]. Also, a multicenter case-control study conducted by Meloni et al. [71] found a significant association between GLY exposure and a 7-fold increased risk of follicular lymphoma. In addition to its previously documented role in oxidative stress-induced cancer [83], Chang et al. [72] identified mosaic loss of chromosome Y (mLOY) as another potential mechanism contributing to hematologic cancers and solid tumors in GLY-intoxicated male applicators. Among participants, 21.4% had detectable mLOY, and 9.8% had expanded mLOY greater than 10% of cells. These findings suggest that GLY may induce genomic instability and genotoxicity, resulting in certain hematological cancers.

Meanwhile, 2,4-D has been classified as possibly carcinogenic to humans (Group 2B) due to its inadequate evidence in humans [84]. Epidemiological studies among 1,000 2,4-D factory workers have also not found a significant increase in overall cancer incidence [85]. However, its carcinogenicity should not be neglected. Several studies have consistently linked 2,4-D exposure to oxidative stress, a known cancer-driving factor [73, 75, 86, 87]. This effect is often mediated through the generation of free radicals from lipid peroxidation and/or the attenuation of antioxidant properties [75]. Malondialdehyde (MDA), a marker of lipid peroxidation, has been found to be elevated in 2,4-D-treated mice [75, 86, 87] and human dental pulp stem cells (hDPSCs) [73]. Moreover, Mariotti et al. [74] observed gastrointestinal changes in 2,4-D-treated rats, including esophageal hyperkeratosis and mild dysplasia in both small and large intestines, suggesting that intestine may be particularly susceptible to the carcinogenic effects of 2,4-D.

Among commonly used herbicides, ATZ has been classified as "not classifiable as to its carcinogenicity to humans" (Group 3) [88]. Despite being widely recognized as an endocrine-disrupting chemical, its ability to induce hormonally sensitive cancer in animals has not been replicated in humans. Studies have reported the absence of intrinsic estrogenic activity in ATZ, leading to uncertainty regarding its carcinogenic potential. However, ATZ exposure was linked to an increased risk of certain non-hormonally sensitive cancers such as lung cancer (RR = 1.24, 95% CI: 1.04–1.46) and NHL (RR = 2.43, 95% CI: 1.10–5.38) in a study examining over 50,000 pesticides applicators [76]. Meanwhile, PQ has not yet been evaluated by IARC for its carcinogenicity. Nevertheless, a study of over 20,000 participants suggested a potential increased risk of NHL among those exposed to PQ (RR = 1.51, 95% CI: 1.01–2.26) [77]. In addition, there is little firm evidence demonstrating its potential to induce oxidative stress related-DNA damage or genotoxicity. Studies conducted by Alizadeh et al. [78] and

Table 3 Herbicide-associated cancer

Herbicide	Subjects	Dose Exposure	Main findings	Ref
Not specifically identified	Human study	-	Significantly associated with 1.5 to 2.0-fold higher risk of diffuse-type gastric cancer.	Shah et al. [64]
			Significantly associated with an increased risk of thyroid cancer.	Han, Kim, and Song [65]
			Significantly associated with endometrial cancer in agricultural, poultry, livestock exposure.	Peñalver-Piñol et al. [67]
			Significantly associated with brain tumor in childhood domestic exposure.	Onyije et al. [69]
Acetochlor	Human study	-	Significantly increased risk of colorectal cancer in high lifetime users and lung cancer in ever and low lifetime users.	Lerro et al. [68]
Imazaquin and Imazethapyr	Human study	-	Significantly increased risk of bladder cancer, especially among non-smokers.	Koutros et al. [66]
GLY	Human study	-	Significantly associated with NHL incidence.	De Roos et al. [70]
			Significantly increased risk of follicular lymphoma.	Meloni et al. [71]
			Significantly associated with detectable mosaic loss of chromosome Y in high lifetime users.	Chang et al. [72]
2,4-D	hDPSCs	0.1 µM to 10 mM	Induced oxidative stress and apoptosis in subjects.	Mahmoudinia et al. [73]
	Male Wistar rats	20 to 52 ppm	Induced hyperkeratosis in esophageal epithelium cells, and mild dysplasia in small and large intestine.	Mariotti et al. [74]
		15, 75 and 150 mg/kg/day	Reduced the body weight, increased liver weight, and hypertrophy of heart, and induced oxidative stress and lipid peroxidation in erythrocytes.	Wafa et al. [75]
ATZ	Human study	-	Significantly associated with NHL incidence.	Remigio et al. [76]
PQ	Human study	-	Significantly increased the risk of NHL in users.	Park et al. [77]
	Male Wistar rats	30 to 200 mg/kg/day	Induced pathological changes and cell death in lung, kidney, and liver tissue, as well as DNA damage in peripheral lymphocytes through oxidative stress.	Alizadeh et al. [78]
	HeLa and Hep G2 cell lines and human peripheral lymphocytes	50 to 300 µM	Induced strand break and oxidized bases of DNA under certain concentration and time of exposure depend on cell types.	Petrovská and Dušinská [79]

Petrovská and Dušinská [79] showed that PQ-induced oxidative stress caused DNA strand breakage, oxidation of DNA bases, and impairment of cell membrane integrity, observed in peripheral lymphocytes of male Wistar rats, isolated human peripheral lymphocytes, and human cell lines. Additionally, molecular docking studies further revealed that the interaction between PQ and H4 histone proteins may disrupt the arrangement of nucleosomes, affecting DNA packaging, chromosomal formation, and genomic stability, potentially leading to carcinogenic effects [89].

Reproductive system disorders

Endocrine disruption typically leads to reproductive system disorders, as hormones are essential for the growth and function of this system [90]. Thus, exposure to endocrine-disrupting herbicides has raised concerns regarding potential adverse effects, as evidenced in Table 4.

ATZ is a notable herbicide that primarily harms the reproductive system and developing organisms through endocrine disruption [102]. A study reported that women exposed to ATZ in municipal drinking water was associated with menstrual cycle length irregularity (OR = 6.16,

Table 4 Herbicide-associated reproductive system disorders

Herbicide	Subjects	Dose Exposure	Main findings	Ref
ATZ	Human study	-	Significantly associated with menstrual cycle length irregularity, reduced reproductive hormone levels and longer follicular phase.	Cragin et al. [91]
	Male and female crayfish	5 to 20 mg/L	Altered both testis and ovary cellular structure, reduced testosterone level, and enhanced estradiol and progesterone levels.	Nassar et al. [92]
	Rat granulosa cells	10 and 20 µM	Inhibited FSH-induced LHR, CYP19A1 mRNA expression and estradiol production through the activation of ERK1/2 signaling pathway.	Fa et al. [93]
	Sprague-Dawley and Long Evans female rats	50 to 100 mg/kg	Inhibited LH surge and reduced the number of corpus luteum and ova shed.	Foradori et al. [94]
	Wistar male rats	120 mg/kg	Induced testicular defects through oxidative stress induction and endocrine disruption.	Rotimi, Ojo, and Adeyemi [95]
	Rat granulosa cells, and H295R adrenal cortical carcinoma cells	1 to 30 µM	Increased estradiol, estrone, and progesterone production, and aromatase activity.	Tinfo et al. [96]
	Human granulosa-luein cells, and endometrial stromal cells	1 nM to 0.1 mM	Increased aromatase activity in granulosa-lutein cells.	Holloway et al. [97]
	In silico study	-	Significantly enriched of miscarriage genes.	Harris et al. [98]
2,4-D	Kunming male mice	50 to 200 mg/kg/day	Disrupted spermatogenesis, and induced testicular damage through endocrine disruption, oxidative stress and apoptosis induction.	Zhang et al. [86]
	Wistar male rats	100 and 200 mg/kg	Altered testicular, seminal vesicles and prostate weight and histology though hormonal (testosterone, FSH, and LH) alteration.	Marouani et al. [99]
	Nulliparous Wistar female rats	70 mg/kg/day	Increased ROS level, lipid peroxidation, and protein oxidation in ventral prostate, ovary, and breast but different pattern depending on ages of subjects.	Pochettino et al. [87]
PQ	Sprague-Dawley male rats	0.5 to 8 mg/kg	Detained Leydig cell regeneration through ROS induction and growth factor, and DHH down-regulation.	Li et al. [100]
	CD-1 female mice	120 mg/mL	Impaired oocyte quality through the disruption of nuclear and cytoplasmic maturation during oocyte meiosis.	Sun et al. [101]

95% CI: 1.29–29.38) [91]. It targets the hypothalamus-pituitary-gonadal (HPG) axis such as the inhibition of the brain-pituitary-ovarian alliance [91–93, 95, 103]. In vivo studies also demonstrated that ATZ caused histological changes and affected the functions of the testis, ovary, and epididymis, confirmed by significant declines in sperm quality, the number of ovulated follicles, hormone production, including testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), and the preovulatory LH surge [94, 95]. Similarly, ATZ-treated granulosa cells showed an increased aromatase activity, an enzyme that converts androgens into estrogens, suggesting a potential for hormonal imbalance [96, 97]. Moreover, it was the only herbicide identified as being associated with an increased risk of miscarriage in multiple species, including human, mouse, and rat [98]. Although Goodman et al. [104] conducted a systematic review across 21 epidemiological studies to support the association between ATZ exposure and adverse pregnancy outcomes, the low quality of the available data, mostly from aggregate rather than individual information, made it difficult to establish a definitive causal relationship. Therefore, the clinical evidence remains limited, pointing out the need for future research.

Meanwhile, 2,4-D and PQ have similar effects on the reproductive system, mainly through the induction of oxidative stress and apoptosis. 2,4-D-induced oxidative stress in mice exhibited signs of testicular damage, including atrophy of the seminiferous tubules, disorganization of seminiferous epithelium, enlarged intracellular space, and loss of gamete cells [86, 99]. Although hormone disruption was not observed in 14 consecutive days, a decrease in testosterone levels and an increase in FSH and LH serum levels were evident after 30 days of exposure [86]. Pochettino et al. [87] found that 2,4-D induced oxidative stress in prostate tissue at all ages. However, breast tissue, especially during puberty and adulthood, was more susceptible to oxidative imbalance, while the oxidative status in the ovary exhibited age-dependent effects. Regarding PQ toxicity, Li et al. [100] demonstrated that PQ delayed Leydig cell development and reduced testosterone production by disrupting Sertoli cell function through the downregulation of SRY-box transcription factor 9 (SOX9) and desert hedgehog (DHH). PQ also impaired oocyte maturation by interfering with spindle assembly and kinetochore-microtubule attachment during meiosis, causing misaligned chromosomes and triggering mitochondrial distribution [101]. In addition, as reviewed by Milesi et al. [105], GLY exposure has been linked to detrimental effects on reproductive health as well as on pre- and post-implantation embryos, through the alterations in estrogen biosynthesis, estrogen receptor expression, and signaling pathways crucial for the implantation process.

Congenital disorders

Genetic abnormalities noteworthily contribute to pathological processes of congenital disorders, but maternal exposure to agrichemicals during pregnancy is one of the driving factors [106]. Herbicide and its potential on congenital disorders are provided in Table 5. Although the Food and Agriculture Organization (FAO) has concluded that ATZ was not a teratogen [107], it has been linked to birth defects (i.e., gastroschisis and choanal atresia) in infants born to mothers residing near high ATZ-contaminated areas [108, 109]. A study by Lee et al. [110] also linked low thyroxine levels to an increased risk of choanal atresia in newborns (adjusted odds ratio (AOR) = 0.85, 95% CI: 0.80–0.90). This finding aligns with the hypothesis that ATZ exposure may disrupt thyroid hormone function. *In ovo* studies demonstrated that ATZ can cause thyroid gland disorganization, characterized by an enlarged thyroid stromal compartment, increased interstitial collagen content, and follicular hyperplasia as well as decreased expression of androgen receptors in the follicular epithelium [111].

A Chinese cohort study by Silver et al. [112] found that prenatal 2,4-D exposure linked to slower auditory signal transmission in newborns, potentially due to impaired myelination of the auditory pathway. Other teratogenic effects of 2,4-D were also observed in vivo [113, 114]. For instance, 2,4-D-treated bullfrog embryos exhibited deformities and developmental delays [113]. Furthermore, Kongtip et al. [115] detected both GLY and PQ in the serum of Thai female agricultural workers during delivery. Although this study did not assess the impact on infants, the presence of these chemicals raises concern about potential exposure through lactation, given findings by Pu et al. [116] demonstrating that maternal exposure to GLY during pregnancy and lactation caused autism spectrum disorder (ASD) in offspring.

Diabetes mellitus (DM)

Surprisingly, a recent case-control study among 2,626 participants Chinese population by Wei et al. [117] exhibited a positive association between plasma herbicide and the risk of DM type 2. The study by Saldana et al. [118] also found that 4.5% of 11,273 pregnant women had the risk of gestational DM after exposure to ATZ, butylate, 2,4,5-T, and 2,4,5-(trichlorophenoxy)propionic acid (2,4,5-TP) during the first trimester of pregnancy (OR = 2.2, 95% CI: 1.5–3.3). Starling et al. [119] additionally reported an association between farmer's wives who exposed to 2,4,5-T and 2,4,5-TP and the development of DM during a 10-year follow-up period (Hazard ratios

Table 5 Herbicide-associated congenital disorders

Herbicide	Subjects	Dose Exposure	Main findings	Ref
ATZ	Human study	-	Significantly associated between maternal exposure and gastroschisis in offspring, especially those who resided less than 25 km from contaminated area.	Waller et al. [108]
	Human study	-	Significantly associated between maternal exposure and the risk for choanal atresia and stenosis in offspring.	Agopian et al. [109]
	C. latirostris	0.2 ppm	Altered thyroid histo-function in embryo, and affected the growth curve from hatching.	Galoppo et al. [111]
2,4-D	Human study	-	Significantly associated between maternal exposure and slower auditory signal transmission in newborn.	Silver et al. [112]
	Bullfrog embryos and tadpoles	150 to 1200 mg/L	Inhibited embryonic growth and induced physical deformation.	Viriato et al. [113]
	Rhinella arenarum embyos	1 to 15 mg/L	Reduced body size, delayed development, microcephaly, agenesis of gills, and abnormal cellular proliferation processes of embryos.	Aronzon et al. [114]
GLY&PQ	Human study	-	Pregnant women who work or are involved in agricultural activities exhibited detectable residue levels in maternal serum and umbilical cord blood.	Kongtip et al. [115]
GLY	ddY mice	0.098% w/v	Maternal exposure led to autism-like behavior and abnormal composition of gut microbiota in offspring through increased of soluble epoxide hydrolase (sHE) activity.	Pu et al. [116]

(HR) = 1.59, 95% CI: 1.00–2.51). These observations have encouraged other studies to establish a causal relationship between herbicide exposure and the likelihood of DM development, as shown in Table 6.

GLY has been shown to activate the nuclear factor kappa B (NFκB) signaling pathway, leading to inflammation and insulin resistance in the liver [120]. Moreover, it induced abnormal glucose uptake in skeletal muscles by disrupting the insulin signaling pathway through protein kinase B (Akt) and insulin receptor substrate (IRS), ultimately reducing glucose transporter type 4 (GLUT4) translocation [121]. Meanwhile, both Gupta et al. [122] and Lim et al. [123] found that ATZ induced mitochondrial dysfunction and insulin resistance through activation of the c-Jun N-terminal kinase (JNK) signaling pathway or suppressing insulin-mediated Akt phosphorylation. On the other hand, PQ-induced oxidative stress inhibited the repression of insulin-like growth factor-binding protein-1 (IGFBP-1) gene expression, leading to increased hepatic glucose production and insulin resistance [124]. In 3T3-L1 adipocytes, PQ-induced oxidative stress also disrupted the binding of phosphatidylinositol 3-kinase (PI3K) to IRS, inactivating the downstream signaling pathway and reducing GLUT4 translocation and glucose uptake [125].

Interestingly, different outcomes of the 2,4-D-altered glucose metabolism were observed. Despite the unstated underlying mechanism, preliminary findings in mice showed a decrease in blood glucose levels without changes in liver function or amylase activity [126]. Furthermore, Sun et al. [127] proposed a novel mechanism involving the induction of the peroxisome proliferator-activated receptor (PPARβ), which was upregulated in a dose-dependent manner, ultimately enhancing glycogen accumulation.

Respiratory system disorders

As shown in Table 7, several investigations revealed a significant relationship between herbicide exposure and its effects on respiratory health. The cross-sectional study among 180 Thai herbicide applicators found a vital prevalence of wheeze and dyspnea, especially in those spraying more than 150 L of chemicals a day, using multiple types of herbicides and improper handling without wearing personal protective equipment (PPE) [128]. In addition, the duration of being an agricultural worker was the most influential factor that reducing respiratory function and was more severe in smoking farmers [129].

Extensive studies have investigated lung toxicity of PQ, as it represents the primary site of action following the uptake [139]. Similar pathological changes seen in acute PQ poisoning cases were also observed after exposure for several weeks [130]. Based on the provided findings [131–134], PQ-induced lung toxicity involves several mechanisms. It increased pro-inflammatory cytokines through the stimulation of high mobility group box 1 (HMGB1) protein and elevated Wnt-induced secreted protein-1 (WISP1) level, a marker of pulmonary fibrosis. Additionally, PQ also disrupted the Keap/Nrf2 signaling pathway, promoting iron accumulation in the lungs, and subsequent lipid peroxidation and ferroptosis. The miRNA-199-mediated decrease in SET protein further

Table 6 Herbicide-associated diabetes mellitus

Herbicide	Subjects	Dose Exposure	Main findings	Ref
Not specifically identified	Human study	-	Significantly associated between plasma herbicide and fasting plasma glucose, fasting insulin and HOMA2-IR (insulin resistance), indicating an increased risk of T2DM.	Wei et al. [117]
ATZ, butylate, 2,4,5-T, and 2,4,5-TP	Human study	-	Significantly associated with the risk of gestational DM in pregnant women who exposed to these herbicides in agricultural activities.	Saldana et al. [118]
2,4,5-T, and 2,4,5-TP	Human study	-	Significantly associated with incident DM during a 10-year follow-up period in farmers' wives who exposed to these herbicides in agricultural activities.	Starling et al. [119]
GLY	Wistar albino male rats	50 to 250 mg/kg	Increased fasting plasma glucose and insulin levels by inducing oxidative stress and disrupting glucose homeostasis in the liver through NFκB signaling pathway.	Prasad et al. [120]
	Wistar albino male rats, and in silico study	50 to 250 mg/kg	Increased fasting plasma glucose and insulin levels through IRS-1/PI3K/Akt signaling pathway resulting in reduced GLUT4 uptake and insulin resistance.	Jayaraman et al. [121]
ATZ	*D. melanogaster*	2 and 20 µg/mL	Increased hemolymph glucose and trehalose levels and induced insulin resistance through oxidative stress mediated JNK signaling pathway.	Gupta et al. [122]
	Sprague-Dawley male rats	30 and 300 µg/kg	Increased fasting plasma glucose and induced insulin resistance through the disruption of mitochondrial function resulting in Akt-signaling pathway inhibition.	Lim et al. [123]
PQ	Rat hepatocytes	2 and 5 mM	Impaired insulin-dependent mTOR activation by reducing IGFBP-1 gene expression through the induction of oxidative stress.	Kimura et al. [124]
	3T3-L1 adipocytes	5 or 10 mM	Reduced glucose uptake by repressing the basal PI3-kinase activity through oxidative stress induction.	Shibata et al. [125]

contributes to lung injury, resulting in edema and hemorrhage. In addition, some PQ poisoning survivors may experience obstructive ventilatory dysfunction even after full recovery, including symptoms such as coughing and wheezing, suggesting the potential for long-term respiratory complications [135].

Although the evidence for lung toxicity induced by exposure to other herbicide may not be extensive as that for PQ, they have also been associated with lung damage. ATZ and 2,4-D shared similar toxic effects with PQ by inducing oxidative stress, disrupting antioxidant defenses, and promoting cell death processes. Besides the disturbance of antioxidant defense system [136, 137], ATZ and 2,4-D promote cell autophagy by increasing a pro-apoptotic protein BAX as well as decreasing an anti-apoptotic BCL-2 [137, 138]. Furthermore, Ganguli et al. [138] proposed a key mechanism of 2,4-D-induced lung cytotoxicity by targeting the tubulin in A549 and WI38 cell lines. In silico experiment additionally confirmed the stable interaction between 2,4-D and tubulin which might lead to the loss of cell shape, morphology, and ultimately cell shrinkage.

Immunological disorders

Herbicides can disturb the immune system in both transient and permanent alterations, as detailed in Table 8. The incidence of rheumatoid arthritis among farmers was associated with the use of ATZ (OR = 1.62, 95% CI: 1.09–2.40) [140], and GLY (OR = 1.4, 95% CI: 1.0–2.1) [141]. The prolonged use of metribuzin for more than 10 days in a year strongly increased the risk of systemic autoimmune diseases (SLEs) and Sjogren's syndrome (SS) in older adults and females (HR = 5.33, 95% CI: 2.19–12.96) [142]. Additionally, several herbicide including 2,4-D, GLY, ATZ, and SIM were also significantly related to allergic wheeze in male farmers [143].

Gao et al. [144] investigated the alterations of T lymphocytes and their subgroups (CD4 and CD8) between the survival and fatal PQ poisoning cases. Studies have

Table 7 Herbicide-associated respiratory system disorders

Herbicide	Subjects	Dose Exposure	Main findings	Ref
Not specifically identified	Human study	-	Significantly associated between high prevalence of respiratory symptoms (wheeze and dyspnea) and farmers who applied high dose and mixed herbicide and ignored wearing PPE.	Sidthilaw et al. [128]
	Human study	-	Significantly associated with poor pulmonary functions in agricultural workers, especially in prolonged and smoking workers.	Babaoglu et al. [129]
PQ	Rhesus monkeys	25 to 80 mg/kg	Induced pulmonary fibrosis with collagen deposition and inflammatory cells infiltration.	Shao et al. [130]
	Human study	-	Increased WISP1 gene expression and developed pulmonary fibrosis in PQ-poisoning cases.	Li et al. [131]
	C57BL/6J mice	40 mg/kg	Induced neutrophil infiltration and lung injury through HBGB1-TLR4-IL23-IL17A axis.	Yan et al. [132]
	Sprague-Dawley male rats	10 and 50 mg/kg	Induced pulmonary fibrosis through Keap1/Nrf2 signaling pathway.	Yang, Xiao, and Shi [133]
	C57BL/6J mice	40 mg/kg	Induced acute lung injury through miR-199-mediated SET.	Cai et al. [134]
	Case report	10 g	Developed asthma attack after successful recovery.	Fan et al. [135]
ATZ	CD1 male mice	25 mg	Induced pulmonary damage and fibrosis through Nrf2 signaling pathway.	D'Amico et al. [136]
	CD1 male mice	250 mg	Induced pulmonary inflammation through the induction of apoptotic Beclin 1/Lc 3 expression and Nrf2 signaling pathway.	D'Amico et al. [137]
2,4-D	A549 and WI38 cell lines	Maximum at 200 µM	Induced lung cytotoxicity through the disruption of the cellular tubulin-microtubule network.	Ganguli et al. [138]

Table 8 Herbicide-associated immunological disorders

Herbicide	Subjects	Dose Exposure	Main findings	Ref
Metribuzin	Human analysis	-	Significantly associated with the risk of systemic autoimmune diseases (SLEs) and Sjogren's syndrome (SS) in participants who exposed more than ten days a year.	Parks et al. [142]
2,4-D, ATZ, GLY, and SIM	Human analysis	-	Significantly associated with allergic wheeze.	Hoppin et al. [143]
PQ	Human analysis	-	Increased neutrophils and decreased lymphocytes levels.	Gao et al. [144]
	C57BL/6J mice	20 mg/kg	Induced the apoptosis in effector or activated lymphocytes resulting in impaired memory immune response.	Shao et al. [145]
GLY	Human analysis	-	Significantly increased the risk of rheumatoid arthritis.	Parks et al. [141]
	Cyprinus carpio	0.25 to 2 mg/L	Induced immune depression effect and altered other biochemical and hematological parameters.	Yousefi et al. [146]
	BALB/c female mice	87.5 µg to 8.75 mg	F0 exhibited a slight eosinophil in lung lavage and increased TH2 cytokine production. Reduced immune response was observed only in female F1 mice. An abundant gut microbiome was also founded in F1offsping.	Buchenauer et al. [147]
ATZ	Human analysis	-	Significantly associated with rheumatoid arthritis in lifetime days of use applicators.	Meyer et al. [140]
	BALB/c female mice	23, 90, and 360 mg/kg	Altered the pathology of immune-related organs and decreased the proliferation ability of lymphocytes.	Chang et al. [148]
	Honeybee	3.73 and 37.3 mg/L	Inhibited the expression of immunity, lipid metabolism, detoxification, and chemosensory genes as well as altered gut microbial composition.	Wang et al. [149]

shown that PQ exposure led to reduced lymphocyte numbers, impaired T-cell function, and reduced antibody production. The reduction in number could result from apoptotic induction of the late-stage effector lymphocyte as reported by Shao et al. [145]. GLY and ATZ have also been linked to immunosuppression [146], suspected that these effects were likely mediated by alterations in gut microbiota [149]. Exposure to ATZ has been shown to reduce spleen weight, splenocyte numbers, and white blood cell counts, as well as impair T and B lymphocytes function [148]. Moreover, Buchenauer et al. [147] studied not only the direct impact of allergic immune response in pure GLY-treated mice but also the influence of its exposure during pregnancy and breastfeeding on the development of asthma in the offspring. Maternal GLY exposure disrupted the immune response in F1 generation offspring, affecting lung inflammation, IgE levels, and cytokine production. The altered responses occurred only in this generation and were speculated to be mediated by microbiota alteration since abundant gut bacteria like *Odoribacter* and *Lachnospiraceae* NK4A136 were found [147].

Diminished implementation of herbicide exposure

The comprehensive review of potential health effects related to herbicide exposure encompasses various groups including not only direct applicators but also nearby residents, pregnant women, newborns, and children. The foremost insights from each finding could bring attention to diverse health concerns, emphasizing the need for collective efforts to alleviate their impacts. Providing well-enforced guidelines and good practices on herbicide usage and investing in research to develop safer options (e.g., herbicide substitution, remediation techniques, and enhanced detection methods) are integral components (Fig. 3). Each implementing strategy possesses distinct characteristics, advantages, and limitations in mitigating risks of herbicide-related human health problems, as provided in Table 9.

Well enforce guidelines and good practices

The regulations and policies set by governmental agencies and international organizations can provide the safety precautions, usage restrictions, and alternative weed control measures to achieve effective weed management, as well as promote sustainable agriculture while safeguarding human health. According to the FAO, good agricultural practice (GAP) was introduced to establish the standard for ensuring sustainable and responsible management in agricultural practices [150, 151]. The critical suggestions regarding health typically include (i) the proper way to handle agrichemicals like pesticides and fertilizers involving the cautious selection of appropriate chemicals for specific pests and strictly following the legal instructions; (ii) the practice of keeping productive areas away from the hazardous contamination such as avoid performing agrichemicals near water sources; (iii) the effective waste management; and (iv) well-trained programs for workers to increase self-literacy in handling the dangerous materials. Moreover, GAP certification enables numerous advantages for farmers and agricultural producers, ultimately benefiting consumers. GAP

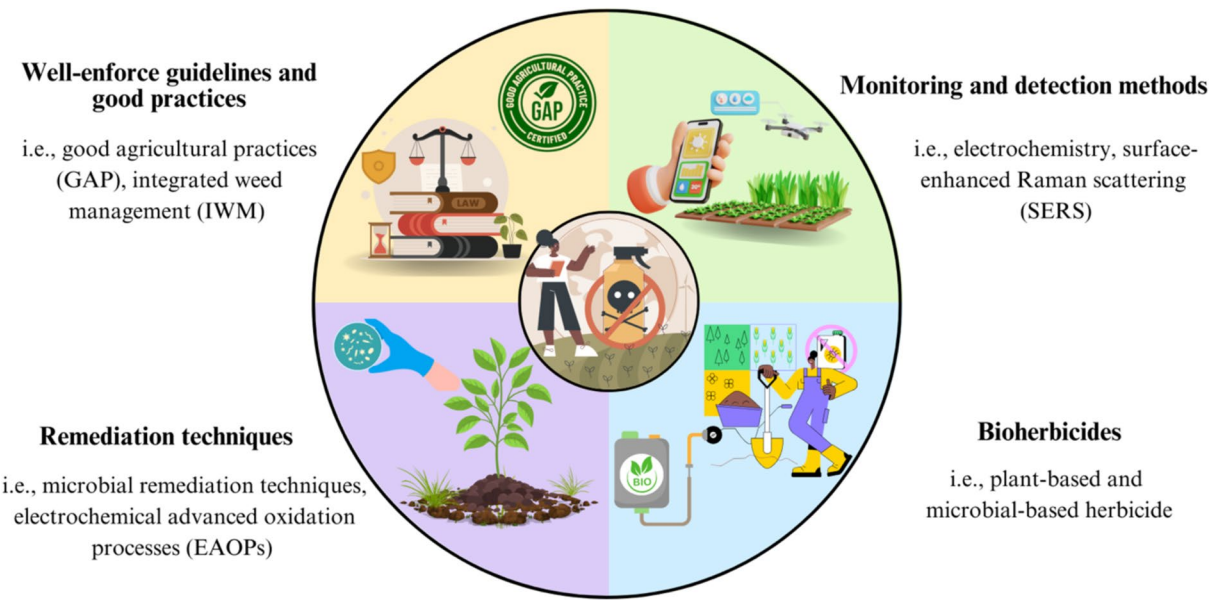

Fig. 3 Diminished implementation of herbicide exposure (By author)

Table 9 Characteristics, advantages, and limitations of diminished implementation of herbicide exposure

Strategy	Key outputs	Advantages	Limitations
Guidelines and practices	• Provide a framework for controlling herbicide usage and minimizing exposure risks. • Standardize practices across the country. • Raise awareness among the community regarding safe handling and disposal procedures.	• Strict adherence to provided guidelines can optimize herbicide use, leading to reduced waste and costs. • Strict adherence to provided guidelines can enhance the credibility and safety of products.	• Compliance may be challenging to monitor effectively, especially in remote areas. • Enforcement varies based on regulatory infrastructure and resources.
Bioherbicides	• Enable to be biodegradable and environmentally friendly.	• Offer potentially safer and more sustainable alternatives. • Enable to reduce the herbicide resistance.	• Development and registration processes are time-consuming and expensive. • Effectiveness varies based on many factors such as timing and environmental conditions.
Remediation techniques	• Provide options for restoring ecosystems and contaminated areas affected by herbicide pollution.	• Enable to increase the value of contaminated properties by making them suitable for redevelopment or reuse.	• Effectiveness varies based on the type and extent of contamination. • Certain remediation techniques are costly and impractical for large-scale implementation.
Monitoring and detection methods	• Allow early detection of herbicide contamination in environmental resources and commodities. • Provide real-time monitoring.	• Enable prompt action to mitigate its effects by timely detect the excessive herbicide residues. • Enable to monitor the effectiveness of remediation efforts and prevent future contamination.	• Certain detection methods may have limited sensitivity and specificity. • Certain detection methods rely on sophisticated equipment and expertise.

certification is often a prerequisite for import/export operations to global commerce, which also expands the market size opportunity and ensures compliance with international trade regulations as required by many countries and retailers [150]. Thus, this certification has fostered competitive products by encouraging the producers to participate in environmentally responsible practices through efficient resource utilization, chemical input reduction, proper waste, and risk management. Furthermore, the integrated weed management (IWM) approach is growing in popularity since it aligns with sustainable and environmentally friendly practices. IWM provides various aspects for weed control that enable to lessen the chemical inputs, reducing the interconnectedness between herbicide remaining and human health. The whole system for this alternative weed management includes four basic strategies which are physical (i.e., hoeing and flaming), biological (i.e., natural enemy utilization), ecological (i.e., crop rotation), and chemical (i.e., proper herbicide selection) management [152]. Although the practices mentioned above predominately focus on herbicide usage in agricultural contexts, its key details could be extrapolated to ensure effective applications in other more minor environmental scales such as private lawns and gardens.

To establish the internationally acceptable residue level that facilitates the standard for global trade harmonization, and ensure food safety in compliance with GAP, the Joint Meeting on Pesticides Residues (JMPR) conducts scientific assessments of pesticide residues in agricultural commodities [153]. Subsequently, the Codex Maximum Residue Level (MRL) has been published regarding the highest pesticides residue level that food or feed can legally contain [154]. In addition, the pesticidal MRLs could be independently determined by the national regulatory agencies sharing the same goal of ensuring the safety of domestically produced and imported products. Examples of national regulatory agencies responsible for, but not limited to, enforcing pesticides MRLs include the Pest Management Regulatory Agency (PMRA) of Canada, the Australian Pesticides and Veterinary Medicines Authority (APVMA) of Australia, and the Environmental Protection Agency (EPA) of the United States [155]. Individual regulatory agencies also hold the authority to take decisive actions such as imposing restrictions or outright bans on highly hazardous agrichemicals when the scientific evidence demonstrates risks to human health. For instance, Thailand's National Hazardous Substance Committee (NHSC) has initiated a review of the safety of PQ, GLY, and chlorpyrifos in 2017. Based on the available scientific literature, the NHSC decided to ban PQ and chlorpyrifos within the country, effective June 1, 2020, whereas GLY remains subject to restrictions for domestic use [156].

Bioherbicides

Bioherbicides (also known as allelopathic or allelochemical compounds) have emerged as a promising method by applying the potential of natural compounds for weed control [157]. They can inhibit the weed growth by releasing toxic metabolites or disrupting regular functions [158]. There are mainly two groups based on the different sources: plant-based and microbial-based herbicides. Plant-based herbicides, such as extracts from *Cynara cardunculus*, have shown effectiveness in controlling various weeds by potentially inhibiting seed growth and germination, leading to necrosis and chlorosis [159]. The performance was also comparable to commercial bioherbicides containing pelargonic acid. Microbial-based herbicides, like toxins produced by *Phoma* sp., can also be effective when formulated with appropriate carriers. Target plants showed severe symptoms after spraying the formulation (e.g., yellowish appearance on leaves, growth retardation, and necrosis) [160]. In addition, several bioherbicides have already been launched in global markets or held patents such as BioWeed™, Organic interceptor®, Katoun Gold®, and Matratec® [157]. Nonetheless, several limitations currently impede the broader adoption of bioherbicides in agricultural practices. To fully reallize the potential of bioherbicides in sustainable weed management, future advancements should prioritize environmental stability, selectivity, absorption efficiency, and cost-effectiveness [157].

Remediation techniques

Implementing removal strategies, including microbial remediation, natural adsorbents, and electrochemical advanced oxidation processes (EAOPs), is a practical approach to reduce the accumulation of the residues in environmental resources. Microbial remediation, mainly derived from bacteria and fungi, is considered an environmentally harmless, cost-effective, and highly efficient technique. It can break down molecules into less toxic byproducts which further serve as the source of energy, carbon, and minerals [161]. For instance, Mohanty and Jena [162] used an isolated *Pseudomonas putida* to degrade butachlor. This strain could effectively remediate 700 mg/L of butachlor within 360 h. and its remediation efficiency was further enhanced by immobilizing on calcium alginate beads. Zhu et al. [163] identified *Bacillus altitudinis* as a fast SIM bio-degrader, with a potency enhanced by bioaugmentation with *Pennisetum rhizosphere* soil. This provided additional enzymes or factors that promoted catalytic activity, resulting in 97% degradation of 30 mg/kg SIM within 5 days.

EAOPs and absorbent techniques are additional options for herbicide removal. EAOPs use electric current to generate ROS that oxidize and degrade organic contaminants into carbon dioxide, water, or less harmful metabolites [164]. This technique offers the independence of auxiliary chemical reagents or the catalyst in the system and applies to both soil and water treatment [164, 165]. On the other hand, absorption strategies use environmentally friendly materials like activated carbon, clay minerals, or agricultural waste, to absorb or remove toxic residues from natural resources [166]. This technique offers simplicity, user-friendliness, versatility, and high efficiency.

Monitoring and detection methods

It is widely acknowledged that conventional detection methods such as chromatography-based techniques could offer high sensitivity and specificity toward complex sample matrix analysis. Nevertheless, these methods are hindered by time-consumed analysis, extensive sample preparation steps, costly instrument setup, and the need for expertise, limiting their widespread adoption, especially in resource-limited settings or among non-expert users. The advancement of residue detection methods has then concurrently gained attention since chemical-based herbicide is unlikely to be suspended in the near future. It is essential to enhance the efficiency of detection methods by considering factors such as time, cost, portability, and ease of use to prevent the excessive accumulation of natural resources, the contamination of edible commodities, or even their application in clinical settings. Electrochemical, surface-enhanced Raman scattering (SERS), and artificial intelligence (AI) techniques are examples of detection methods that pose favorable properties to meet these criteria [167]. Interestingly, computational power is believed to provide innovative solutions and improve agricultural practices, whether by automated weed detection or robotic spraying vehicles [168]. However, all these promising options still require development and testing such as for reliability, stability, and feasibility testing under real-world scenarios before authorization.

Conclusion and future prospective

The substantial utilization of herbicide conceivably causes various health implications. These chemicals can induce threats at any life stage and affect most biological systems through multiple pathways whether by inducing oxidative stress or directly disrupting processes at both molecular and cellular levels. The potential adverse effects on human health should remain a concern, despite some scientific evidence demonstrating conflict outcomes. The main findings emphasize the urgent need for concerted efforts to reduce these impacts on public health. Individuals, communities, and national regulatory bodies are all responsible for fostering a safer society. This may include strengthening health awareness, developing better practices and technologies, as well as improving monitoring and surveillance systems. Furthermore, future research is urged to explore the relationship between human health and herbicide exposure, as certain aspects remain inadequately studied. Conducting such studies is crucial for facilitating early decision-making concerning agricultural practices, regulatory policies, and public health measures.

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Authors' contributions

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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