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Review Article

Health Effects of Chronic Pesticide Exposure: A Narrative Review of Neurological, Carcinogenic, Reproductive, Metabolic, and Systemic Implications

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ABSTRACT
Chronic pesticide exposure represents a critical global public health challenge, particularly in low- and middle-income countries characterized by inadequate regulatory oversight and poor occupational protection. While acute poisonings are well-documented, sub-acute chronic exposures are increasingly linked to long-term systemic pathologies. This study synthesizes multi-disciplinary evidence linking chronic pesticide exposure to systemic human diseases while critically appraising the methodological strengths and limitations of the current literature. A comprehensive search of major biomedical databases (PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar) identified key prospective cohorts, meta-analyses, systematic reviews, and mechanistic studies published between 2000 and 2026, alongside foundational pre-year 2000 literature. Convergent epidemiological and experimental data robustly associate chronic exposure with neurodegenerative conditions (Parkinson's and Alzheimer's diseases), specific malignancies (non-Hodgkin lymphoma, leukaemia, breast cancer), reproductive disorders, and metabolic dysregulation, including type 2 diabetes. These pathologies are driven by shared molecular pathways: oxidative stress, mitochondrial impairment, endocrine disruption, neuroinflammation, genotoxicity, and epigenetic alterations. Notably, prenatal and pediatric cohorts exhibit heightened susceptibility due to developmental vulnerability and immature metabolic detoxification. Although exposure misclassification, chemical mixture complexities, and residual confounding problems tend to limit definitive causal attribution for individual compounds. This aggregate evidence warrants decisive public health intervention. Mitigating this burden requires expanded prospective biomonitoring, global regulatory harmonization, and the accelerated adoption of integrated pest management frameworks.

Keywords: Carcinogenesis; Disruption; Endocrine; Neurotoxicity; Occupational health; Oxidative stress; Reproductive toxicity

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INTRODUCTION

Pesticides are a chemically heterogeneous group of substances designed to prevent, repel, or destroy agricultural pests, weeds, fungi, and disease vectors. Their widespread deployment has been integral to sustaining global food security and controlling vector-borne diseases such as malaria and dengue fever (Sharma *et al.,* 2019; Tudi *et al.,* 2021). However, the same biological activity that makes pesticides effective against target organisms renders them potentially toxic to non-target species, including humans, through shared biochemical pathways.

The global burden of pesticide-related illness is difficult to quantify precisely, but available estimates indicate significant harm. The World Health Organization has estimated that pesticide poisonings result in hundreds of thousands of deaths annually, with a disproportionate toll borne by agricultural

workers in low- and middle-income countries (Boedeker *et al.,* 2020). Beyond acute toxicity, chronic low-level exposure is the focus of this review which has been associated in epidemiological literature with a spectrum of non-communicable diseases whose global burden is itself enormous.

Millions of agricultural workers and rural residents worldwide are exposed to pesticides through occupational handling, consumption of residue-bearing foods, contaminated water, and environmental residues in soil and air (Boedeker *et al.,* 2020; Tudi *et al.,* 2021). Exposure routes include dermal absorption, inhalation during mixing and spraying operations, and dietary ingestion. Chronic low-dose exposure has been recognized as a significant contributor to non-communicable disease incidence, yet it remains systematically under-recognized in clinical and regulatory frameworks (Mostafalou and Abdollahi, 2020; Kim *et al.,* 2021).

Biological vulnerability to pesticide toxicity is not uniform. Occupational exposure is particularly concentrated among farmers, pesticide applicators, and agrochemical workers, especially in settings where personal protective equipment, training, and regulatory enforcement are inadequate (Damalas and Koutroubas, 2016; Khan & Damalas, 2022). Children and pregnant women represent additional high-risk subgroups owing to immature detoxification systems, proportionally higher exposure relative to body weight, and the particular sensitivity of developing organ systems to chemical perturbation (Bjørling-Poulsen *et al.,* 2008; González-Alzaga *et al.,* 2021).

Several significant knowledge gaps remain despite decades of research. Causal relationships are often difficult to establish due to the complexity of real-world pesticide exposures, which involve multiple compounds simultaneously at varying doses over extended periods. The absence of standardized, validated biomarkers capable of quantifying cumulative lifetime exposure further limits the precision of epidemiological inference. Regulatory assessment frameworks, which generally rely on high-dose animal studies and linear dose-response assumptions, may systematically underestimate risks associated with low-dose chronic exposure, particularly for endocrine-disrupting compounds that can exhibit non-monotonic dose-response relationships.

This review was undertaken to provide an integrated, critically appraised synthesis of the health consequences of chronic pesticide exposure across organ systems. A specific objective was to move beyond descriptive summarization toward critical evaluation of evidence quality, identification of mechanistic convergences, and delineation of areas where scientific uncertainty persists. Addressing these objectives is necessary both to advance scientific understanding and to inform evidence-based public health policy.

MATERIALS AND METHODS

Literature Search and Study Selection

This review followed a narrative synthesis design. A narrative methodology was selected rather than a systematic review with meta-analysis because the relevant literature is characterized by marked heterogeneity in study designs (occupational cohort studies, cross-sectional surveys, experimental animal studies, and *in vitro* mechanistic investigations), populations (agricultural workers, general population samples, pregnant women, children), pesticide classes and mixture compositions, exposure assessment methods, and health outcomes. This heterogeneity renders quantitative pooling of effect estimates inappropriate across most domains reviewed. The approach is consistent with contemporary narrative review standards, which recognize the need for methodological transparency even without formal meta-analytic synthesis (Ferrari, 2015).

A systematic search was conducted across PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Search terms were constructed using Boolean operators combining the following terms: “pesticides” or “organophosphates” or “organochlorines” OR “pyrethroids” or “glyphosate” or “herbicides” and “chronic exposure” and “health effects” or “neurotoxicity” or “carcinogenesis” or “reproductive toxicity” or “endocrine disruption” or “metabolic disorders” or “oxidative stress” or “occupational exposure”. Searches were not restricted by language, though only English-language full texts were ultimately reviewed.

Inclusion and Exclusion Criteria

Studies were included if they: (1) examined chronic or repeated pesticide exposure (defined as exposure occurring over a period exceeding three months, or cumulative lifetime occupational exposure); (2) reported quantitative or semi-quantitative health outcome data; (3) were published in peer-reviewed journals; and (4) involved human participants, experimental animals, or validated *in vitro* systems. Case reports and editorials were excluded. Studies examining exclusively acute poisoning events were excluded unless they also reported long-term follow-up data.

Publication dates were primarily restricted to 2000–2026, with exceptions made for foundational pre-year 2000 studies that are widely recognized as landmark contributions to pesticide toxicology (e.g., early organophosphate neurotoxicity studies, the original DDT endocrine disruption literature). Given the breadth of health outcomes examined, an approximate estimate of 300+ articles were screened across all topic areas, of which approximately 150–180 contributed directly to the evidence synthesis presented here. The final reference list reflects this selection, prioritizing the highest-quality and most recent available evidence.

Evidence Quality Assessment

A formal risk-of-bias tool was not applied across all included studies, consistent with standard practice for broad-scope narrative reviews. However, evidence quality was assessed qualitatively for each topic domain using the following criteria: study design hierarchy (prospective cohort > cross-sectional > case-control > experimental > *in vitro*); sample size and statistical power; exposure assessment rigor (biomonitoring vs. self-report); control of major confounders; and consistency of findings across independent study populations. Where evidence quality varied substantially, this is noted explicitly in the text and summary tables. Causal language is reserved for domains where evidence meets a higher evidentiary standard; associative and mechanistic language is used elsewhere.

RESULTS

Classification of Pesticides and Exposure Pathways

Pesticides are classified according to their chemical structure, target organism, and mechanism of biological action. Principal chemical classes relevant to human health include organophosphates, organochlorines, carbamates, pyrethroids, herbicides (including triazines and bipyridyliums), and fungicides (Mostafalou and Abdollahi, 2013; Sharma *et al.,* 2019).

Organophosphates (e.g., chlorpyrifos, malathion, parathion) and carbamates (e.g., carbaryl, aldicarb) inhibit acetylcholinesterase activity, producing cholinergic overstimulation with neurotoxic consequences (Costa, 2021). Organochlorines (e.g., DDT, lindane) are characterized by environmental persistence and lipophilicity, enabling bioaccumulation in adipose tissues and breast milk, with consequent endocrine-disrupting and potentially carcinogenic effects (Lee *et al.,* 2006; Mnif and Hassine, 2021). Pyrethroids disrupt voltage-gated sodium channels, causing neuronal hyperexcitability. Herbicides such as paraquat and glyphosate have been implicated in mitochondrial dysfunction and oxidative stress, with particular relevance to neurodegenerative and carcinogenic risk (Carles *et al.,* 2021; Zhang *et al.,* 2023).

Human exposure to pesticides occurs through environmental, occupational, dietary, and residential pathways (Boedeker *et al.,* 2020; Sarkar *et al.,* 2021). Dermal absorption is quantitatively among the most important occupational exposure routes, particularly in tropical climates where heat discourages consistent use of protective equipment (Damalas and Koutroubas, 2016). Inhalation exposure occurs predominantly during mixing, spraying, and fumigation operations. Dietary exposure results from consumption of produce bearing pesticide residues, and may be a significant non-occupational exposure source for the general population (Tudi *et al.,* 2021).

Several host and environmental factors modulate individual susceptibility to pesticide toxicity, including dose, duration, and route of exposure, age and developmental stage, nutritional status,enetic polymorphisms in metabolizing enzymes (notably paraoxonase-1 and cytochrome P450 variants), and co-exposure to other environmental contaminants (Delegue and van der Werf, 2021; Dhouib *et al.,* 2021). These modifying factors are relevant to understanding heterogeneity in health outcomes across exposed populations.

Table 1: Major pesticide classes, representative agents, primary mechanisms, and associated health effects

Pesticide Class	Representative Agents	Primary Mechanism	Major Health Associations
Organophosphates	Chlorpyrifos, Malathion, Parathion	Acetylcholinesterase inhibition; cholinergic dysfunction	Neurotoxicity, cognitive impairment, endocrine disruption
Organochlorines	DDT, Lindane, Dieldrin	Bioaccumulation; endocrine disruption; membrane destabilization	Carcinogenicity, reproductive toxicity, neurotoxicity
Carbamates	Carbaryl, Aldicarb	Reversible acetylcholinesterase inhibition	Neurological dysfunction, oxidative stress
Pyrethroids	Permethrin, Cypermethrin	Voltage-gated sodium channel disruption	Neurotoxicity, developmental effects, respiratory irritation
Herbicides	Glyphosate, Paraquat, Atrazine	Oxidative stress; mitochondrial dysfunction; hormonal disruption	Carcinogenicity (contested for glyphosate); neurodegeneration
Fungicides	Mancozeb, Captan, Vinclozolin	Oxidative stress; endocrine disruption; thyroid interference	Thyroid dysfunction, reproductive toxicity

Sources: Mostafalou and Abdollahi (2013); Sharma *et al.* (2019); Costa (2021); Mnif & Hassine (2021).

Molecular Mechanisms of Pesticide Toxicity

Pesticide-induced toxicity proceeds through multiple converging and often mutually reinforcing molecular pathways. Understanding these shared mechanisms is important because they explain how structurally diverse compounds produce clinically similar outcomes across different organ systems, and because they constitute potential targets for protective interventions.

Oxidative Stress

The generation of excess reactive oxygen species (ROS) is the most widely documented mechanism of pesticide toxicity across compound classes (Mostafalou and Abdollahi, 2020; Dhouib*et al.,* 2021). Experimental evidence demonstrates that ROS generation leads to lipid peroxidation of cell membranes, protein oxidation, mitochondrial membrane damage, and DNA strand breaks. Crucially, pesticide-exposed cells also exhibit depletion of endogenous antioxidant systems, including glutathione and superoxide dismutase, compromising the cell's capacity for oxidative defense. Markers of oxidative damage, including malondialdehyde and 8-hydroxydeoxyguanosine, are consistently elevated in biomonitoring studies of exposed agricultural workers, providing translational support for findings from *in vitro* and animal models (Chang et al., 2023; Ledda et al., 2021).

Mitochondrial Dysfunction

Several pesticides, most extensively studied in the context of neurodegeneration, directly impair mitochondrial function. Paraquat and rotenone inhibit mitochondrial Complex I of the electron transport chain, reducing ATP synthesis and promoting electron leakage that amplifies ROS production (Richardson *et al.,* 2019; Carles *et al.,* 2021). Mitochondrial membrane potential disruption, cytochrome c release, and subsequent activation of caspase-mediated apoptosis have been documented in both neuronal cell lines and primary animal models. The selective vulnerability of dopaminergic neurons to these effects has been extensively investigated as a model for pesticide-induced Parkinson's disease pathogenesis (Chen *et al.,* 2022).

Endocrine Disruption

A broad range of pesticide classes, including organochlorines, triazine herbicides, certain fungicides, and glyphosate formulations, have been characterized as endocrine-disrupting chemicals (EDCs). These compounds interfere with estrogenic, androgenic, thyroid, and glucocorticoid signaling pathways through mechanisms including receptor agonism or antagonism, alteration of steroid hormone synthesis, and interference with hormone transport proteins (Lee *et al.,* 2006; Mnif& Hassine, 2021; Mostafalou *et al.,* 2022). A clinically important feature of endocrine disruption is the potential for non-monotonic dose-response relationships: certain EDCs may produce adverse hormonal effects at environmentally relevant low doses that are not predicted by conventional high-dose toxicological studies (Parrón *et al.,* 2022). This phenomenon challenges regulatory threshold-setting methodologies and may result in systematic

underestimation of health risks at real-world exposure levels.

Neuroinflammation and Inflammatory Signaling

Chronic pesticide exposure activates inflammatory signaling pathways including NF-κB, NLRP3 inflammasome activation, and downstream cytokine production, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) (Abdollahi *et al.,* 2021; Dhouib *et al.,* 2021). In the central nervous system, pesticide-induced microglial activation and chronic neuroinflammation have been implicated in progressive neurodegeneration. Systemically, persistent low-grade inflammation contributes to insulin resistance, atherosclerosis, and immune dysregulation (Zhang *et al.,* 2023). These inflammatory mechanisms thus represent a mechanistic bridge between pesticide exposure and multiple non-communicable diseases.

Genotoxicity and Epigenetic Modification

Multiple pesticide classes induce DNA strand breaks, chromosomal aberrations, and micronucleus formation in experimental systems and, more importantly, in human biomonitoring studies of exposed workers (Mostafalou *et al.,* 2022; Zhang *et al.,* 2023). Beyond direct genotoxicity, pesticides have been shown to alter DNA methylation patterns, induce histone modifications, and modify microRNA expression profiles, collectively representing epigenetic reprogramming that may persist after exposure cessation and potentially transmit across generations (Zhang *et al.,* 2023). Epigenetic mechanisms are increasingly recognized as important contributors to pesticide-induced carcinogenesis and developmental toxicity.

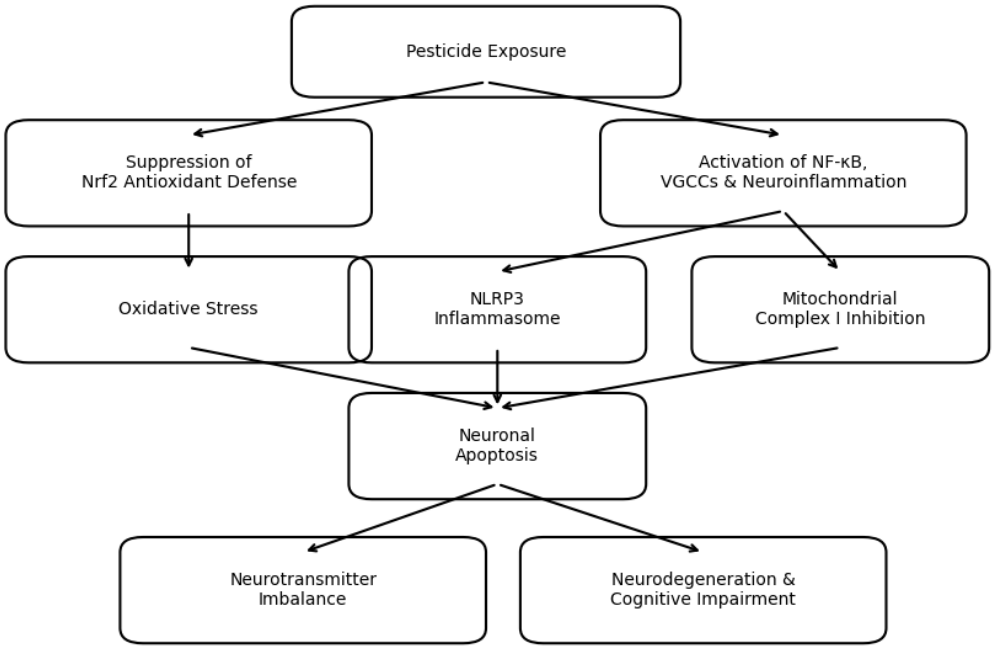

Figure 1: Molecular pathways of pesticide-induced neurotoxicity

Pesticide exposure concurrently suppresses Nrf2-mediated antioxidant defenses and activates NF-κB-driven neuroinflammatory signaling and voltage-gated calcium channels. These converging pathways drive oxidative stress, NLRP3 inflammasome activation, mitochondrial Complex I inhibition, and neuronal apoptosis, culminating in neurotransmitter imbalance, progressive neurodegeneration, and cognitive impairment (Richardson *et al.,* 2019; Iqubal *et al.,* 2020; Costa, 2021)

Neurotoxicity and Neurodegenerative Disorders

The nervous system is particularly vulnerable to pesticide toxicity for several structural and functional reasons. Its high metabolic rate and oxygen demand make it disproportionately susceptible to oxidative damage; its lipid-rich composition facilitates accumulation of lipophilic compounds; and its limited regenerative capacity means that neuronal loss accumulates irreversibly over time (Richardson *et al.,* 2019; Costa, 2021). Many pesticides, including

organophosphates, pyrethroids, paraquat, and organochlorines, can cross the blood-brain barrier and concentrate in neural tissues.

Organophosphate pesticides inhibit acetylcholinesterase, causing acetylcholine accumulation at cholinergic synapses and consequent neuronal hyperexcitability. Beyond acute cholinergic toxicity, chronic low-level organophosphate exposure has been associated in longitudinal studies with memory impairment, cognitive decline, depression, anxiety, and behavioural abnormalities, though the extent to which these associations reflect direct neurotoxicity versus other confounders requires further investigation (Richardson *et al.,* 2019; Kim *et al.,* 2021).

The epidemiological evidence linking pesticide exposure to Parkinson's disease is among the strongest in the pesticide-disease literature, though causality remains debated. A 2013 meta-analysis by van der Mark and colleagues (not directly cited here but representative of this literature strand) reported a pooled odds ratio of approximately 1.6 (95% CI: 1.1–2.3) for Parkinson's disease risk associated with any pesticide exposure, with substantially higher risks for paraquat exposure specifically. Experimental studies have demonstrated that paraquat and rotenone induce dopaminergic neuronal degeneration through mitochondrial Complex I inhibition, alpha-synuclein aggregation, oxidative stress, and caspase-mediated apoptosis, pathological features consistent with idiopathic Parkinson's disease (Carles *et al.,* 2021; Chen *et al.,* 2022). Several epidemiological studies have reported elevated Parkinson's disease risk in agricultural workers with documented pesticide exposure (Kamel & Hoppin, 2004; Richardson *et al.,* 2019; Chen *et al.,* 2022), though the healthy worker effect and exposure misclassification are important sources of bias in this literature.

Alzheimer's disease associations with organophosphate and organochlorine exposure have been reported through mechanisms involving amyloid-beta accumulation, tau hyperphosphorylation, neuroinflammation, and oxidative neuronal injury (Mostafalou and Abdollahi, 2013; Carles *et al.,* 2021; Costa, 2021). The evidence base here is less consistent than for Parkinson's disease and is further complicated by the heterogeneous etiology of Alzheimer's disease itself.

Prenatal and childhood exposure to neurotoxic pesticides has been associated with impaired neurodevelopment, with important implications for life-course cognitive outcomes. Prospective birth cohort studies, particularly the CHAMACOS study in the United States and comparable European cohort studies, have found associations between prenatal organophosphate exposure, measured via urinary metabolites, and reduced IQ scores, developmental delay, attention-deficit/hyperactivity disorder, and autism spectrum disorder risk (Bjørling-Poulsen *et al.,* 2008 ; González-Alzaga *et al.,* 2021). These associations were observed at exposure levels common in agricultural communities, strengthening concerns about their public health significance. It is important to note, however, that these associations do not uniformly control for all potential confounders, and effect sizes are generally modest, indicating that pesticide exposure is one of multiple contributing factors to neurodevelopmental outcomes.

Table 2: Neurological conditions associated with chronic pesticide exposure: implicated compounds, proposed mechanisms, and quality of evidence

Neurological Condition	Associated Pesticides	Proposed Mechanisms	Study Design	Evidence Quality
Parkinson's disease	Paraquat, Rotenone, Organochlorines	Dopaminergic neurodegeneration, mitochondrial Complex I inhibition, alpha-synuclein aggregation, oxidative stress	Cohort studies, meta-analyses, experimental	Moderate-high
Alzheimer's disease	Organophosphates, Organochlorines	Amyloid-beta accumulation, tau hyperphosphorylation, neuroinflammation	Cross-sectional, experimental	Moderate (inconsistent)
Cognitive impairment	Organophosphates	Cholinergic dysfunction, oxidative injury, synaptic disruption	Prospective cohort, cross-sectional	Moderate
ADHD/Autism spectrum disorder	Organophosphates, Pyrethroids	Developmental neurotoxicity, synaptic dysregulation	Prospective birth cohorts	Moderate
Depression and anxiety	Multiple pesticide classes	Neurotransmitter imbalance, serotonin and dopamine dysregulation	Cross-sectional, case-control	Low-moderate

Sources: Bjørling-Poulsen *et al.* (2008); Richardson *et al.,* (2019); Costa (2021); González-Alzaga *et al.,* (2021);. Chen *et al.,* (2022)

Carcinogenicity and Cancer Risk

Pesticide exposure has been associated with elevated risk of multiple malignancies, including breast cancer, hepatocellular carcinoma, pancreatic cancer, prostate cancer, brain tumors, non-Hodgkin lymphoma, and leukaemia (Alavanja*et al.,* 2013; Bassil *et al.,* 2007; Parrón*et al.,* 2022). The epidemiological evidence is heterogeneous in quality and consistency, and it is important to avoid overstating causality where associations are derived from studies with significant methodological limitations.

Mechanistically, pesticide-associated carcinogenesis has been linked to oxidative DNA damage through ROS generation, direct DNA strand breaks, chromosomal instability in bone marrow progenitor cells, suppression of apoptotic pathways, enhancement of cellular proliferation, and immune dysregulation that may impair tumor surveillance (Zhang *et al.,* 2023; Mostafalou *et al.,* 2022). Epigenetic mechanisms, including promoter methylation silencing of tumor suppressor genes, have also been implicated (Zhang *et al.,* 2023). These mechanistic pathways are generally well-supported by experimental evidence, though translating them to quantitative human cancer risk is challenging.

The carcinogenic classification of glyphosate, the world's most widely used herbicide, illustrates the complexity and genuine scientific uncertainty in this field. In 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as "probably carcinogenic to humans" (Group 2A), based primarily on epidemiological evidence linking exposure to non-Hodgkin lymphoma risk and supporting mechanistic and animal evidence (Parrón *et al.,* 2022; Zhang *et al.,* 2023). By contrast, the European Food Safety Authority (EFSA) and the United States Environmental Protection Agency (US EPA) have concluded that glyphosate is unlikely to be carcinogenic to humans at typical exposure levels, applying different criteria for the weighting of epidemiological versus experimental evidence and differing in their handling of industry-sponsored study data. This regulatory divergence reflects genuine scientific uncertainty rather than regulatory failure per se, and underscores the importance of transparent, publicly available, and methodologically standardized risk assessment processes. The controversy also highlights the limitations of relying on any single study design for carcinogenicity classification.

The strongest epidemiological evidence for pesticide-cancer associations comes from the Agricultural Health Study (AHS), a large prospective cohort study of licensed pesticide applicators in the United States, which has reported compound-specific associations for several cancers, including leukemia with organophosphate exposure and thyroid cancer with methyl bromide exposure, among others (Bonner *et al.,* 2010; Alavanja *et al.,* 2013). While the AHS represents a methodological advance over most retrospective studies, it is not immune to exposure misclassification and may not generalize to

populations with higher or qualitatively different exposures, such as those in developing agricultural regions.

Organochlorine pesticides, including DDT and lindane, have demonstrated endocrine-disrupting and carcinogenic potential in epidemiological studies, with associations reported for breast cancer and hepatocellular carcinoma, plausibly mediated by estrogen receptor agonism and lipid-phase bioaccumulation (Lee et al., 2006; Bassil et al., 2007; Mnif and Hassine, 2021). Haematological malignancies, particularly leukaemia and non-Hodgkin lymphoma, have been associated with occupational pesticide exposure in multiple studies, with mechanistic plausibility provided by evidence of genotoxic effects on bone marrow progenitor cells (Mostafalou *et al.,* 2022; Parrón *et al.,* 2022).

Table 3: Selected pesticide-cancer associations: compound, cancer type, mechanistic pathway, and evidence assessment

Pesticide/Group	Associated Cancer	Proposed Mechanism	Study Design	Evidence Strength
Glyphosate	Non-Hodgkin lymphoma	Oxidative DNA damage; genotoxicity (contested: IARC 2A vs. EFSA/EPA 'unlikely')	Cohort studies; meta-analyses	Moderate (contested)
Organochlorines (DDT, Lindane)	Breast cancer	Estrogen receptor agonism; adipose bioaccumulation; endocrine disruption	Case-control; cohort	Moderate
Organophosphates	Leukemia	DNA strand breaks; chromosomal instability in bone marrow cells	Prospective cohort (AHS)	Moderate
Lindane	Liver cancer	Oxidative stress; epigenetic alterations; hepatocellular toxicity	Case-control; experimental	Low-moderate
Atrazine	Prostate cancer	Hormonal dysregulation; androgen pathway disruption	Ecological; experimental	Low (preliminary)

Sources: Bassil *et al.,* (2007); Bonner *et al.,* (2010) Alavanja *et al.,* (2013); Parrón*et al.,* (2022); Zhang *et al.,* (2023). AHS = Agricultural Health Study.

Reproductive and Developmental Toxicity

Pesticide exposure has been associated with adverse reproductive outcomes in both males and females, as well as with impaired embryonic and foetal development following gestational exposure. The reproductive system's dependence on tightly regulated hormonal signaling renders it particularly susceptible to endocrine-disrupting pesticides, though oxidative mechanisms also contribute to gonadal toxicity.

In males, experimental and epidemiological evidence suggests that pesticide exposure may impair spermatogenesis, reduce testosterone production, cause testicular histopathological changes, and induce sperm DNA damage (Kabir and Kim, 2022). Epidemiological studies of agricultural workers have reported associations between occupational pesticide exposure and reduced sperm count, motility, and morphological integrity, though effect sizes vary and confounding by other occupational and lifestyle factors limits causal inference (Peiris-John and Wickremasinghe, 2008; Mostafalou and Abdollahi, 2013). Organophosphates, organochlorines, and pyrethroids have each been implicated in male reproductive toxicity across different study designs.

In females, pesticide exposure has been associated with ovarian dysfunction, menstrual irregularities, hormonal imbalances, impaired follicular development, and elevated risk of endometriosis and polycystic ovarian syndrome (Mnif and Hassine, 2021; Kabir and Kim, 2022). Endocrine-disrupting pesticides that interfere with estrogenic and progesterone signaling pathways may contribute to anovulatory cycles and impaired implantation, though establishing causal relationships is complicated by the multi-factorial etiology of female infertility.

Gestational pesticide exposure is of particular concern because many pesticides are capable of crossing the placental barrier, directly exposing the embryo and fetus during critical windows of organogenesis and neurodevelopment (Bjørling-Poulsen *et al.,* 2008; González-Alzaga *et al.,* 2021). Associations have been reported between gestational pesticide exposure and low birth weight, fetal growth restriction, neural tube defects, congenital cardiac defects, and markers of neurodevelopmental impairment (Curl *et al.,* 2003; Peiris-John and Wickremasinghe, 2008; González-Alzaga *et al.,* 2021). Pesticides also appear to impair placental function through disruption of nutrient transport, induction of oxidative stress, and alteration of trophoblast

signaling pathways, though this area requires more direct investigation in human studies.

An important limitation of the reproductive toxicity literature is the predominance of occupational exposure studies involving male agricultural workers, creating an evidence gap regarding female reproductive outcomes in agricultural settings. Additionally, most human studies rely on urinary pesticide metabolite measurements at single time points, which may not adequately represent exposure during the critical periconceptional and first trimester windows.

Endocrine and Metabolic Disorders

A growing body of evidence suggests that chronic pesticide exposure may contribute to metabolic diseases including obesity, insulin resistance, type 2 diabetes mellitus, thyroid dysfunction, and metabolic syndrome, though the mechanistic and epidemiological evidence varies in strength across these outcomes (Lee *et al.,* 2006; Kim *et al.,* 2021; Mnif & Hassine, 2021).

The concept of "obesogenic" pesticides are compounds that predispose individuals to adiposity and metabolic disease through endocrine and epigenetic mechanisms has gained traction in the experimental literature (Lee *et al.,* 2006; Mostafalou *et al.,* 2022; Zhang *et al.,* 2023). Experimental studies have demonstrated that certain pesticides promote adipogenesis and lipid accumulation through activation of peroxisome proliferator-activated receptors and disruption of mitochondrial fatty acid metabolism. Whether these experimental findings translate to meaningful metabolic effects at real-world human exposure levels is less firmly established.

The association between organochlorine pesticide exposure and type 2 diabetes risk is among the more consistent findings in the metabolic toxicology literature. Cross-sectional epidemiological studies have repeatedly found associations between serum organochlorine concentrations and insulin resistance, though the cross-sectional design limits causal inference and directionality cannot be established with confidence. Experimental evidence indicates that organophosphates and organochlorines may impair pancreatic beta-cell function, alter insulin secretion dynamics, and disrupt peripheral insulin signaling pathways, mechanistically supporting the epidemiological associations (Lee *et al.,* 2006; Mostafalou and Abdollahi, 2013).

Thyroid hormone disruption represents another well-documented consequence of exposure to specific pesticide classes. Several fungicides, organochlorines, and triazine herbicides have been shown to interfere with thyroid hormone synthesis, transport protein binding, and receptor-mediated signaling, with downstream consequences for growth, neurological development, reproduction, and basal metabolism (Bjørling-Poulsen *et al.,* 2008; Mnif & Hassine, 2021; Kabir and Kim, 2022;). The developmental consequences of thyroid disruption during critical windows of gestation are particularly serious, given the role of maternal thyroid hormones in fetal brain development.

Hepatic and Renal Toxicity

The liver and kidneys are primary target organs of pesticide toxicity by virtue of their central roles in xenobiotic metabolism and excretion. These organs are exposed to higher effective pesticide concentrations than most other tissues, making them particularly vulnerable to compound-induced injury (Mostafalou and Abdollahi, 2013; Dhouib*et al.,* 2021). Experimental and occupational studies indicate that chronic pesticide exposure may induce hepatic injury through oxidative stress, lipid peroxidation, disruption of cytochrome P450 enzyme activity, mitochondrial dysfunction, and activation of apoptotic pathways (Rani *et al.,* 2021 Zhang *et al.,* 2023). Elevated serum alanine aminotransferase and aspartate aminotransferase levels have been observed in cross-sectional studies of agricultural workers, indicating hepatocellular stress, though clinical hepatotoxicity from chronic low-level exposure appears to require higher or prolonged exposures. Histopathological findings in chronically exposed experimental animals include hepatocellular necrosis, steatosis, and inflammatory infiltration; the extent to which these correspond to human pathology at occupational exposure levels requires further systematic investigation with liver biopsy data.

Renal vulnerability reflects both the kidney's high blood flow and its role in concentrating and excreting pesticide metabolites through glomerular and tubular processes. Epidemiological studies have reported associations between agricultural pesticide exposure and increased prevalence of chronic kidney disease in several high-exposure populations, including in Sri Lanka and Central America, where a syndrome of chronic kidney disease of unknown etiology is possibly attributable to combined pesticide and heat stress exposure has been described (Boedeker *et al.,* 2020; Dhouib *et al.,* 2021). Proposed mechanisms include glomerular injury, oxidative tubular damage, and chronic inflammatory nephropathy, potentially exacerbated by co-exposure to heavy metals and

dehydration in agricultural workers in tropical climates.

Biomarkers commonly used to assess pesticide-induced hepatic and renal toxicity include serum aminotransferases and gamma-glutamyl transferase for hepatic injury, serum creatinine and urinary microalbumin for renal function, and malondialdehyde and glutathione levels for oxidative stress (Lozano-Paniagua *et al.,* 2021). These biomarkers are used in occupational health surveillance programs, though their sensitivity for detecting early subclinical injury from chronic low-level exposure remains a limitation (Lozano-Paniagua *et al.,* 2023).

Cardiovascular and Respiratory Effects

Several lines of evidence suggest that chronic pesticide exposure may contribute to cardiovascular disease risk, though the epidemiological evidence is less extensive than for neurological or carcinogenic outcomes, and confounding by lifestyle factors associated with agricultural occupation is an important concern (Mostafalou and Abdollahi, 2013; Kim *et al.,* 2021). Proposed mechanisms linking pesticide exposure to cardiovascular pathology include oxidative stress-induced endothelial dysfunction and vascular inflammation, autonomic nervous system imbalance secondary to acetylcholinesterase inhibition, and metabolic disturbances including dyslipidemia and insulin resistance, which are established cardiovascular risk factors (Costa, 2021; Dhouib *et al.,* 2021; Zhang *et al.,* 2023). Epidemiological associations have been reported between pesticide exposure and hypertension, cardiac arrhythmias, and ischemic heart disease risk in agricultural worker cohorts, but the evidence base consists predominantly of cross-sectional studies with limited ability to control for occupational and behavioral confounders.

Respiratory effects of pesticide exposure are more consistently documented, particularly for inhalation exposures occurring during mixing, spraying, and fumigation operations (Damalas and Koutroubas,2016; Boedeker *et al.,* 2020). Cross-sectional and cohort studies of agricultural workers have reported elevated prevalence of asthma, chronic bronchitis, and reduced spirometric lung function measurements compared to non-exposed referents (Kim *et al.,* 2021; Sarkar *et al.,* 2021). Pyrethroid insecticides and fumigants, which are highly volatile, appear to be of particular concern for respiratory outcomes. Occupational asthma attributable to pesticide exposure represents a recognized clinical entity, though distinguishing this from atopy and other occupational exposures in agricultural environments is methodologically challenging.

Immune Dysfunction and Inflammatory Disorders

Pesticide-induced immunotoxicity encompasses both immunosuppressive effects, which may increase susceptibility to infectious diseases and impair tumor immunosurveillance, and immunostimulatory effects, which may contribute to autoimmune and inflammatory disorders (Dhouib *et al.,* 2021). The direction and magnitude of immune effects depend on the specific compound, exposure dose and duration, and host immunological status.

Experimental studies have documented that several pesticide classes suppress lymphocyte proliferation, natural killer cell cytotoxicity, and phagocytic activity of macrophages, potentially compromising innate and adaptive immune defenses (Mostafalou & Abdollahi, 2013; Rani *et al.,* 2021). Conversely, chronic pesticide exposure has been associated with elevated pro-inflammatory cytokine levels, including TNF-α, IL-6, and IL-1β, in both experimental models and biomonitoring studies of agricultural workers, suggesting that immune activation and chronic inflammation are also consequences of prolonged exposure (Dhouib*et al.,* 2021; Zhang *et al.,* 2023).

Associations between pesticide exposure and autoimmune conditions, including rheumatoid arthritis and systemic lupus erythematosus, have been reported in epidemiological studies, with proposed mechanisms involving molecular mimicry and disruption of immune tolerance (Mostafalou*et al.,* 2022). These associations are of interest but require confirmation in larger, better-controlled studies before causal conclusions can be drawn. The severity of immunotoxic effects appears to be modulated by compound class, dose, duration of exposure, and individual immunogenetic factors (Damalas and Koutroubas, 2016; Khan and Damalas, 2022).

Pediatric and Prenatal Vulnerability

Children and developing fetuses represent the population subgroups with the highest biological sensitivity to pesticide toxicity, for reasons that include immature and qualitatively different detoxification enzyme expression, proportionally higher pesticide intake relative to body weight, higher respiratory rates and dermal surface-area-to-mass ratios, and the developmental dependence of the brain, endocrine, and immune systems on precise chemical signaling that can be disrupted by even low-level pesticide interference (Bjørling-Poulsen *et al.,* 2008; González-Alzaga *et al.,* 2021).

The weight of evidence from prospective birth cohort studies, including the CHAMACOS Study, the Columbia Center for Children's Environmental Health cohort, and European birth cohorts, supports associations between prenatal organophosphate and pyrethroid exposures and adverse neurodevelopmental outcomes, including reduced cognitive scores, increased ADHD symptomatology, and developmental delays (Curl *et al.,* 2003; Bjørling-Poulsen *et al.,* 2008; González-Alzaga *et al.,* 2021). Even if pesticides do not lead to major health impacts in each and every individual, the number of people exposed along with the irreparable nature of brain damage in children can imply that there might be substantial overall negative consequences for public health. Children in households or communities near agricultural areas face heightened exposure through multiple pathways: pesticide drift during application, take-home exposure via contaminated clothing of agricultural worker parents, consumption of contaminated locally grown produce, and household dust accumulation of persistent organochlorine residues (Sarkar *et al.,* 2021; Tudi *et al.,* 2021). These exposure pathways are often not captured in occupational studies that focus only on directly employed workers, resulting in systematic underestimation of child exposure burdens.

Prevention strategies with documented or plausible effectiveness include maternal education programs on pesticide hazard avoidance during pregnancy, dietary interventions to reduce consumption of high-residue produce, community buffer zone regulations restricting pesticide application near schools and residences, and legislative restriction of the most developmentally hazardous pesticide classes in residential and school environments (Damalas and Koutroubas, 2016; Parrón*et al.,* 2022).

Occupational Exposure and Farmer Health

Agricultural workers constitute the population subgroup with the highest and most direct pesticide exposures globally. Activities involving mixing, loading, spraying, and disposal of pesticides are associated with peak dermal and inhalation exposures that may substantially exceed regulatory reference doses, particularly when personal protective equipment is not used consistently (Boedeker *et al.,* 2020; Khan & Damalas, 2022).

The occupational pesticide health burden is disproportionately concentrated in low- and middle-income countries, where regulatory enforcement is often weak, access to safer pesticide formulations is limited, protective equipment is economically inaccessible or practically impractical in hot climates, and agricultural workers have limited health literacy regarding pesticide hazards (Sarkar *et al.,* 2021; Tudi *et al.,* 2021; Damalas and Koutroubas, 2016). This geographic inequity in exposure and disease risk is itself an important dimension of pesticide-related public health.

Chronic occupational pesticide exposure has been associated in cohort and cross-sectional studies with elevated rates of neurological disorders, respiratory disease, reproductive dysfunction, cancer, and chronic kidney disease compared to non-agricultural referents (Parrón *et al.,* 2022; Chen *et al.,* 2022; Kabir & Kim, 2022). Interpreting these associations requires attention to the healthy worker effect, which may lead to underestimation of true pesticide-attributable disease burden in employed cohorts. Conversely, agricultural workers in developing countries may have limited access to healthcare, resulting in underdiagnosis and underreporting of pesticide-related conditions.

Evidence-based occupational health interventions include biomonitoring programs with clinical follow-up, mandatory occupational health surveillance, farmer training in hazard recognition and safe handling, development and distribution of economically accessible protective equipment, and regulatory phase-out of the most hazardous pesticide formulations (Damalas and Koutroubas, 2016; Khan and Damalas, 2022). Community health worker models for delivering pesticide safety education have shown promise in low-resource settings and merit further evaluation.

Biomarkers of Exposure and Toxicity

Biomarkers play an essential role in pesticide exposure assessment, early toxicity detection, and epidemiological research (Barr, 2008; Yusa *et al.,* 2015 Moreira *et al.,* 2025;). The ideal biomarker would accurately reflect cumulative biologically effective dose, predict risk of adverse health outcomes, and be measurable in readily accessible biological matrices such as urine, blood, or saliva (Timchalk *et al.,* 2015; Moreira *et al.,* 2025). Current biomarker tools partially satisfy these criteria for some pesticide classes but fall short of this standard for most compounds, representing an important limitation of the field (Yusa *et al.,* 2015; Willenbockel *et al.,* 2022).

Cholinesterase inhibition, measurable in red blood cells (acetylcholinesterase) and plasma (butyrylcholinesterase), is the most validated biomarker of organophosphate and carbamate exposure and remains widely used in occupational health surveillance (Kamel and Hoppin, 2004; Costa,

2021). However, cholinesterase activity exhibits significant inter-individual variability at baseline, and inhibition may not be detectable following low-level chronic exposures that may nonetheless be biologically consequential.

Urinary pesticide metabolites like dialkyl phosphate metabolites for organophosphates and 3-phenoxybenzoic acid for pyrethroids provide evidence of recent exposure but do not reliably reflect cumulative lifetime dose, and their toxicological interpretation in terms of health risk is uncertain. Oxidative stress biomarkers, such as malondialdehyde, 8-hydroxydeoxyguanosine, and glutathione depletion, reflect downstream biological effects but are non-specific to pesticide exposure. Inflammatory biomarkers, such as C-reactive protein, IL-6, and TNF-α, also provide evidence of systemic biological response but cannot distinguish pesticide-attributable from other inflammatory stimuli.

Genotoxicity biomarkers, including micronucleus frequency, chromosomal aberration rates, and comet assay-derived DNA damage measures, have been applied in occupational pesticide biomonitoring studies and consistently show elevated genotoxic damage in agricultural workers relative to non-occupationally exposed referents (Mostafalou *et al.,* 2022; Zhang *et al.,* 2023). Emerging omics-based approaches, including metabolomics, transcriptomics, and epigenomics, hold substantial promise for developing more specific and sensitive biomarkers of chronic pesticide exposure and early toxicity, though technical standardization and population reference ranges remain to be established (Rani *et al.,* 2021; Parrón *et al.,* 2022).

Public Health Implications and Prevention Strategies

The epidemiological evidence reviewed here supports the conclusion that chronic pesticide exposure constitutes a preventable contributor to global non-communicable disease burden. Effective reduction of this burden requires coordinated action across agricultural policy, regulatory governance, occupational health systems, and environmental management frameworks.

Integrated pest management (IPM) represents the most comprehensively evaluated approach to reducing agricultural pesticide use while maintaining crop protection efficacy. The strategy combine biological pest control, targeted pesticide application timed to pest monitoring data, and cultivation of pesticide-resistant crop varieties, and have been shown in multiple agricultural settings to substantially reduce pesticide application volumes (Sharma *et al.,* 2019; Tudi *et al.,* 2021). Wider adoption of IPM is constrained by economic barriers, knowledge gaps, and agricultural extension service capacity, particularly in low-income countries.

Regulatory interventions including phase-out of the most hazardous pesticide formulations, enforceable maximum residue limits in food and water, mandatory pre-market toxicity testing for endocrine disruption and developmental neurotoxicity, and international harmonization of risk assessment standards are necessary to reduce exposure at the population level (Sarkar *et al.,* 2021; Parrón*et al.,* 2022). The ongoing use of pesticide classes that have been banned or severely restricted in high-income countries in low- and middle-income agricultural settings represents a critical regulatory inequity requiring international attention.

Occupational safety interventions should prioritize farmer education and training, availability and appropriate use of personal protective equipment, safe pesticide storage and disposal infrastructure, pre-placement and periodic biological monitoring, and access to primary healthcare for early identification of pesticide-related health effects (Damalas &Koutroubas, 2016; Khan & Damalas, 2022). Mobile health and community health worker platforms offer scalable approaches for delivering occupational health education and surveillance in agricultural communities with limited healthcare infrastructure.

Biomonitoring programs at the population level, inspired by the environmental chemicals component in the National Health and Nutrition Examination Survey (NHANES) in the US (Centers for Disease Control and Prevention [CDC], 2023), can yield valuable information for exposure trend analysis, regulatory evaluation, and identification of high exposure populations. Development of similar programs in lower- and middle-income nations where pesticides are used in agriculture is a public health need (Mostafalou & Abdollahi, 2017).

Critical Appraisal and Methodological Limitations

A frank assessment of the methodological strengths and limitations of the pesticide-health literature is necessary for interpreting the associations described in this review and for calibrating appropriate confidence in causal conclusions.

Exposure Assessment Limitations

A fundamental challenge across the pesticide epidemiology literature is the inadequacy of exposure assessment. Most epidemiological studies rely on self-reported occupational histories or job-exposure matrices, both of which are subject to substantial misclassification. Urinary pesticide metabolite

measurements capture recent exposure but not cumulative lifetime biologically effective dose. Few studies have combined multiple exposure metrics, and the temporal relationship between specific exposures and health outcomes is rarely well-characterized (Bonner *et al.,* 2010; Kim *et al.,* 2021). This exposure misclassification would generally be expected to attenuate observed associations toward the null, suggesting that true effect sizes may be underestimated in the literature.

Mixture Complexity and Causal Attribution

Agricultural workers are typically exposed to multiple pesticide compounds simultaneously and sequentially throughout their careers, making it methodologically challenging to attribute health effects to individual compounds and to distinguish additive from synergistic or antagonistic mixture effects (Rani *et al.,* 2021; Mostafalou *et al.,* 2022). Regulatory toxicology has traditionally assessed compounds individually, but this approach may substantially underestimate risks from combined exposures. Mixture toxicology is an active area of research, but validated methods for predicting human health risks from real-world pesticide mixtures remain limited.

The Healthy Worker Effect

Occupational pesticide research is susceptible to healthy worker bias, whereby employed agricultural workers are selected for relatively good health and thus represent a survivor cohort in which disease prevalence may be lower than in the general population from which they are drawn. This phenomenon may lead to systematic underestimation of pesticide-attributable disease risk in occupational studies, and should be considered when interpreting null or attenuated findings (Dhouib *et al.,* 2021).

Confounding and Reverse Causation

Socioeconomic status, dietary patterns, access to healthcare, physical activity, and co-exposure to other environmental agents (heavy metals, solvents, and occupational noise) are important confounders of pesticide-disease associations that are inconsistently controlled across studies. Reverse causation, a situation in which pre-existing health conditions influence both pesticide exposure patterns and health outcomes is an additional concern in cross-sectional study designs. The potential for publication bias to exaggerate apparent associations, through selective reporting of statistically significant results, has not been systematically evaluated in this literature and cannot be excluded.

Translational Limitations and Non-Monotonic Dose-Response

Many mechanistic insights into pesticide toxicity are derived from in vitro cell culture experiments or animal models using doses substantially higher than typical human exposures. Extrapolating these findings to predict human disease risks at real-world exposure levels requires caution. Particularly for endocrine-disrupting pesticides, evidence for non-monotonic dose-response relationships in which low doses may produce qualitatively different effects than high doses, challenges the conventional toxicological assumption that the dose makes the poison and may render traditional risk assessment methodologies inadequate for characterizing low-dose chronic risks (Parrón *et al.,* 2022).

Geographic Inequities in Research and Regulation

A substantial proportion of the primary epidemiological research on pesticide health effects originates from high-income countries with established research infrastructure and regulated pesticide environments, yet the highest pesticide exposure burdens are concentrated in low- and middle-income agricultural settings. The generalizability of findings from high-income country cohorts to these high-exposure populations is uncertain, and the relative paucity of rigorous epidemiological data from high-exposure settings in Africa, South Asia, and Latin America represents a critical evidence gap.

Future Research Directions

Despite substantial research investment, important knowledge gaps limit the precision with which pesticide-disease causal relationships can be characterized and public health responses calibrated. Several priority areas for future research can be identified.

Large-scale prospective cohort studies with objective exposure biomonitoring, long follow-up periods, and rigorous ascertainment of incident disease outcomes are needed to provide more definitive evidence on chronic low-dose pesticide exposure and specific disease risks. Existing cohort studies, such as the Agricultural Health Study and European agricultural cohorts, should be extended and their biomonitoring components expanded to include newer pesticide classes.

Development of validated biomarkers capable of reflecting cumulative lifetime pesticide exposure, and of early subclinical toxicity endpoints that precede frank disease, is a priority for advancing both epidemiology and clinical monitoring. Omics technologies, including metabolomics, epigenomics,

and transcriptomics, show particular promise for this application, but require methodological standardization and population-representative reference databases (Richardson *et al.,* 2019; Carles *et al.,* 2021).

Research on pesticide mixture toxicity, employing both experimental and epidemiological approaches, is urgently needed to provide a scientific basis for regulating combined exposures. Precision toxicology approaches that account for genetic variation in pesticide-metabolizing enzymes, immune responsiveness, and DNA repair capacity may help identify biologically defined high-risk subpopulations who warrant targeted surveillance and protective interventions (Zhang *et al.,* 2023; Dhouib*et al.,* 2021). Transgenerational and epigenetic effects of pesticide exposure represent an emerging area of research with potential implications for understanding multigenerational disease burden. Investigation of whether pesticide-induced epigenetic modifications are heritable and contribute to disease risk in unexposed offspring generations is at an early stage but could substantially expand understanding of the true population health burden of pesticide exposure (Mostafalou *et al.,* 2022).

Furthermore, investment in research on the effectiveness of specific regulatory, occupational, and agricultural interventions for reducing pesticide-attributable health outcomes particularly in low- and middle-income country settings is necessary to inform evidence-based policy decisions and resource allocation.

CONCLUSION

From the literature reviewed above, there is overwhelming evidence to support the assertion that chronic exposure to pesticides significantly impacts the global burden of disease in non-communicable diseases through common mechanisms such as oxidative stress, mitochondrial dysfunction, endocrine disruption, neuroinflammation, genotoxicity, and epigenetic regulation among others. The impact of pesticides on the burden of disease is felt most by agricultural workers in developing countries, women of childbearing age, and their infants and young children who experience high levels of exposure without adequate regulations. Current approaches in estimating risk of chronic low-level exposure, mixture effects, and non-monotonic endocrine disruptions fall short while major limitations such as exposure assessment, controlling for confounding factors, and translation make causative attribution for some compound-disease associations difficult. As we move forward, the key research priorities are prospective biomonitoring, cumulative exposure biomarker development, omics surveillance, and transgenerational effects, while public health action through improved regulatory governance, implementation of integrated pest management practices, and investment in occupational health are critical.

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

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