



Review article

Overview of pesticides and their mechanisms of nervous system toxicity: A comprehensive review

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Abstract

Pesticides are chemical or biological agents engineered to prevent, control, attract or eliminate pests. They differ widely in their physical, chemical and toxicological characteristics and these differences form the basis for their classification into distinct categories. Pesticides are used extensively in different fields such as agriculture, forestry, aquaculture and the food industry. However, their increasing use over the years has raised serious concerns about environmental and public health risks. Improper or excessive application of pesticides can lead to severe ecological damage and adverse effects on living organisms. Even low-level exposure has been linked to several neurological disorders. This review explored the effects of pesticide exposure for long and repeated periods on the onset and progression of various neurodegenerative and neurodevelopmental diseases, including Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, cognitive and behavioral impairments and autism spectrum disorder. In addition, the importance was underscored of responsible pesticide management and the adoption of integrated pest management practices to minimize exposure risks. By providing an in-depth overview of pesticide classifications, mechanisms of action and their health and environmental consequences, this review seeks to encourage safer and more sustainable approaches to pest control and agricultural productivity.

Introduction

Human activities have altered extensively the global

ecosystem, disrupted natural cycles and reduced biodiversity, making them all increasingly unsustainable (Barnett et al., 2008). Often, intensive land use for agriculture and livestock production lead to desertification and soil erosion.

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Furthermore, the expansion of industrialization, urbanization and motorized transportation has resulted in substantial emissions that contaminate the air, water and soil. These anthropogenic actions exert major detrimental effects on the environment, which, in turn, have far-reaching social and economic consequences (Moreno and Urbina, 2008). Pollution, defined as the dissemination of harmful substances into or around the environment, poses a major potential harm to all living organisms (Garcia et al., 2012). One of the most widely used pollutants by humans is pesticides which are defined as chemical or biological components prepared and used to prevent, control, attract and eliminate pests. Pesticides have various chemical components, physical properties, structures and levels of toxicity (Kaur et al., 2019). Although applied primarily in agricultural practices to protect crops from weeds, pests and diseases, pesticides are also used in public health initiatives to safeguard humans from vector-borne diseases (Nicolopoulou-Stamati et al., 2016). Beyond agricultural applications, pesticides are applied in maintaining non-agricultural environments such as public parks, urban green spaces and sports fields (Dittemore et al., 2025). Unlike many other chemical substances, pesticides are intentionally released into the environment to target specific pest species. Consequently, they are inherently biologically active and exhibit varying levels of toxicity. Due to their toxicity, which is not in all cases limited to the target organisms, their use may endanger the ecosystem, non-target animals' survival and human health (Hu et al., 2015). The effects of pesticides on the nervous system have become a growing concern. For example, recent evidence indicates that both acute and chronic pesticide exposures can result in neurotoxicity manifested as cognitive impairments, memory and learning deficits, neuroinflammation and neurodegenerative changes. Several studies have reported that exposure to pesticides can disrupt mitochondrial function and redox balance, alter neurotransmitter signalling and increase the risk of neurodevelopmental and neurodegenerative disorders (van Melis et al., 2024; Wei et al., 2024).

Therefore, this review provides current scientific information about the chemical classifications, physicochemical properties and toxicological profiles of major pesticide groups, with emphasis on their potential role in neurological disorders. Chronic pesticide exposure can contribute to disease onset and progression through mechanisms such as oxidative stress, mitochondrial dysfunction, neuroinflammation and disrupted neurotransmission. The review also highlights the environmental and public health impacts of pesticide use and underscores the urgent need for sustainable management

strategies, including integrated pest management (IPM), to minimize exposure and safeguard neurological and ecological health.

Pesticide classification

Classification by origin

Pesticides may be classified based on their origin, comprising naturally derived compounds and those synthesized through chemical processes (Abubakar et al., 2020). Naturally derived pesticides originate from plants, minerals or microorganisms such as pyrethrins from chrysanthemum flowers, rotenone from certain legumes and microbial products like *Bacillus thuringiensis* (Manda et al., 2020). Typically, natural pesticides degrade more quickly into the environment and are often considered less harmful to non-target organisms, although they may pose risks (Yadav and Devi, 2017). In contrast, synthetic pesticides are manufactured chemically and may involve a wide range of compounds, including organophosphate, carbamate, pyrethroid and neonicotinoid (Lalah et al., 2022). This type of pesticides is designed to increase efficacy, persistence and a broad spectrum of action, but may have greater environmental and health impacts. Biopesticides act selectively on target pests and their associated organisms, while chemical pesticides generally exhibit a broad spectrum of efficacy, affecting a wide range of non-target species. Due to their lower toxicity, rapid degradation and effectiveness in smaller quantities, biopesticides are considered more environmentally sustainable than traditional chemical pesticides, with the latter often persisting in the environment, leading to environmental pollution and being a major adverse factor impacting ecosystems (Hassaan and El Nemr, 2020). Furthermore, biopesticides are less likely to induce resistance in pest populations due to limited genetic adaptability, whereas chemical pesticides frequently encounter resistance development. Collectively, these characteristics underscore the potential of biopesticides as safer and more sustainable components within integrated pest management strategies (Umina et al., 2023).

Classification by chemical structure

The chemical composition of a pesticide represents a fundamental criterion for its classification, as it determines the compound's molecular structure, physicochemical behavior

and biological activity. This composition serves as a major contributing factor in defining the mechanism of action, environmental persistence, toxicity level and degradation pathways of each substance (Hassaan and El Nemr, 2020). According to their structural composition, pesticides are broadly divided into four main categories: organochlorines organophosphorus compounds, carbamates and pyrethroid/pyrethrin, as shown in Fig. 1 (Mdeni et al., 2022). Each of these groups includes distinct chemical bonds, stability profiles and modes of action that influence their toxicological and environmental properties (Abubakar et al., 2020). This chemical-based classification system is one of the most widely adopted frameworks in toxicology and environmental science, as it provides a comprehensive understanding of how structural attributes influence the pesticide's mode of action, persistence, toxicity and environmental fate (Hassaan and El Nemr, 2020).

Organochlorine pesticides

Organochlorine pesticides (OCPs) are organic substances containing at least five chlorine atoms (Yadav and Devi, 2017). These substances are chemically stable and highly persistent in the environment, with a strong tendency to accumulate in adipose tissue. This class of pesticides constitutes one of the earliest groups synthesized and utilized in both agricultural and public health applications. They have been used widely to control a broad range of insect species and are distinguished by their long-lasting residual activity and environmental persistence (Richmond, 2022). The accumulation of organochlorine compounds is largely attributed to their unique physical and chemical properties, including low water solubility, high lipid solubility and non-polar molecular structure (Bernardes et al., 2015). These attributes enable them to remain stable under various environmental conditions and resist metabolic breakdown. Among the most commonly used OCPs are dichlorodiphenyltrichloroethane (DDT), lindane, endosulfan, aldrin, dieldrin and chlordane (Ahamad et al., 2023).

Organophosphate pesticides

Organophosphate pesticides (OPs) are synthetic esters that are derived from phosphoric acid and are one of the broad-spectrum pesticides that control a wide range of pests because of their various modes of action (Fest and Schmidt, 2012). They are identified according to their action as, contact, stomach and fumigant poison compounds, which ultimately lead to neurotoxic disorder. Unlike other pesticides,

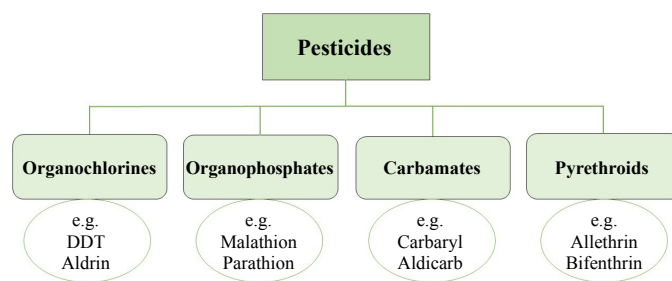


Fig. 1 Types of pesticides classified according to their chemical structures. DDT = dichlorodiphenyltrichloroethane.

which persist in the environment for long periods, organophosphates are chemically less stable and more biodegradable, allowing them to decompose more rapidly under environmental conditions such as light, temperature and microbial activity. This biodegradability contributes to reduced environmental persistence and contamination, as well as a lower potential for long-term bioaccumulation and pest resistance (Kaur et al., 2019). Commonly used organophosphorus pesticides include parathion, malathion, diazinon and glyphosate which have been applied extensively in agriculture for crop protection and vector control programs (Richmond, 2022).

Carbamate pesticides

Structurally, carbamate pesticides share notable similarities with organophosphates pesticides, particularly in their mechanism of action; however, they differ fundamentally in their chemical origin and structure. Carbamates are synthetic derivatives of carbamic acid (NH_2COOH) applied extensively in agricultural pest management, horticulture, forestry, public health and veterinary medicine (Ripley and Chau, 2020). The mode of action of carbamate pesticides closely parallels that of organophosphates, by disrupting neurotransmission (Jali, 2025). However, in contrast to organophosphates, which irreversibly phosphorylate the acetylcholinesterase (AChE) enzyme, carbamates bind non-covalently, allowing enzyme reactivation within hours after exposure and consequently reducing the duration and severity of toxicity (Lorke and Petroianu, 2019). Carbamate pesticides have lower persistence than organochlorine compounds due to their susceptibility to hydrolysis, photodegradation and microbial decomposition. They degrade relatively rapidly in soil and aquatic systems, minimizing long-term accumulation. Nonetheless, their high-water solubility increases the potential for leaching into groundwater, which poses risks to aquatic ecosystems and drinking water sources (Nath et al., 2023).

Pyrethroid pesticides

Pyrethroids pesticides are a class of synthetic insecticides structurally derived from natural pyrethrins, which are organic compounds extracted from the flowers of *Chrysanthemum* species. These synthetic analogs were developed to enhance the stability, potency and residual activity of natural pyrethrins, which degrade rapidly upon exposure to light, air and temperature (Sun et al., 2020). Globally, pyrethroids have become one of the most widely used groups of insecticides, due to their high insecticidal efficacy, low application rates and relatively favorable safety profile compared to older pesticide classes. They are used extensively in agriculture, public health vector control, household insecticide formulations and veterinary medicine for the management of ectoparasites such as ticks, fleas and lice (Anadón et al., 2025).

The primary mode of action of pyrethroids involves interference with the nervous system of target organisms. They act specifically on voltage-gated sodium channels located in neuronal cell membranes, where they delay the closure of sodium channels, resulting in prolonged sodium influx into nerve cells (Soderlund, 2012). Commonly utilized pyrethroid compounds include allethrin, bifenthrin, tefluthrin, deltamethrin, cypermethrin and bioresmethrin (Ahmad and Kumar, 2023).

Classification by toxicity

The toxicity of pesticides is a critical parameter that defines their potential hazard to humans and animals, as well as the environment. The level of toxicity is influenced chiefly by two interrelated factors: dose (the quantity of the chemical absorbed by an organism) and exposure duration or frequency (how often the organism is exposed to the chemical) (Ansari et al., 2021). The severity of risk associated with pesticide exposure is determined by multiple variables, including the intrinsic toxicity of the compound, the route of exposure (inhalation, ingestion or dermal absorption) and the duration and frequency of contact (Costa et al., 2008). Highly toxic pesticides may induce severe or fatal outcomes even at low

concentrations, whereas less toxic compounds can still exert adverse effects following continuous or cumulative exposure (Mostafalou and Abdollahi, 2017). These factors give rise to two distinct types of toxicity: acute and chronic (Manimekalai et al., 2022).

Acute toxicity

Acute toxicity refers to the adverse effects that occur shortly after a single or brief exposure to a pesticide. This toxicity represents the immediate hazard posed by a chemical and is of particular importance for occupational safety and accidental exposures (Tugcu et al., 2023). Acute toxicity can be measured experimentally using standardized biological tests to determine acute lethal dose (LD_{50}) values for oral, dermal and inhalation exposures, which indicate the dose sufficient to cause death in 50% of a test sample (Mostert et al., 2021). Pesticides with low LD_{50} values are considered highly toxic, as even trace amounts can cause serious physiological disturbances, including neurotoxicity, hepatotoxicity or systemic failure.

The World Health Organization (WHO) emphasizes acute toxicity as the primary basis for pesticide classification. According to the WHO, pesticides are categorized based on their acute oral and dermal toxicity, using the estimated lethal dose (LD_{50}) values. The classification system ranks pesticides from extremely toxic to slightly toxic, corresponding to categories I through IV, respectively, representing a scale from the highest to the lowest level of toxicity (Table 1).

Chronic toxicity

Chronic toxicity refers to the delayed or cumulative adverse effects of pesticides that occur as a result of prolonged or repeated exposure. Chronic exposure can lead to sub-lethal physiological and biochemical alterations such as carcinogenesis, mutagenesis, endocrine disruption, immunotoxicity, neurodegeneration or reproductive toxicity (Shanmugam et al., 2023). Chronic toxicity is a concern not only for agricultural workers but also for the general human population due to residual pesticide contamination in food, water and air. Often, these effects are

Table 1 World Health Organization (WHO) classifications of pesticides according to toxicity (World Health Organization, 2009).

WHO class	Toxicity level	LD_{50} for rat (mg/kg body weight)	
		Oral	Dermal
Class Ia	Extremely hazardous	<5	<50
Class Ib	Highly hazardous	5–50	50–200
Class II	Moderately hazardous	50–2,000	200–2,000
Class III	Slightly hazardous	>2,000	>2,000
Class IV	Unlikely to present acute hazard in normal use	≥5,000	

evaluated through long-term animal studies and epidemiological investigations in humans (Akashe et al., 2018).

Environmental fate and pollution of pesticides

Pesticide behavior in the environment

When pesticides are used by farmers or those working to control agricultural and environmental pests in specific areas, they not only remain confined to the target site, but are also transported throughout the environment, via water, air currents or by animal or insect vectors (Chitra et al., 2006). Once they enter the ecosystem, pesticides can affect non-target organisms, including plants, invertebrates and vertebrates, potentially disrupting ecological balance and biodiversity (Tudi et al., 2021). In the environment, pesticides undergo complex degradation pathways that occur through chemical and biological processes. The chemical processes involve oxidation-reduction reactions and hydrolysis. Biological degradation is primarily driven by microorganisms in soil and water that are capable of metabolizing pesticides into intermediate compounds or end products (Pantayak et al., 2026). The toxicity of these transformation products, known as metabolites, can vary greatly; some are harmless, while others may be more persistent or more toxic than the original compound, posing additional risks to the ecosystem. In addition, these pesticides can adsorb to soil particles, seep into groundwater, run off into rivers and lakes and volatilize into the atmosphere. Highly adsorbed pesticides tend to persist longer in the soil, potentially accumulating over time and causing long-term toxic effects on soil microbes, nutrient cycling and plant growth (Chen et al., 2012). In contrast, highly concentrated pesticides can contaminate water bodies and affect aquatic organisms and may enter the nutrient flow system (food chain), where they may accumulate and biomagnify, ultimately posing risks to wildlife and health of humans. In general, the behavior and fate of pesticides in ecosystems are determined by a complex interplay between chemical properties, environmental conditions and biological interactions, highlighting the importance of understanding these dynamics for sustainable pesticide management to protect the environment from these pollutants (Bhat et al., 2022).

Environmental pollution is one of the most serious global challenges, considered an anthropogenic disaster that poses a substantial threat to human health. Consequently, it is essential to evaluate carefully the benefit-risk balance when assessing the use of pollutants, particularly pesticides. Due to their

limited species specificity, pesticides developed to eliminate target pests often exert adverse effects on non-target organisms, including humans, animals and beneficial insects (Kaur et al., 2019). The excessive or improper application of pesticides considerably increases the potential for environmental contamination, adversely affecting soil quality, water systems and air composition (Queyrel et al., 2016).

According to the WHO, approximately 3 million cases of pesticide poisoning occur annually, leading to as many as 220,000 deaths, with the majority reported in developing nations (Kaur et al., 2019). There are currently about 500 distinct pesticide formulations in use globally, most of which are used in agricultural production systems. Concern over these chemical agents' detrimental effects on non-target creatures has grown as a result of their widespread and ongoing use (Özkara et al., 2016).

Effects on soil ecosystems

The physical and chemical features of pesticides, such as their molecular weight, ionizability, lipophilicity, polarity and volatility, play fundamental roles in determining their behavior and biological activity in soil (Beulke et al., 2004). The persistence of pesticides in soil ecosystems is affected by abiotic processes, which are controlled by physical and chemical properties and by biotic transformations mediated by soil microorganisms and other organisms (Pathak et al., 2022). Collectively, these properties determine pesticide mobility, degradation rate and resilience under varying environmental conditions, ultimately affecting their ecological impact and efficacy (Pereira et al., 2016). Pesticide degradation products may interact actively with a variety of soil matrix constituents, including native microbial communities. Such interactions may result in major changes in the variety and makeup of the soil microbiota, as well as in the biochemical pathways and enzymatic activities that are critical for soil fertility and nutrient cycling. By affecting microbial metabolism, enzyme-mediated transformations and the general functional stability of the soil ecosystem, the presence of these degraded leftovers might upset the ecological balance of the soil environment (Munoz-Leoz et al., 2011). Sometimes, after using a pesticide in a specific area, it is transported by air currents to distant or nearby areas and then settles on the soil. As a result, the soils become interpretive sources of pollutants due to air-soil exchange (Pathak et al., 2022).

Effects on aquatic systems

Pesticide residues that drift into water bodies pose a serious threat to the aquatic environment, presenting a severe risk to aquatic organisms and potentially contaminating human health.

These chemicals can reach water bodies through several pathways, including surface runoff, leaching from treated soils, accidental spills, industrial discharge, cleaning of spraying equipment and atmospheric drift during application (Singh and Mandal, 2013; Gill and Garg, 2014). Persistent organic pesticides and current-use pesticides can also enter aquatic systems through atmospheric deposition and the release of untreated industrial or agricultural wastewater (Socorro et al., 2016). Once in aquatic environments, pesticides can disperse over long distances, leading to widespread contamination and ecological disruption. Within aquatic environments, pesticides tend to accumulate and biomagnify along food chains, moving from low level to higher trophic levels (Thanomsit et al., 2025). This not only directly affects aquatic plants and animals but also leads to harmful effects on human health via the consumption of contaminated water and aquatic organisms (Woodrow et al., 2018).

Furthermore, plants can absorb pesticides present in the soil, convert them into other chemical compounds and then filter them through into the groundwater. Heavy rainfall increases the likelihood of pesticide leaching, increasing the risk of groundwater contamination. Once pesticides reach groundwater, they impair its quality, making it dangerous for humans to consume and harmful to plants and animals (Hassan and Al-Nimr, 2020). Removing pesticides from groundwater is technically difficult and expensive, making pollution prevention a major concern (Hassan and Al-Nimr, 2020).

Effects on air quality

The existence of pesticides in the air is influenced by

various factors, including spray drift, volatilization from pesticide-treated surfaces and the extent of pesticide drift, which is primarily determined by droplet size and wind speed (Yadav and Devi, 2017). Spray drift occurs when pesticide droplets are carried away from the target area during or shortly after application. Smaller droplets remain suspended in the air for extended periods and can travel considerable distances, while larger droplets settle quickly and are less likely to disperse. Strong air currents further increase the likelihood of drift, leading to unintended deposition and environmental contamination far from the application site (Zaller, 2020).

After application, pesticides that remain on soil, crops or other surfaces can evaporate gradually into the atmosphere. This transfer of pesticides from treated surfaces to the air is called volatilization and represents a major pathway through which these chemicals contribute to atmospheric pollution (Boonupara et al., 2023). Specifically, volatilization refers to the phase transition of pesticides from a liquid or solid state into a gaseous form, enabling their transport into upper atmospheric layers, where they may participate in long-range dispersion and secondary contamination (Kubiak et al., 2008). Spraying drift and the volatilization processes that follow are the main sources of pesticide-related air pollution (Gil and Sinfort, 2005), as shown in Fig. 2.

Routes of pesticide exposure

Humans can be exposed to pesticides through both direct and indirect pathways (Shekhar et al., 2024). Direct exposure occurs

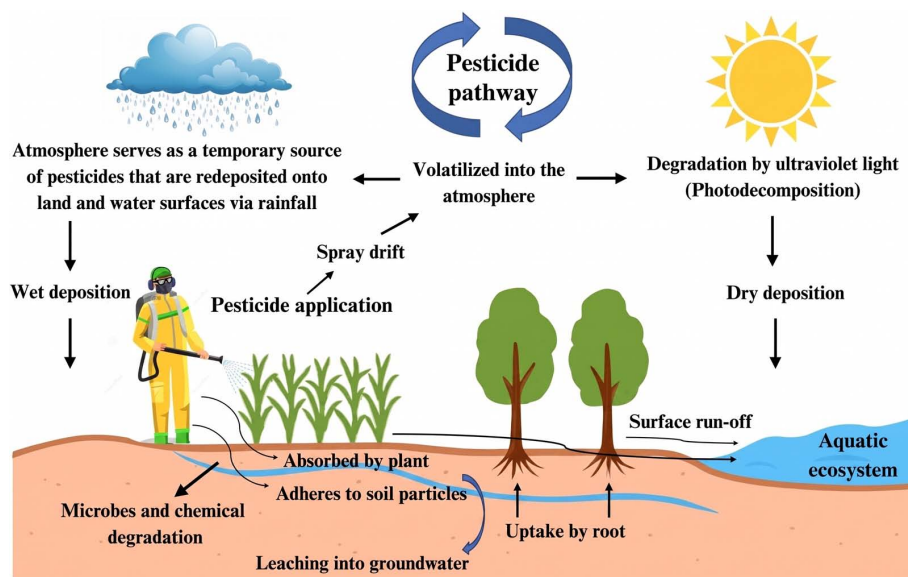


Fig. 2 Transport pathways of pesticides in environment

during occupational, agricultural or household activities, where pesticides are applied using various methods, such as spraying, dusting or seed treatment. On the other hand, indirect exposure arises from contact with contaminated environmental factors, including air, water, soil and food, which may carry pesticide residues even in areas far from application sites (Shekhar et al., 2024). The type, duration and route of exposure greatly influence the toxicity and health risks associated with pesticide use (Yan et al., 2021). The primary routes through which pesticides enter the human body include dermal absorption (through the skin) oral ingestion (through contaminated food or water) and inhalation (through respiratory uptake of airborne pesticides), as illustrated in Fig. 3 (Tudi et al., 2021). The physical state of the pesticide, whether solid, liquid or gaseous, also plays a critical role in determining its ability to penetrate biological barriers and reach target organs (Berthet et al., 2014). Furthermore, the physical and chemical properties of each pesticide, such as solubility, volatility and molecular size, as well as environmental factors, such as temperature, humidity and weather conditions, can greatly alter exposure levels. Human behavior and safety measures, including personal hygiene practices, such as washing hands and the proper use of personal protective equipment, strongly influence the degree of exposure and subsequent risks (Ye et al., 2013). Overall, pesticide exposure is a multifaceted process influenced by chemical, environmental and human-related factors, all of which collectively determine the potential for toxicity.

Dermal exposure

Dermal exposure represents one of the most important

pathways by which farmers are exposed to pesticides, resulting from splashing, spillage or pesticide spray drift, especially during the application of pesticides in agriculture or in household activities (Damalas and Koutroubas, 2016). Three main mechanisms (emission, deposition, transfer) are responsible for the movement of the pesticide mass from its source to the skin's surface, according to conceptual models of dermal exposure put forward in the literature. The dynamic processes by which pesticides are discharged into the environment, land on surfaces and then come into direct or indirect contact with human skin, potentially resulting in absorption and systemic exposure, are all described by these mechanisms taken together (Udin et al., 2019). The degree of harm from dermal absorption depends on the pesticide's toxicity to the skin, the duration of exposure, the pesticide formulation and the body region contaminated (Baldi et al., 2006). Powder, dust and granular pesticide formulations are generally absorbed less readily via the skin and other body tissues compared to liquid formulations. In contrast, liquid pesticides, particularly those containing organic solvents or oil-based carriers, are absorbed more rapidly than dry formulations, which increases the risk of systemic exposure (Damalas and Koutroubas, 2016).

Oral exposure

Oral exposure represents the most prevalent pathway of pesticide poisoning and poses substantial risks to human health. Individuals involved in the production or application of pesticides may experience oral exposure when proper

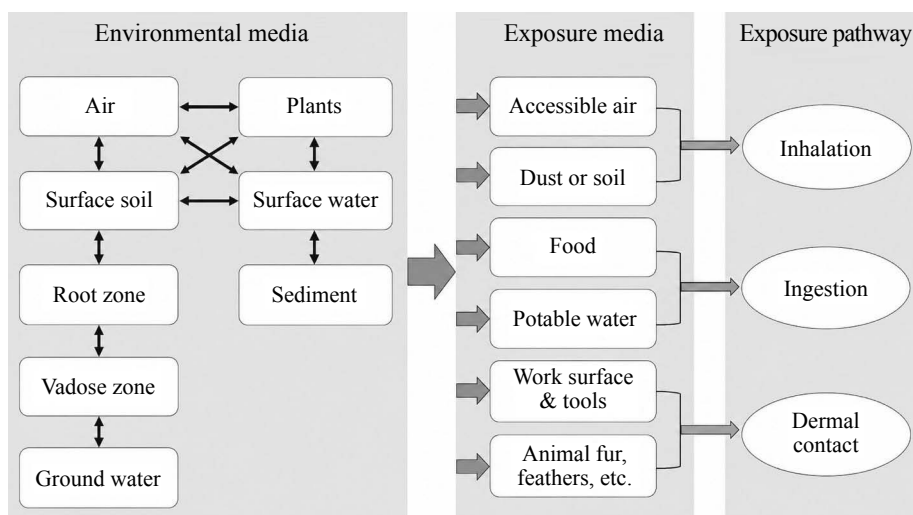


Fig. 3 Source and exposure routes of pesticides

hygiene practices are not observed such as handwashing before eating, drinking or smoking. Furthermore, the general population may be exposed through the ingestion of food or water contaminated with pesticide residues (Tudi et al., 2022). Primarily, substances are absorbed through the small intestine, which is the primary site due to its large surface area, rich blood supply and efficient transport mechanisms. Following absorption, these substances enter the bloodstream, allowing for systemic distribution to various organs and tissues (Damalas and Koutroubas, 2016).

Inhalation exposure

Respiratory exposure to pesticides, occurring through the inhalation of contaminated air, can have a major impact on workers' health, particularly when airborne concentrations of volatile pesticide compounds are high (Chen et al., 2022). It is estimated that respiratory absorption accounts for around 10% of total pesticide exposure in agricultural work situations, with inhaling airborne pesticide droplets, vapors or dust particles produced during application, formulation handling or post-spray drift is usually the cause of this exposure (Dowling and Seiber, 2002). When non-volatile pesticides are sprayed in an inhalable form, respiratory inhalation also takes place (Ye et al., 2013). Furthermore, exposure may occur in environments subjected to disinfection or contamination, such as poorly ventilated enclosed spaces or dust-laden areas, where aerosols or particulates carrying pesticide residues are present (Tarmure et al., 2020).

Toxicological impact of pesticides on humans

General toxicological effects

Human exposure to pesticides occurs through direct and indirect routes. Typically, direct exposure arises during the handling or application of pesticides in agricultural activities, where contact may occur through the skin, eyes, mouth or respiratory tract. Such exposure can cause acute health effects, such as headaches, eye and skin irritation, vomiting, sneezing and dermatological reactions, with the severity depending on the duration and concentration of exposure. Generally, once pesticides enter the body, they are metabolized and excreted via urinary, biliary and glandular secretions (Kalyabina et al., 2021). Primary indirect exposure arises during the consumption of food and water that have been

contaminated with pesticide residues. Vegetables, fruits and other agricultural products grown in pesticide-contaminated soil or irrigated with polluted water represent a major source of chronic exposure to humans. While some pesticides may cause immediate toxic effects, many accumulate gradually in environmental media and, subsequently, in human tissues over time. This bioaccumulation can lead to a spectrum of chronic health disorders, including neurotoxicity, carcinogenesis, tissue necrosis, respiratory conditions such as asthma, reproductive and developmental disorders, cardiovascular disease and metabolic disturbances such as diabetes (Calvert et al., 2008; Evaristo et al., 2022). The cumulative and multifaceted nature of pesticide exposure underscores the importance of monitoring both acute and long-term health risks, as well as implementing strategies to reduce environmental contamination and human exposure to these toxic compounds.

Neurotoxicity

This refers to any harmful effect of chemical, biological or physical agents on the central or peripheral nervous system (Soleimani et al., 2016). One study showed that a variety of compounds, such as heavy metals, industrial chemicals, solvents, natural toxins, pharmacological agents, drugs of abuse and pesticides, have the potential to be neurotoxic (Iqbal et al., 2020). Among various organic environmental toxicants, pesticides represent a major class known to impair neuronal function. This broad and diverse group includes insecticides, herbicides and fungicides. Increasing evidence suggests that exposure to pesticides is a substantial environmental risk factor for the development of neurological and neurodegenerative diseases (van Melis et al., 2024).

The nervous system is particularly vulnerable to toxic damage due to several intrinsic characteristics, including its high dependence on aerobic metabolism, the presence of axonal transport mechanisms and the complexity of neurotransmission processes (Meyer-Baron et al., 2012). Neurotoxic substances can induce neuronal death (neuropathy) through necrotic or apoptotic pathways, leading to irreversible neuronal loss. When specific neuronal populations are affected, this damage can result in the loss of particular neurological functions or generalized brain dysfunction (encephalopathy), with the clinical manifestations of pesticide-induced neurotoxicity varying in severity and duration (Costa et al., 2008). Acute symptoms may include headache, nausea, dizziness, sensory paresthesia, tremors, incoordination and dystonia. In severe cases, neuronal hyperexcitability can lead to generalized

tonic-clonic seizures or myoclonic jerks. On the other hand, chronic exposure may cause persistent muscle weakness often associated with spasticity, as well as cognitive impairments such as confusion or loss of consciousness (Keifer and Firestone, 2007).

Mechanisms of pesticide-induced neurotoxicity

Oxidative stress, mitochondrial dysfunction and DNA damage

Pesticides have been implicated in various neuropathological sequences due to their ability to impair normal neuronal function and induce structural and molecular damage in the nervous system (van Melis et al., 2024). Including oxidative stress, mitochondrial dysfunction and genotoxic damage, can disrupt the normal function of the nervous system, leading to neurological disorders or impairments. Frequent exposure to pesticides can lead to excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), this excessive generation of reactive species overwhelms the endogenous antioxidant defense system, resulting in oxidative stress and disruption of neuronal redox homeostasis. (Suli et al., 2022). This oxidative imbalance leads to lipid peroxidation, protein oxidation and nucleic acid modification, ultimately compromising neuronal membrane integrity and synaptic signaling (Rodríguez et al., 2025). One study demonstrated that occupational exposure to pesticides was associated with increased oxidative stress and DNA damage in agricultural workers. In the controlled study, workers exposed to various pesticides exhibited elevated levels of oxidative stress biomarkers. These findings highlight the importance of monitoring oxidative stress markers as early indicators of pesticide-induced molecular and cellular dysfunction, providing insight into potential mechanisms underlying long-term health effects (Ledda et al., 2021).

Mitochondria, which serve as the primary site of oxygen consumption and adenosine triphosphate (ATP) generation, are especially vulnerable targets of pesticide toxicity. Pesticide-induced mitochondrial dysfunction interferes with electron transport chain activity, promotes uncoupled oxidative phosphorylation and increases electron leakage that further enhances ROS production (Ghasemi et al., 2015; Rodríguez et al., 2025). These disturbances impair ATP synthesis and energy availability, leading to neuronal energy failure and activation of apoptotic pathways (Güven et al., 2018). The accumulation of free radicals also damages mitochondrial DNA and alters the redox status of mitochondrial enzymes, aggravating oxidative stress and perpetuating a self-reinforcing

cycle of mitochondrial injury (Taha et al., 2021). The study by Palanisamy et al. (2022) confirmed the effect of the pesticide-exposed primary rodent enteric glial cells to neurotoxic pesticides (rotenone and tebufenpyrad) and assessed mitochondrial function via ATP production, basal respiration and mitochondrial superoxide levels. Auto lysosomal activity was measured using lysosomal and autophagy assays. Co-culture with enteric neurons evaluated the impact on neuronal viability, oxidative stress and inflammation, linking pesticide-induced mitochondrial impairment in glial cells to enteric neuronal degeneration.

In parallel, numerous pesticides exhibit genotoxic properties through both direct and indirect mechanisms. The pesticides can interact directly with DNA, causing strand breaks and base-pair alterations or induce genotoxicity indirectly through oxidative stress mediated DNA oxidation (Lundqvist et al., 2016). These genotoxic effects may result in mutations, chromosomal aberrations and defective DNA repair responses in neural stem and progenitor cells, disrupting normal neurogenesis and cell cycle regulation (Wijesekara et al., 2025). Together, persistent DNA damage and mitochondrial dysfunction compromise neuronal survival, leading to apoptosis or degeneration of vulnerable neuronal populations (Usman et al., 2021). This disorder was supported by Ojha et al. (2013), who investigated both acute and chronic exposure to the organophosphate pesticides chlorpyrifos, methyl parathion and malathion and reported significantly elevated DNA damage in multiple rat tissues, including the liver, brain, kidney and spleen, when measured 24 hours after treatment, with the brain having the greatest level of damage among tissues. Additionally, DNA damage showed some partial repair at 48 and 72 hours post-treatment. Based on these results, exposure to these OP pesticides induces genotoxic effects *in vivo*, affecting vital organs, including the nervous system. Overall, these mechanistic insights demonstrate that pesticide exposure initiates a complex network of oxidative, mitochondrial and genomic disturbances that converge to impair neuronal integrity and function.

Epigenetic dysregulation

In addition to direct changes in DNA sequences, pesticides can affect and dysregulate the gene expression through epigenetic mechanisms, which regulate gene activity without altering or changing the underlying genetic code (Bordoni et al., 2019). One of the most important epigenetic modifications is DNA methylation, a process in which methyl groups are added to cytosine residues in DNA, often resulting in gene

silencing. Research findings have suggested that the exposure to different types of pesticides were associated with aberrant DNA methylation patterns, which can disrupt normal gene regulation (Alexander et al., 2017). Genes implicated in the etiology of Alzheimer's disease (AD) are of particular interest. For example, the gene encoding paraoxonase-1 (PON1), an enzyme involved in detoxification and protection against oxidative stress, has been shown to exhibit altered expression following pesticide exposure, potentially contributing to the pathogenesis of AD (Cervellati et al., 2019). In addition, pesticides can affect microRNA (miRNA) expression, which plays a critical role in post-transcriptional gene regulation. Some pesticides, such as paraquat, have been reported to modify specific miRNAs that target components of the Wnt signalling pathway, a key regulator of neuronal development, synaptic plasticity and neuroprotection (Palomer et al., 2019). Evidence for this impairment includes a study in which pregnant mice were exposed to the organochlorine pesticide dieldrin during fetal neurodevelopment. DNA from the offspring's midbrain was analyzed for gene-specific and genome-wide methylation using bisulfite sequencing. The results revealed persistent, sex-specific DNA methylation changes at genes essential for dopaminergic neuron development, indicating that early-life pesticide exposure establishes "poised" epigenetic states that enhance neuronal vulnerability and may contribute to the development of late-onset neurodegenerative disorders (Kochmanski et al., 2019). In the same manner, Song et al. (2010) demonstrated that exposure to the neurotoxic pesticide dieldrin induces a rapid increase in the acetylation of core histones H3 and H4 in dopaminergic neuronal cells. This effect is mediated by proteasomal dysfunction and the consequent accumulation of histone acetyltransferase (CBP), leading to activation of apoptotic pathways and neuronal cell death. The same study also reported that chronic (30-day) exposure to dieldrin in mouse models increased histone acetylation in dopaminergic brain regions, including the striatum and substantia nigra, indicating that epigenetic dysregulation also occurs in vivo (Song et al., 2010).

Tau phosphorylation dysregulation

Phosphorylation is the primary modification of physiological tau that modifies its connection with microtubules and probably additional mechanisms (Chang et al., 2018). According to Noble et al. (2013), tau is a phosphorylated protein with 85 possible phosphorylation sites, which are located at serine, threonine and tyrosine. Pathological situations cause tau to

become more phosphorylated, which decreases its affinity for microtubules and, as a result, destabilizes the cytoskeleton, especially in neurons (Guo et al., 2017). Other research has confirmed that 28 days of exposure to deltamethrin and carbofuran in rats impaired spatial learning and memory, accompanied by reduced synaptic protein expression and tau hyperphosphorylation in the hippocampus and cortex. Excessive tau phosphorylation is caused by the activation of glycogen synthase kinase-3 β and the suppression of protein phosphatase-2A. These findings suggest that pesticide-induced tau dysregulation drives synaptic dysfunction, neuronal loss and cognitive deficits, linking environmental pesticide exposure to neurodegenerative processes (Chen et al., 2012). Tau phosphorylation causes two-stranded and entangled neurofibrils to form in nerve cells (Ghasemi et al., 2015). These neurofibrils can cause microtubules to break down, cells to lose their structure and neurological functions to malfunction (Iqbal et al., 2005), with numerous tau mutations. Additionally, tau has been linked to dendritic and synaptic mitochondrial ATP reduction (Ghasemi et al., 2015).

Neurotoxic beta-amyloid accumulation

Studies have suggested that amyloid beta (A β) peptides, formed from the amyloid precursor protein (APP), play a pivotal role in the pathogenesis of neuronal diseases. APP is a membrane protein whose functions are still not fully understood in various cell types, including neurons (Li et al., 2013). Proteolytic processing of APP by beta- and gamma-secretases produces peptides ranging from 38 to 43 amino acids in length. These peptides are capable of forming soluble, flexible and polymorphic oligomers (Ghasemi et al., 2015). A recent experimental study examined the effects of chronic low-dose exposure to fungicide residues (cyprodinil, mepanipyrim, pyrimethanil) on β -amyloid (A β) pathology in a transgenic J20 mouse model of AD. Mice received these fungicides via drinking water at regulated concentrations (~ 0.1 μ g/L) over several months. Long-term exposure enhanced A β aggregation, increased β -secretase activity and promoted neuroinflammation, contributing to neuronal loss and vascular amyloid deposition. These results indicate that even low-level, chronic pesticide exposure can exacerbate amyloidogenic processes (Lafon et al., 2020).

According to Salazar et al. (2011), prolonged exposure to some organophosphate pesticides, such as chlorpyrifos, raised beta-amyloid levels in the brain. These toxins may be released into the blood after fast weight loss, despite the fact that they are continuously retained in adipose tissue (Ghasemi

et al., 2015). Long-term exposure to poisons such as DDT and dichlorodiphenyldichloroethylene (DDE) may raise AP levels, which are linked to the development of beta-amyloid plaques (Eid et al., 2022). Additionally, when Alzheimer's patients lose weight regularly, these chlorinated organophosphates are released into their blood, which speeds up the progression of the disease (Richardson et al., 2014).

Neuropathological consequences of pesticide exposure

Neurodegenerative diseases: Parkinson's disease

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that affects primarily middle-aged and elderly individuals (Ahmad et al., 2023). According to epidemiological estimates, there will be more than 10 million confirmed instances of PD worldwide by 2040, highlighting the disease's increasing importance for public health (Afsheen et al., 2024). A major reduction in dopamine in the striatal areas results from the specific degradation and death of dopaminergic neurons in the midbrain's substantia nigra pars compacta, which is the neuropathological hallmark of PD (Wang et al., 2020). The underlying pathogenesis involves the abnormal aggregation of misfolded α -synuclein proteins, forming Lewy bodies and Lewy neurites, which disrupt synaptic function and contribute to neuronal death (Ghosh et al., 2017). Clinically, PD is characterized by a constellation of motor symptoms including resting tremor, muscular rigidity, bradykinesia and postural instability alongside a range of non-motor manifestations, such as cognitive decline, psychosis, sensory abnormalities, autonomic dysfunction and sleep disturbances (Wang et al., 2020). Dopaminergic neurodegeneration is the result of a complex cascade that includes aberrant protein aggregation, oxidative stress, mitochondrial dysfunction, poor proteostasis and neuroinflammation. Pesticide exposure in the environment was reported by Chin-Chan et al. (2015) to be a substantial risk factor for sporadic PD, where developmental exposure to the organochlorine pesticide dieldrin induced persistent, sex-specific alterations in DNA methylation in the midbrain, particularly at genes involved in dopaminergic neuron development and maintenance. Mechanistically, these early-life epigenetic changes may create "poised" genomic states that alter gene expression patterns, making neurons more susceptible to subsequent environmental stressors or toxic insults. Such epigenetic dysregulation provides a potential link between pesticide exposure during neurodevelopment and increased risk of late-onset neurodegenerative disorders, including PD, by affecting the stability and function of dopaminergic neural

circuits (Kochmanski et al., 2019). Another study reported that Parkinson's disease patients had higher serum levels of the organochlorine pesticide β -hexachlorocyclohexane (β -HCH) than both healthy controls and AD patients. This finding suggests that β -HCH accumulation may contribute to dopaminergic neuron degeneration, highlighting organochlorine pesticides as potential environmental risk factors in the development of PD (Richardson et al., 2009).

Although pesticides, such as insecticides, fungicides and herbicides, are essential to agriculture because they reduce crop loss and manage vector-borne illnesses, their neurotoxic potential raises major issues for public health (Afsheen et al., 2024). Epidemiological and experimental evidence suggest that chronic or high-dose pesticide exposure can initiate or accelerate PD pathogenesis through direct neurotoxic effects and indirect cellular stress mechanisms. Overproduction of rROS is one of the main processes, which causes oxidative stress and consequent harm to proteins, lipids and nucleic acids (Kiani et al., 2022). In PD and other neurodegenerative diseases, ROS-mediated oxidative stress is acknowledged as a key pathogenic event (Li et al., 2013; Sule et al., 2022).

Additionally, pesticides can induce mitochondrial dysfunction, particularly through inhibition of complex I (NADH: ubiquinone oxidoreductase) of the electron transport chain. Complex I inhibition has been documented in muscle tissue, platelets and the brain of PD patients and pesticide-induced complex I deficits replicate key PD features, including selective loss of dopaminergic neurons, enhanced oxidative stress and α -synuclein accumulation (Liu et al., 2003). While a small fraction (~1%) of PD cases are attributed to monogenic mutations, the vast majority (~99%) are believed to result from complex gene-environment interactions, in which environmental toxicants, such as pesticides, interact with individual genetic susceptibilities to trigger disease onset (Costa et al., 2008). In addition to a variety of non-motor symptoms, such as anxiety, depression, constipation, urinary dysfunction, dementia and sleep disturbances, typically, patients with PD exhibit a progressive impairment in voluntary motor control, which manifests as tremors, muscle rigidity, bradykinesia and postural instability.

Neurodegenerative diseases: Alzheimer's disease

This is the most prevalent progressive neurodegenerative disorder and is characterized by irreversible loss of neurons and synaptic connections within the brain (Nussbaum and Ellis, 2003). The most prevalent type of AD is late-onset, which usually appears in people older than 60 years. It is characterized

by a gradual onset of dementia, memory loss and cognitive decline that eventually results in loss of independence and the ability to carry out daily living or work-related tasks (Ringman et al., 2015). The disease follows a gradual course, with progression encompassing language and speech impairments, disorientation, mood instability, diminished self-care capacity and behavioral disturbances (Burns and Iliffe 2009). A complex interaction between genetic predisposition, lifestyle choices and environmental variables contributes to the multi-faceted and yet poorly understood etiology of AD (Killin et al., 2016). Pesticide exposure is one of these environmental factors that has been identified as a substantial risk factor linked to the development and advancement of AD pathology (Hayden et al., 2010). Insecticides, herbicides and fungicides pesticides represent a broad class of organic toxicants that can interfere with neuronal homeostasis (Mostafalou and Abdollahi, 2018). Due to their lipophilic properties, many pesticides accumulate in adipose tissue and persist for extended periods within the body, undergoing slow metabolic degradation and bioaccumulation through the food chain. This persistence results in long-term, low-level exposure in humans, especially in populations residing in agricultural regions or consuming contaminated food. At high concentrations, pesticides can induce acute neurotoxicity through direct cytotoxic effects on neurons, disruption of neurotransmitter systems and induction of oxidative stress (Cassereau et al., 2017). However, in the context of late-onset sporadic AD, the more relevant exposure pattern is chronic, low-dose, long-term environmental or occupational contact, which may subtly disrupt neuronal function over decades.

Mechanistically, pesticides may accelerate AD onset or exacerbate disease progression by modulating its two central neuropathological processes: amyloid-beta ($A\beta$) deposition and tau protein hyperphosphorylation. Experimental studies have demonstrated that certain pesticides can influence both $A\beta$ and tau pathology. For example, the mitochondrial complex I inhibitor rotenone, a naturally derived pesticide, impairs mitochondrial electron transport chain activity, thereby elevating oxidative stress and triggering tau hyperphosphorylation, along with enhanced $A\beta$ aggregation, in cultured rat neurons (Chaves et al., 2010). Similarly, in rodent models, exposure to the carbamate pesticide carbofuran or the pyrethroid deltamethrin induced tau hyperphosphorylation through activation of GSK-3 β and inhibition of PP2A, a key tau-dephosphorylating enzyme. This was accompanied by neuronal loss in the hippocampus and cortex, indicating that these pesticides can trigger Alzheimer's-like pathological changes (Chen et al.,

2012). In a case-control study, Kiani et al. (2022) measured serum levels of organochlorine pesticides (α -HCH, β -HCH, γ -HCH, 2,4-DDT, 4,4-DDT, 2,4-DDE, 4,4-DDE) in 63 AD patients and 50 healthy controls. In addition, they assessed oxidative stress biomarkers to explore potential mechanisms linking pesticide exposure to neurodegeneration. They found that AD patients had significantly higher pesticide levels and altered oxidative stress markers than the controls. The authors concluded that pesticides may contribute to AD development, at least in part, by inducing oxidative stress, highlighting a potential environmental factor in AD pathogenesis. Another pyrethroid compound, cypermethrin, has been shown to induce a GSK-3 β -dependent increase in both $A\beta$ accumulation and phosphorylated tau (p-tau) levels in the rat brain (Maurya et al., 2016).

Collectively, these findings support the hypothesis that pesticides contribute to AD pathogenesis by simultaneously impairing mitochondrial bioenergetics, promoting oxidative stress and dysregulating the enzymatic pathways governing $A\beta$ metabolism and tau phosphorylation. Over time, such alterations may synergize with age-related neuronal vulnerabilities, ultimately precipitating the neurodegenerative cascade characteristic of AD.

Neurodegenerative diseases: Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is the most prevalent form of motor neuron disease, encompassing a group of disorders characterized by the gradual degeneration of lower motor neurons found in the brainstem and spinal cord, as well as in upper motor neurons found in the motor cortex. ALS is a relentlessly progressive neurodegenerative condition that leads to selective motor neuron loss, resulting in muscle weakness, atrophy, spasticity, dysarthria, dysphagia and ultimately respiratory failure (Feldman et al., 2022). Clinically, ALS often begins with a focal onset, most commonly manifesting as unilateral distal weakness in an upper limb and progresses predictably to involve other regions, eventually affecting bulbar muscles responsible for speech and swallowing. Both sporadic ALS, which constitutes approximately 90–95% of cases and familial ALS, accounting for 5–10% of cases, share similar neuropathological features, although their etiological underpinnings differ. The exact cause of ALS remains elusive; however, current evidence supports a multifactorial pathogenesis involving complex gene environment interactions (Feldman et al., 2022). Among the proposed environmental risk factors, pesticide exposure has developed as a major concern. Observational epidemiological studies have reported

a consistent association between occupational or residential exposure to pesticides and an increased risk of ALS (McKay et al., 2021). Multiple cohort and case-control studies, including those relying on self-reported pesticide exposure histories, have identified an elevated incidence of ALS in individuals with prolonged or high-intensity contact with agricultural chemicals (Andrew et al., 2017). In a population-based case-control study in northern Italy, Bonvicini et al. (2010) investigated the association between occupational pesticide exposure and ALS risk. Participants included ALS patients and matched controls and exposure assessment focused on individuals with at least 6 mth of work-related contact with pesticides. The study found that a higher proportion of ALS cases reported pesticide exposure compared with controls and statistical analysis indicated a significantly elevated ALS risk (relative risk ≈ 3.6) among exposed individuals. These findings suggest that occupational pesticide exposure is a potential environmental risk factor for ALS, highlighting the need for further research into specific pesticide classes and exposure mechanisms contributing to motor neuron degeneration.

Mechanistically, one proposed biological link between pesticides and ALS susceptibility involves paraoxonase 1 (PON1), a calcium-dependent esterase enzyme that hydrolyzes and detoxifies organophosphate (OP) compounds, a class of widely used insecticides. Individuals with higher PON1 activity have greater resistance to OP-induced neurotoxicity, as the enzyme facilitates the breakdown of toxic oxon metabolites before they can irreversibly inhibit acetylcholinesterase and induce oxidative neuronal damage. Conversely, reduced PON1 activity leads to impaired detoxification capacity, increasing vulnerability to OP neurotoxicity. Genetic studies (Furlong et al., 2006; Costa et al., 2013) have revealed that single-nucleotide polymorphisms (SNPs) in the PON1 gene can substantially alter the catalytic efficiency and substrate specificity of the enzyme. Certain polymorphic variants, particularly those affecting the coding regions or regulatory promoter sequences, have been linked to reduced PON1 serum activity and altered organophosphate metabolism. These variants have been associated with an increased risk of sporadic ALS, suggesting that impaired OP detoxification capacity may serve as a gene-environment susceptibility factor for disease initiation and progression (Morahan et al., 2007). This interaction between pesticide exposure and genetically determined PON1 functionality underscores the broader concept that ALS pathogenesis may result from the synergistic effects of environmental toxicants and host genetic vulnerabilities, ultimately leading to oxidative stress,

mitochondrial dysfunction, glutamate excitotoxicity and motor neuron degeneration.

Neurodevelopmental and cognitive disorders: Autism spectrum disorder

The complex neurodevelopmental illness known as autism spectrum disorder (ASD) is typified by limited and repetitive patterns of behavior, interests or hobbies, as well as ongoing difficulties with social communication and engagement. Individual differences in the intensity, onset and presentation of these symptoms demonstrate the disorder's extreme heterogeneity (Hodis et al., 2025). Even while ASD has become much more common in recent decades, nothing is known about the underlying causes of this increase (Fombonne, 2018). The substantial impact of non-genetic factors in the etiology of ASD is highlighted by some more recent research, which indicated that environmental determinants, particularly those related to prenatal, perinatal and early postnatal exposures, may contribute 60–65% of ASD cases, while genetic factors may account for 35–40% of cases (Pu et al., 2021). Exposure to environmental pollutants, especially pesticides, during critical stages of neurodevelopment may make people more vulnerable to neurodevelopmental problems, such as ASD, according to Yang et al. (2023). Clarifying the part that environmental contaminants play in the etiology and pathophysiology of ASD has become a greater focus of research (Dutheil et al., 2021). Epidemiological studies have shown consistently that maternal exposure to airborne pollutants, including pesticides, nitrogen oxides, fine particulate matter and organic solvents, was positively correlated with an offspring's higher risk of ASD (Rahman et al., 2022).

Certain classes of pesticides, such as organochlorines, are capable of crossing the placental barrier and disrupting neurodevelopmental pathways through endocrine modulation, immunotoxicity and neurotoxicity, affecting both the central and peripheral nervous systems (Wolff and Landrigan, 2002). Maternal exposure to pyrethroids, including bifenthrin, during critical gestational windows has been linked to a higher risk of ASD in children (Roberts et al., 2007). Likewise, low-dose postnatal exposure to organophosphorus pesticides can impair neural development, particularly during early infancy when the brain's detoxification systems are immature (Moradpour et al., 2023). In a population-based case control study (Román et al., 2024), ASD prevalence was evaluated across regions with varying levels of agricultural pesticide activity, using long-term environmental exposure data. The analysis demonstrated that areas with higher pesticide

application had a significantly increased prevalence of autism spectrum disorder, with the association being more pronounced among males. These findings support the hypothesis that chronic environmental exposure to pesticides may contribute to ASD risk, highlighting the potential role of pesticide-related neurodevelopmental toxicity during critical periods of brain development. Additional evidence comes from a Californian-based case control study conducted by von Ehrenstein et al. (2019) that examined the association between early-life pesticide exposure and the risk of ASD. The study involved 2,961 children diagnosed with ASD and matched controls at a 10:1 ratio. Prenatal exposure to organophosphate pesticides, assessed by residential proximity within 2,000 m of the maternal home during pregnancy, was found to be positively associated with ASD risk. Specifically, increased odds ratio (OR) values of ASD were observed with prenatal exposure to glyphosate (OR = 1.16; 95% confidence interval, CI: 1.06–1.27), chlorpyrifos (OR = 1.13; 95% CI: 1.05–1.23), diazinon (OR = 1.11; 95% CI: 1.01–1.21) and malathion (OR = 1.11; 95% CI: 1.01–1.22), supporting a link between gestational organophosphate exposure and ASD development.

In addition, experimental studies in animal models have elucidated the neurobehavioral consequences of pesticide exposure. Prenatal exposure to chlorpyrifos in rodents has been shown to alter social behavior and induce deficits resembling ASD-like phenotypes, including delayed motor development and persistence of immature movement patterns (Perez-Fernandez et al., 2022). Similarly, perinatal exposure to glyphosate has been associated with neurobiological changes and behavioral alterations akin to those observed in autism, implicating disruptions in neural circuits critical for social cognition and learning (Pu et al., 2020). Mechanistically, these pesticides are thought to induce oxidative stress and generate reactive oxygen species in brain regions central to behavior regulation, such as the prefrontal cortex and hippocampus, thereby altering synaptic plasticity and neurodevelopmental trajectories (de Oliveira et al., 2022). Epidemiological data have corroborated these findings. Regions characterized by intensive pesticide use report significantly higher ASD prevalence, particularly among males, suggesting a potential dose-dependent relationship between environmental pesticide exposure and ASD risk (Román et al., 2024).

Neurodevelopmental and cognitive disorders: Cognitive and behavioral disorders

Exposure to pesticides, most notably during important phases of neurodevelopment, such as gestation and early childhood, has been linked strongly to cognitive and behavioral

impairments (Honatel et al., 2024). These compounds exert neurotoxic effects through multiple pathways, including inhibition of AChE, disruption of endocrine signaling and induction of oxidative stress and neuroinflammation within developing neural tissues. Such perturbations can impair synaptogenesis, neuronal differentiation and circuit formation, ultimately compromising cognitive functions such as learning, memory and attention. Epidemiological studies in birth cohorts have reported that children exposed to OPs, including chlorpyrifos, during gestation exhibit delayed psychomotor development and reduced intelligence quotient, along with a higher chance of attention-deficit/hyperactivity disorder, some of which can last into puberty (Rauh et al., 2012; Shelton et al., 2014).

A recent experimental study by López-Merino et al. (2023) investigated the effects of perinatal exposure to multiple pesticides including organochlorines (dieldrin, endosulfan, chlordane) and the organophosphate chlorpyrifos-oxon on neurodevelopment in rodent models. Using behavioral assays and electrophysiological analyses, the study demonstrated that pesticide exposure led to persistent disruptions in synaptic signaling, including prolonged activation of the MAPK/ERK pathway and impaired metabotropic glutamate receptor-dependent long-term depression. These synaptic alterations were accompanied by behavioral deficits resembling neurodevelopmental disorders, such as delayed motor development, increased anxiety, impaired memory and reduced social interactions. The findings indicate that developmental pesticide exposure can disrupt synaptic plasticity and neuronal circuitry, contributing to long-term cognitive and behavioral dysfunction. The observational studies suggested that diverse types of pesticides, such as insecticides, herbicides and fungicides, could impair cognitive functions in both humans and non-target animal species through mechanisms involving synaptic dysfunction, mitochondrial impairment and altered neurotransmitter signaling (Honatel et al., 2024). Young children are particularly vulnerable due to their immature detoxification systems, higher relative intake of contaminated food and water and ongoing neurodevelopmental processes, which amplify susceptibility to neurotoxic insult. Chronic or repeated exposure further exacerbates these risks, contributing to deficits in memory, learning, attention and executive function, as well as heightened susceptibility to anxiety, depression and mood disorders. Specifically, pyrethroid exposure targets neuronal excitability by modulating voltage-gated sodium channels in axonal membranes, leading to prolonged depolarization, calcium dysregulation and apoptosis

of neuronal populations (Saillenfait et al., 2015). An animal study demonstrated that early-life exposure to pyrethroids reduced muscarinic cholinergic receptor density and altered dopaminergic neurotransmission, resulting in persistent behavioral abnormalities and cognitive impairments in adulthood (de Joode, 2016).

Conclusion

Exposure to pesticides represents a major environmental risk factor for a spectrum of neurodegenerative and neurodevelopmental disorders. In neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis, pesticides contribute to oxidative stress, mitochondrial dysfunction, protein misfolding and neuroinflammation, processes that collectively accelerate neuronal degeneration and loss of motor and cognitive function. Similarly, in neurodevelopmental and cognitive disorders, including cognitive and behavioral impairments and autism spectrum disorder, prenatal, perinatal and early postnatal exposure to pesticides has been associated with disruptions in synaptic development, altered neurotransmitter signaling and aberrant neural circuit formation, ultimately affecting learning, memory and social behavior. The mechanistic convergence of these effects, ranging from oxidative stress and epigenetic modifications to endocrine disruption, underscores the multifaceted impact of pesticides on the nervous system throughout the lifespan. These reports underscore the critical importance of minimizing environmental pesticide exposure and support the need for continued research into protective strategies, regulatory policies and therapeutic interventions aimed at mitigating the neurotoxic effects of pesticides.

Conflicts of Interest

The authors declare no conflicts of interest.

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