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INVITED REVIEW

Neurotoxic Effects of Pyrethroid Insecticides: Mechanisms, Health Risks, and Future Perspectives

Mohd Zaid Khan, Faiqua Haque*

ABSTRACT: Pyrethroid insecticides, synthetic derivatives of natural pyrethrins, are widely used in agriculture and public health due to their potent insecticidal properties and relatively low mammalian toxicity. However, emerging evidence highlights their neurotoxic potential, raising concerns about human and environmental health. This review comprehensively examines the mechanisms of pyrethroid toxicity, focusing on their interaction with voltage-gated sodium, calcium, and chloride channels in neuronal membranes. Pyrethroids prolong sodium channel activation, leading to repetitive nerve firing, hyperexcitation, and, in severe cases, seizures or paralysis. Additionally, they disrupt calcium homeostasis and inhibit chloride channels, exacerbating neurotoxic effects. These compounds are classified into Type I (non-cyano) and Type II (α-cyano) pyrethroids, each eliciting distinct neurotoxic syndromes—T-syndrome (tremors) and CS-syndrome (choreoathetosis-salivation), respectively. While adult mammals exhibit lower sensitivity due to differential sodium channel isoforms, developing organisms are particularly vulnerable, with prenatal and childhood exposure linked to cognitive deficits, developmental delays, and behavioral disorders. Beyond neurotoxicity, pyrethroids disrupt endocrine function, impair reproductive health, and induce organ damage, particularly in the liver, heart, and kidneys. Occupational exposure in agricultural workers and environmental contamination further amplify public health risks. Despite regulatory restrictions on certain pyrethroids, their widespread use persists, necessitating further research into long-term low-dose exposure effects and safer alternatives. This review synthesizes current knowledge on pyrethroid neurotoxicity, emphasizing the need for enhanced regulatory policies, advanced neuroprotective strategies, and sustainable pest control solutions to mitigate health risks.

Keywords: Pyrethroid neurotoxicity, Voltage-gated sodium channels, Pesticide-induced neurodegeneration, Endocrine disruption, Developmental neurotoxicity, Environmental health risks.

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1. INTRODUCTION

Pesticides represent a broad class of chemical agents designed to eliminate or manage pests, including insects, rodents, weeds, birds (Aves), and other undesirable organisms [1]. The historical use of pesticides traces back to ancient civilizations, where elemental sulfur was employed as one of the earliest pest control agents, a practice that persists today, particularly in viticulture [2]. As agricultural practices evolved, so did the sophistication of pest control methods. By the early 20th century, toxic metals such as arsenic and its derivatives became widely used, despite their non-selective toxicity and environmental persistence [3-7]. Concurrently, natural insecticides like pyrethrin, extracted from *Chrysanthemum cinerariaefolium*, and rotenone, derived from leguminous plants, gained prominence due to their relatively lower mammalian toxicity and rapid degradation in the environment [3]. However, the limited availability and instability of these natural compounds under sunlight exposure spurred the development of synthetic alternatives.

Department of Zoology, Aligarh Muslim University, Aligarh-202002, Uttar Pradesh, India.

* Author to whom correspondence should be addressed: faiqua06@gmail.com (Faiqua Haque)

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The mid-20th century marked a pivotal shift with the introduction of synthetic organic pesticides, including beta-hexachlorocyclohexane (BHC) and dichloro-diphenyl-trichloroethane (DDT), which revolutionized pest control and disease prevention [4]. DDT, in particular, played a crucial role in combating vector-borne diseases such as malaria and typhus, earning widespread acclaim before its ecological and health risks became apparent. Despite their efficacy, these early synthetic pesticides were later found to exhibit severe environmental persistence, bioaccumulation, and unintended toxicity to non-target species, leading to stringent regulatory restrictions under treaties like the Stockholm Convention on Persistent Organic Pollutants [8-11]. This historical progression underscores the ongoing challenge of balancing pest control efficacy with environmental and human safety.

Among modern synthetic pesticides, pyrethroids have emerged as one of the most widely used classes due to their structural similarity to natural pyrethrins, enhanced stability, and potent insecticidal activity [12-14]. These compounds are synthetic esters modeled after pyrethrin I and II, the active constituents of pyrethrum, but with modified chemical structures to improve resistance to photodegradation and broaden their insecticidal spectrum [15]. Pyrethroids are classified into two major groups: Type I (non-cyano) and Type II (α-cyano), distinguished by their chemical structure and toxicological effects. Type I pyrethroids, such as permethrin and allethrin, induce tremors and hyperexcitation (T-syndrome), whereas Type II pyrethroids, including deltamethrin and cypermethrin, cause choreoathetosis and salivation (CS-syndrome) in intoxicated organisms [16-18]. Despite their lower acute toxicity in mammals compared to insects, emerging evidence suggests that pyrethroids exert significant neurotoxic effects through their interaction with voltage-gated ion channels in the nervous system [19-21].

The primary neurotoxic mechanism of pyrethroids involves the modulation of voltage-gated sodium channels (VGSCs), where they delay channel inactivation, leading to prolonged depolarization and repetitive neuronal firing [22]. This disruption of normal nerve signaling is responsible for the insecticidal action of pyrethroids but also raises concerns about their impact on mammalian neurophysiology, particularly in developing organisms. Mammalian VGSCs exhibit differential sensitivity to pyrethroids, with certain isoforms (e.g., Nav1.3 in fetal brains and Nav1.8 in sensory neurons) being more susceptible than others [23-31]. Beyond sodium channels, pyrethroids also interfere with voltage-gated calcium (Ca^{2+}) and chloride (Cl^{-}) channels, further exacerbating neuronal dysfunction. For instance, Type II pyrethroids inhibit chloride channels, potentially contributing to the hypersalivation and motor disturbances observed in poisoning cases [32-34]. These multi-channel interactions highlight the complexity of pyrethroid neurotoxicity and its implications for human health.

Human exposure to pyrethroids occurs through multiple pathways, including agricultural applications, household insecticide use, and contaminated food sources. Occupational exposure among farmworkers has been linked to acute neurotoxic symptoms such as dizziness, paresthesia, and, in severe cases, seizures [35]. Chronic low-level exposure, particularly during critical developmental stages, is increasingly associated with neurobehavioral deficits, including cognitive impairments, attention disorders, and reduced motor function in children [36, 37]. Furthermore, pyrethroids have been implicated in endocrine disruption, reproductive toxicity, and organ damage, with studies demonstrating their ability to alter steroidogenesis, reduce sperm viability, and induce oxidative stress in hepatic and cardiac tissues [38-42]. The growing recognition of these adverse effects has prompted regulatory reevaluations, yet pyrethroids remain extensively used due to their perceived safety relative to older organochlorine and organophosphate pesticides.

This review provides a comprehensive synthesis of the neurotoxic mechanisms of pyrethroid insecticides, integrating recent advances in ion channel pharmacology, developmental neurotoxicity, and epidemiological findings. Unlike previous reviews that focus narrowly on acute toxicity, this paper critically examines the long-term consequences of chronic pyrethroid exposure, particularly in vulnerable populations such as pregnant women and children. It also explores the understudied role of pyrethroids in disrupting calcium and chloride channels, offering new insights into their broader neurotoxic potential. Furthermore, the review highlights emerging evidence linking pyrethroid exposure to epigenetic modifications and neurodegenerative pathways, suggesting persistent effects beyond immediate neuroexcitation. By bridging gaps between molecular toxicology, clinical observations, and regulatory science, this work aims to inform future research directions and policy decisions to mitigate the unintended health impacts of pyrethroid use.

The continued reliance on pyrethroids in global agriculture and public health necessitates a deeper understanding of their risks and the development of safer alternatives. This review underscores the need for interdisciplinary approaches—combining toxicology, neuroscience, and environmental science—to address the complex challenges posed by these widely used insecticides. By elucidating the mechanisms of pyrethroid neurotoxicity and their implications for human health, this paper contributes to the ongoing discourse on sustainable pest management and environmental safety.

2. THE CRITICAL ROLE OF PESTICIDES IN MODERN SOCIETY

Pesticides constitute one of the most transformative chemical innovations in modern agriculture and public health, serving as essential tools for controlling organisms that threaten food production, infrastructure, and human well-being. These chemical agents encompass a diverse array of compounds specifically designed to target various pest categories, including insects (insecticides), weeds (herbicides), rodents (rodenticides), fungi (fungicides), nematodes (nematicides),

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and other undesirable organisms that compromise agricultural productivity and public health [1]. The global pesticide market has witnessed exponential growth since the mid-20th century, with current valuations exceeding $80 billion annually, underscoring their indispensable role in ensuring food security for an ever-expanding population and controlling vector-borne diseases such as malaria, dengue, and Lyme disease [1].

The development and deployment of pesticides have been instrumental in increasing crop yields, reducing post-harvest losses, and preventing the spread of deadly pathogens. However, their widespread use has also raised significant concerns regarding environmental contamination, non-target toxicity, and long-term health effects in humans and wildlife. These concerns necessitate a systematic approach to classifying pesticides, which facilitates scientific research, regulatory oversight, and informed decision-making in pest management strategies.

3. THE IMPORTANCE OF PESTICIDE CLASSIFICATION

The classification of pesticides serves multiple critical functions across scientific, regulatory, and agricultural domains. For researchers, a well-defined classification system enables the study of structure-activity relationships, helping to elucidate how chemical modifications influence pesticidal efficacy, environmental persistence, and toxicity profiles. Regulatory agencies rely on these classifications to establish safety guidelines, determine acceptable exposure limits, and implement restrictions on high-risk compounds. Farmers and pest control professionals, meanwhile, utilize classification schemes to select the most appropriate pesticides for specific applications, balancing efficacy with environmental and human safety considerations [2].

The classification of pesticides by route of entry, mode of action, and chemical composition provides a multidimensional framework for understanding their applications, risks, and regulatory considerations. While chemical classification remains the most comprehensive approach, integrating all three systems enables more informed decision-making in pest management, balancing efficacy with environmental and human health protections. As pesticide science evolves, continued refinement of these classification systems will be essential for addressing emerging challenges such as resistance management, mixture toxicology, and the development of safer, more sustainable pest control solutions. Three primary classification systems have emerged as standard frameworks in pesticide toxicology, each offering unique insights into pesticide behavior and risk assessment (Figure 1).

3.1. Classification by Route of Entry

This system categorizes pesticides based on the pathway through which they enter the target organism's body, which directly influences their application methods and efficacy.

Contact pesticides represent one of the most common categories, requiring direct physical interaction with the pest to exert their toxic effects. These compounds, such as pyrethroids and certain organophosphates, penetrate the pest's exoskeleton or cuticle, disrupting physiological processes upon absorption. Their mode of action makes them particularly effective against insects with soft bodies, such as aphids and caterpillars, but they often require thorough coverage during application to ensure contact with the target pests [2].

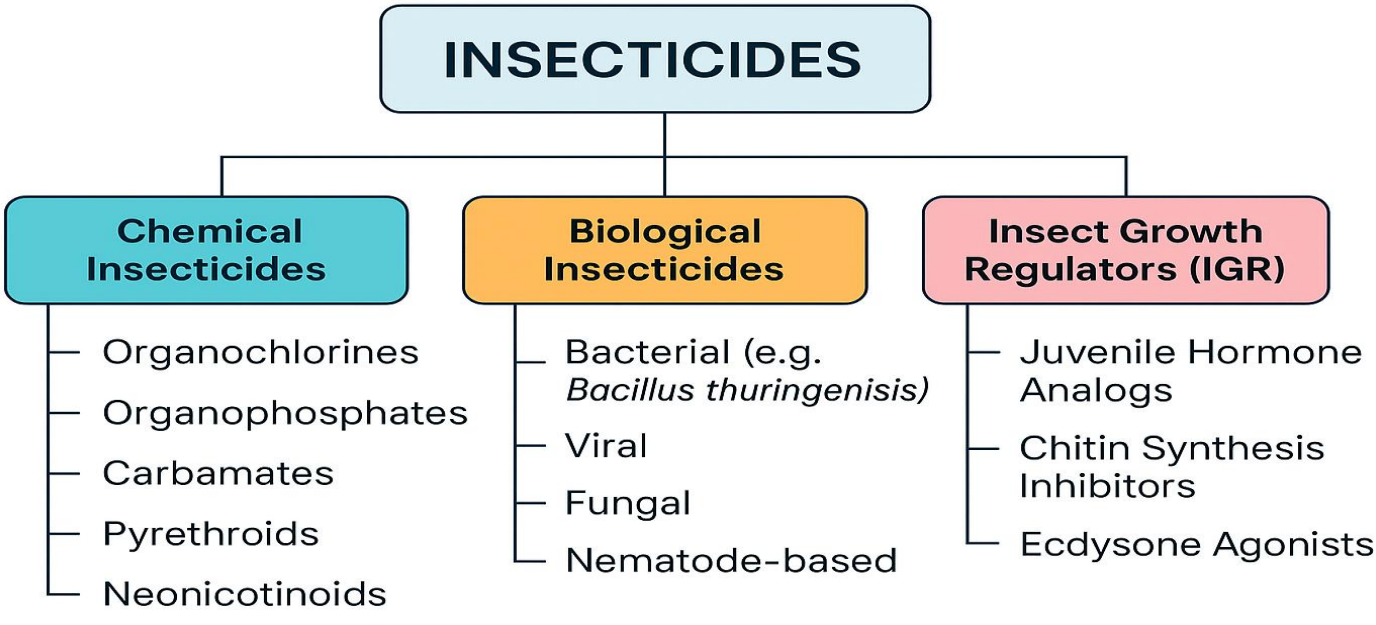

Fig. 1. Broad Classification of Insecticides.

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Stomach poisons must be ingested by the pest to deliver their toxic effects. These pesticides, including metaldehyde (used in slug and snail control) and certain arsenical compounds, are typically applied to plant surfaces or mixed with bait formulations. Their efficacy depends on the pest's feeding behavior, making them suitable for controlling chewing insects like beetles and caterpillars but less effective against piercing-sucking pests such as aphids, which bypass the treated surfaces [2].

Fumigants are volatile pesticides that enter the pest's body through the respiratory system. Compounds like methyl bromide and phosphine gas are used in soil sterilization, stored grain protection, and structural pest control. Their gaseous nature allows them to penetrate deep into substrates, reaching pests that would otherwise be inaccessible to liquid or solid formulations. However, their high volatility also poses significant inhalation risks to humans and non-target organisms, necessitating stringent safety measures during application [2].

Systemic pesticides are absorbed by plants and distributed throughout their vascular systems, rendering the entire plant toxic to feeding pests. Neonicotinoids, such as imidacloprid, and certain carbamates are prime examples of systemic insecticides. These compounds are particularly valuable for controlling sap-sucking insects and soil-dwelling pests, as they provide long-lasting protection without requiring direct contact with the target organism. However, their systemic nature also raises concerns about non-target exposure, particularly for pollinators that may ingest contaminated nectar or pollen [2].

3.2. Classification by Mode of Action

This approach groups pesticides according to their biochemical and physiological targets within the pest organism, providing critical insights into their mechanisms of toxicity and potential resistance development.

Neurotoxic insecticides represent the largest and most widely used class of pesticides, targeting the nervous systems of insects and other pests. Organophosphates (e.g., malathion), carbamates (e.g., carbaryl), and pyrethroids (e.g., permethrin) all disrupt neural signaling, albeit through distinct mechanisms. Organophosphates and carbamates inhibit acetylcholinesterase, leading to acetylcholine accumulation and hyperstimulation of cholinergic synapses, while pyrethroids modify voltage-gated sodium channels, causing prolonged neuronal excitation. These differences in mode of action influence their spectrum of activity, mammalian toxicity, and environmental persistence [3].

Insect growth regulators (IGRs) interfere with the developmental processes of insects, preventing them from reaching reproductive maturity. Chitin synthesis inhibitors, such as diflubenzuron, disrupt the formation of the insect exoskeleton during molting, while juvenile hormone analogs (e.g., methoprene) mimic hormones that regulate metamorphosis, leading to abnormal development and sterility. Because IGRs target processes unique to arthropods, they generally exhibit lower toxicity to mammals, making them attractive alternatives for integrated pest management (IPM) programs [3].

Photosynthesis inhibitors are primarily herbicides that block critical steps in the photosynthetic electron transport chain, leading to oxidative damage and plant death. Triazine herbicides (e.g., atrazine) and urea derivatives (e.g., diuron) bind to specific proteins in photosystem II, preventing energy production. These compounds are selective in their action, affecting broadleaf weeds more than grasses, but their persistence in the environment has raised concerns about groundwater contamination and non-target plant toxicity [3].

Respiratory inhibitors disrupt cellular energy production by interfering with mitochondrial function. Rotenone, a classical example, blocks electron transfer in Complex I of the mitochondrial respiratory chain, leading to ATP depletion and cell death. While highly effective against fish and insects, its broad-spectrum toxicity has led to restricted use in many jurisdictions. Similarly, cyanide-based fumigants like hydrogen cyanide inhibit cytochrome c oxidase, paralyzing cellular respiration in all aerobic organisms [3].

3.3. Classification by Chemical Composition

The chemical classification system organizes pesticides based on their core molecular structures, providing the most comprehensive framework for understanding their properties, environmental behavior, and toxicological profiles.

3.3.1. Organochlorines

Organochlorine pesticides (OCPs) are synthetic chlorinated hydrocarbons that were historically used on a large scale in agriculture and public health due to their effectiveness against a wide range of pests. Chemically, they are composed of carbon, hydrogen, and chlorine atoms, often forming aromatic or aliphatic structures. These compounds are known for their environmental persistence, resistance to degradation, and high lipid solubility, which leads to bioaccumulation in the food chain and long-term ecological impact [8]. Common examples include DDT (Dichlorodiphenyltrichloroethane), lindane, chlordane, aldrin, and dieldrin, all of which have been shown to persist in soil and aquatic environments for years. Their toxicological profile is concerning, as exposure to OCPs is linked to endocrine disruption, neurotoxicity, reproductive toxicity, and even carcinogenic effects in humans and animals. Due to these risks, most organochlorines have been banned or severely restricted under global treaties such as the Stockholm Convention on Persistent Organic Pollutants, although limited use—such as

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DDT for malaria control—still exists in certain regions. Despite their historical significance, the long-term environmental and health hazards associated with OCPs underscore the importance of regulatory control and the development of safer, more sustainable pest control alternatives [9].

3.3.2. Organophosphates

Organophosphate pesticides are a widely used class of synthetic chemicals primarily employed in agriculture and public health for controlling pests. They act as cholinesterase inhibitors, blocking the enzyme acetylcholinesterase, which is responsible for breaking down the neurotransmitter acetylcholine. As a result, acetylcholine accumulates in synaptic junctions, leading to continuous nerve stimulation. This prolonged synaptic activity causes involuntary muscle twitching, and ultimately paralysis and death due to respiratory failure. Since these compounds interfere with a fundamental neurological pathway, they pose a significantly greater threat to vertebrates than invertebrates, as vertebrate nervous systems are more dependent on cholinergic transmission [10]. Common organophosphates include chlorpyrifos, malathion, parathion, and diazinon, which have been used extensively in both household and agricultural settings. Acute exposure can cause a variety of symptoms including headaches, sweating, salivation, vomiting, and blurred vision, while chronic exposure has been linked to neurobehavioral disorders, cognitive impairments, and peripheral neuropathy [11]. Furthermore, prenatal exposure has been associated with developmental delays, reduced IQ, and impaired respiratory health in children [12]. Due to these health hazards, the use of many organophosphates has been restricted or banned in several countries, with the U.S. EPA banning food uses of chlorpyrifos in 2021. Despite these regulations, organophosphates continue to be used in various parts of the world, raising concerns over their ongoing impact on human health and the environment.

3.3.3. Carbamates

Carbamate pesticides are a class of chemicals widely used in agriculture and public health for pest control. Carbamates including carbaryl and aldicarb, share a similar mechanism of action with organophosphates but feature a carbamate group instead of a phosphate moiety. Their reversible inhibition of acetylcholinesterase generally results in shorter-lived toxic effects, though highly toxic compounds like aldicarb have been withdrawn from many markets due to poisoning risks [4]. They function as reversible acetylcholinesterase inhibitors, temporarily preventing the breakdown of acetylcholine at synapses and neuromuscular junctions. This accumulation of acetylcholine leads to overstimulation of muscles, glands, and the central nervous system, resulting in symptoms such as sweating, excessive salivation, nausea, vomiting, diarrhea, and, in severe cases, paralysis and respiratory failure. Unlike organophosphates, carbamates bind to acetylcholinesterase reversibly, typically causing a shorter duration of toxic effects [13]. Common carbamates include carbofuran, carbaryl, aldicarb, oxamyl, methomyl, and propoxur). While their acute toxicity is generally considered lower than that of organophosphates, chronic exposure has been associated with multiple health issues. Research has shown links between carbamate exposure and immunotoxic effects, such as hypersensitivity, autoimmune conditions, and even increased cancer risk [14]. Furthermore, carbamates have been identified as endocrine-disrupting chemicals capable of interfering with the hypothalamic-pituitary-gonadal axis, which can result in male reproductive dysfunctions like reduced sperm count, motility, and viability. Due to these risks, the use of certain carbamate compounds has been restricted or banned in various countries, although several remain in use in different regions worldwide.

3.3.4. Neonicotinoids

Neonicotinoids**,** such as imidacloprid and thiamethoxam, represent a newer class of systemic insecticides that target nicotinic acetylcholine receptors in insects. Their high selectivity for insect over mammalian receptors initially made them appear safer than older compounds, but emerging evidence of pollinator toxicity has led to widespread restrictions in the European Union and elsewhere [4].

3.3.5. Biopesticides

Biopesticides, derived from natural materials like bacteria, fungi, and plant extracts, offer environmentally friendly alternatives to synthetic chemicals. Bacillus thuringiensis (Bt) toxins, for example, specifically target caterpillar pests while posing minimal risk to non-target organisms. The growing demand for sustainable pest control has spurred significant investment in biopesticide research and development [4].

3.3.6. Pyrethroids

Pyrethroids are the synthetic analogs of natural pyrethrins. These are among the most widely used insecticides today. Their low mammalian toxicity and rapid knockdown effects make them popular for agricultural and household applications, though concerns about aquatic toxicity and insect resistance are growing. Compounds like permethrin and deltamethrin are classified into Type I (non-cyano) and Type II (α-cyano) pyrethroids based on their chemical structures and toxicological syndromes [4]. Originally pyrethrum derived from flowers of *Tanacetum cinerariaefolium* are the main insecticides which finds their utilization in household chores and to control post-harvest insect attack due to their minimal toxic effect on mammals, fast knockdown activity, and efficient working power against

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the wide range of pests, especially mosquitoes. These flowers are mainly grown in southern china, australlia and East Africa. According to survey conducted in 2016, the production of dried flower seed approximately 10,000 metric tons in china. Pyrethrins break down swiftly in the environment, especially when exposed to sunlight. In terms of structure, pyrethroids are synthetic compounds that are similar to pyrethrins, but they frequently kill more insects and animals and linger in the environment for a longer time [15]. The chemical permethrin, often known as PERM, is a type I pyrethroid; type II pyrethroids have an alpha-cyano moiety. These two categories of pyrethroids are distinguished by their chemical compositions (i.e. cypermethrin, CY). Type I pyrethroids cause the type I poisoning syndrome, or "T syndrome," whereas type II pyrethroids cause the type II choreoathetosis syndrome, or “CS syndrome” [16]. Table 1 gives classification of pyrethroid along with examples.

Table 1. Classification of Pyrethroids.

Type- I Pyrethroid	Type-II Pyrethroid
Allethrin	Cyfluthrin
Bifenthrin	Cypermethrin
Bioresmethrin	Deltamethrin
Resmethrin	Fenvalerate
Tefluthrin	Flumethrin
Tetramethrin	Fluvanilate
d- phenothrin	Tralomethrin
Permethrin	Fenpropathrin

4. STRUCTURE AND TOXICITY OF PYRETHROIDS

Two pyrethrin compounds, first identified in 1924, were recognized as the primary agents responsible for the insecticidal properties of pyrethrum [17]. These compounds were named Pyrethrin I and Pyrethrin II. Pyrethrin I contains a chrysanthemic acid moiety, whereas Pyrethrin II features a dicarboxylic acid component known as pyrethric acid. Initial insecticidal studies using *Aphis rumicis* L. (aphids), building on earlier experiments involving cockroaches, indicated that Pyrethrin I exhibited greater effectiveness. Early research suggested that Pyrethrin I was likely the main contributor to pyrethrum’s insecticidal action. However, subsequent studies produced mixed results—some demonstrated higher potency for Pyrethrin II, while others continued to support the superior activity of Pyrethrin I. These inconsistencies were initially attributed to challenges such as difficulties in isolating pure forms of each compound, degradation due to light exposure during storage, and variability in the test insect species used. [17,18,19]. Eventually, it was concluded that Pyrethrin II was generally more effective at immobilizing insects, whereas Pyrethrin I showed greater efficacy in actually killing them.[20] Chrysanthemic acid, a key component of Pyrethrin I, served as the structural model for the acid portions of pyrethrins. This acid is characterized by the presence of a cyclopropane ring, a feature not found in many modern synthetic pyrethroids such as fenvalerate, which is based on phenylisovalerate. A major advancement in insecticidal potency came with the introduction of a cyano (–CN) group at the carbon of the 3-phenoxybenzyl alcohol segment. This modification enhanced insecticidal activity by approximately 3 to 6 times compared to pyrethroids lacking the cyano group. As a result of the presence or absence of this cyano group, synthetic pyrethroids are typically classified into two categories. Type I pyrethroids, such as permethrin, do not contain a cyano group, while Type II pyrethroids, like cypermethrin, include this functional group. Most pyrethroids possess multiple stereogenic centers, display considerable molecular flexibility, and can adopt a variety of potential three-dimensional conformations [21].

5. MODE OF ACTION OF PYRETHROID

Pyrethroid insecticides exert their neurotoxic effects primarily by interacting with voltage-gated sodium (Na^+) channels in nerve membranes. These compounds bind to the Na^+ channels, leading to prolonged depolarization and repetitive nerve firing, which disrupts normal nerve function. This mechanism is considered the principal mode of action for pyrethroids in both insects and mammals. The pyrethroid-induced modification of Na^+ channels is characterized by its state-dependent nature, meaning that pyrethroids preferentially bind to channels in specific conformations, such as the open or inactivated states. This selective binding alters the gating kinetics of the channels, resulting in delayed repolarization and sustained nerve impulses [22]. While the primary target remains the Na^+ channels, some pyrethroids also affect other ion channels, including voltage-gated calcium (Ca^{2+}) and chloride (Cl^-) channels. These interactions may contribute to the overall neurotoxic effects, although they are generally considered secondary to the primary action on Na^+ channel. The differential effects of pyrethroids on Na^+ channel kinetics are associated with their classification into Type I and Type II compounds. Type I pyrethroids typically cause repetitive nerve firing without significant depolarization, while Type II pyrethroids induce more pronounced depolarization and persistent nerve activity [23]. Understanding these mechanisms is crucial for assessing the neurotoxic risks associated with pyrethroid exposure and for developing strategies to mitigate potential adverse effects. Figure 2 shows toxic effects of pyrethroids on nerve impulse and on different voltage gated channels.

5.1. Toxic Effect of Pyrethroids on nerve impulse/ Neurotoxicity

Pyrethroids exhibit neurotoxic effects by altering the normal conduction of nerve impulses, primarily through their interaction with voltage-gated sodium channels in neuronal membranes. These compounds prolong the opening of sodium channels, delaying their inactivation and causing

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prolonged sodium influx during depolarization. As a result, neurons experience repetitive firing and hyperexcitation, disrupting the transmission of normal nerve impulses [24]. This continuous stimulation can lead to a range of neurotoxic symptoms in insects, including tremors, paralysis, and eventual death. In mammals, although pyrethroids are less potent due to differences in sodium channel structure and detoxification mechanisms, high exposure can still result in symptoms such as dizziness, ataxia, and in severe cases, seizures [25]. The type of neurotoxic effect is influenced by whether the pyrethroid is Type I or Type II: Type I pyrethroids typically induce tremors by causing repetitive discharges, while Type II compounds lead to more persistent depolarization and may result in choreoathetosis and salivation (CS-syndrome) [26]. Thus, the neurotoxicity of pyrethroids is closely linked to their action on ion channels, particularly the persistent activation of sodium channels, which disrupts normal nerve impulse transmission.

5.2. Toxic Effect of Pyrethroid on Voltage gated Calcium Channel

Pyrethroid insecticides, while primarily known for targeting voltage-gated sodium channels, also affect voltage-gated calcium channels (VGCCs), contributing to their neurotoxic effects. For instance, the type I pyrethroid allethrin has been shown to block various VGCC subtypes in mammalian cells, including T-type (CaV3.1), L-type (CaV1.2), and P/Q-type (CaV2.1) channels, with IC_{50} values around 6.7–7.0 µM. This blockade results in accelerated inactivation kinetics and hyperpolarizing shifts in voltage dependence, differing from the prolonged activation seen with sodium channels [27]. Moreover, several pyrethroids, such as deltamethrin, tefluthrin, and cypermethrin, have been observed to induce calcium influx in neocortical neurons. This influx is mediated through VGSCs and involves NMDA receptor activation, L-type VGCCs, and the reverse mode of the Na^+/Ca^{2+} exchanger. In rat brain synaptosomes, deltamethrin has been found to increase calcium influx and neurotransmitter release via N-type VGCCs (CaV2.2), with the effect being stereospecific and blocked by ω-conotoxin GVIA [28]. These interactions with VGCCs suggest that pyrethroids can disrupt calcium homeostasis, potentially leading to altered neuronal signaling and contributing to their overall neurotoxic profile [29].

5.3. Toxic effect of Pyrethroid on mammalian voltage-gated Sodium Channels

The alpha subunit of voltage-gated sodium channels (VGSCs) in mammals shares a high degree of structural and amino acid sequence similarity with that of insects. In mammals, there are nine distinct VGSC genes, each exhibiting unique tissue distribution and functional characteristics. Additionally, alternative splicing of these genes further enhances the functional diversity of sodium channels. Mammalian VGSCs also rely on auxiliary β subunits for proper localization to the plasma membrane. These β subunits not only assist in trafficking but also influence the channel's voltage-dependence and gating kinetics. There are four β subunit genes (β1–β4), all of which are expressed in the central nervous system and heart, whereas skeletal muscle predominantly expresses the β1 subunit. Similar to their effects in insects, pyrethroids increase neuronal excitability in mammals by delaying the inactivation of sodium channels, thereby shortening the falling phase of the action potential.

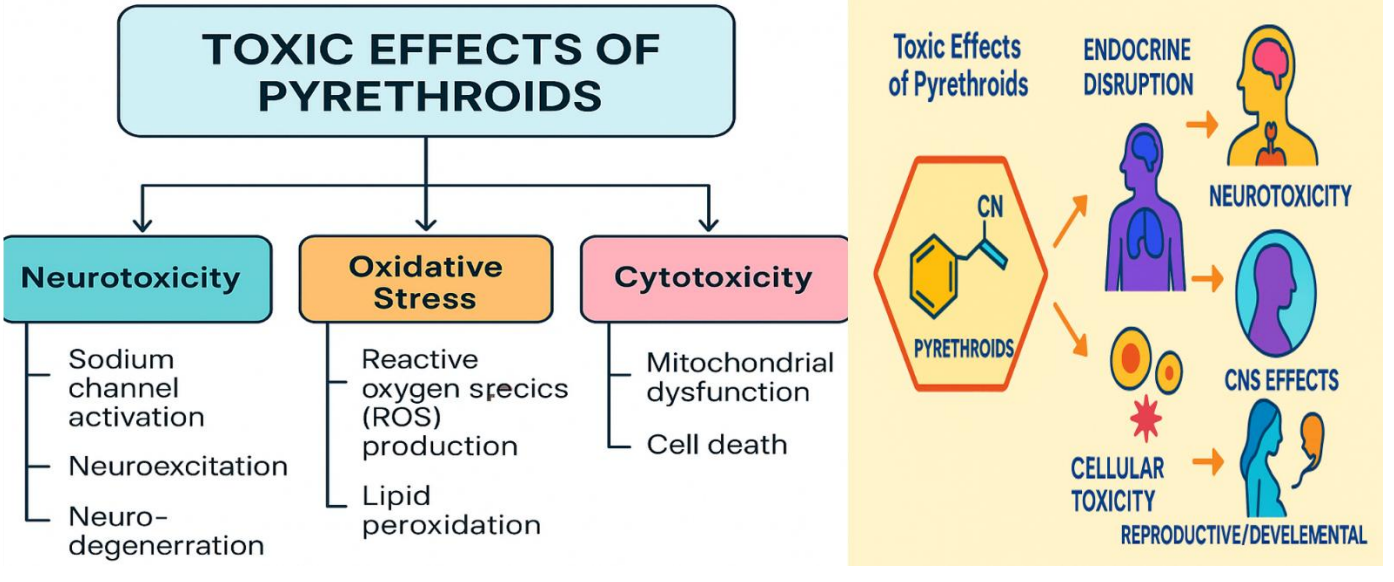

Fig. 2. Toxic effects of pyrethroids on different channels.

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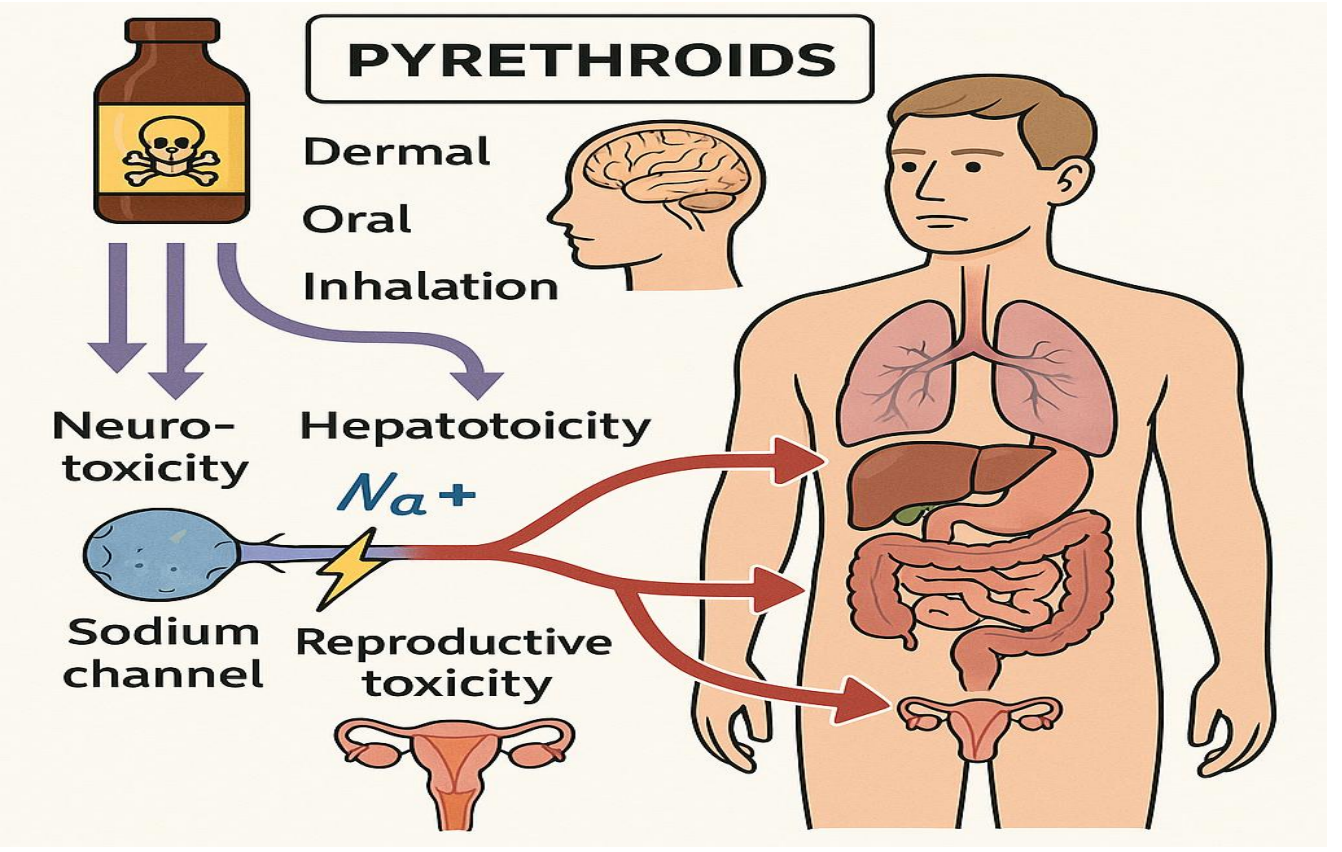

Fig. 3. Route of administration and toxicity caused by pyrethroids.

Both Type I and Type II pyrethroids extend the duration of sodium currents, with Type II pyrethroids causing a more pronounced prolongation by holding VGSCs open for a longer period. For example, tetramethrin, a Type I pyrethroid, was shown to increase the open time of sodium channels in mouse neuroblastoma cells, a cell line derived from a spontaneous tumor of neural crest origin [30]. There is variation in pyrethroid sensitivity among the channel isoforms, despite the fact that mammalian VGSCs are less sensitive to pyrethroids than insect VGSCs. Sensory neurons known as dorsal root ganglion cells express two types of VGSCs: TTX-sensitive and TTX-resistant channels. Action potential production is stopped by the strong VGSC inhibitor TTX. Although Nav1.8 and Nav1.9 are resistant to TTX (Tetrodotoxin), they are extremely susceptible to pyrethroids. The Nav1.2 sub-type was found to be less prone to pyrethroid alteration than other sub-types in X. laevis oocyte expression and voltage clamp investigations [31]. The enhanced neurotoxicity of pyrethroid on developing mammals may be caused by the elevated pyrethroid sensitivity of Nav1.3. Nav1.6, which is extensively expressed in the adult brain, is fifteen times more susceptible to tefluthrin and deltamethrin than Nav1.2 [32].

5.4. Toxic effect of Pyrethroid on voltage-gated Cl^- channels

Pyrethroid insecticides, primarily known for targeting voltage-gated sodium channels, have also been shown to interact with voltage-gated chloride channels, contributing to their neurotoxic effects. Studies have demonstrated that Type II pyrethroids, such as deltamethrin and cypermethrin, can decrease the open channel probability (P_o) of voltage-gated chloride channels in neuroblastoma cells, indicating a potential inhibitory effect on chloride conductance. These interactions with chloride channels are thought to exacerbate the neurotoxic symptoms associated with pyrethroid exposure. For instance, the CS (choreoathetosis and salivation) syndrome observed in pyrethroid poisoning may be linked to the modulation of chloride channels, as evidenced by the effects of chloride channel agonists like ivermectin and pentobarbitone in mitigating symptoms *in vivo*. However, the role of chloride channel modulation in pyrethroid toxicity is complex and may vary among different pyrethroid compounds. Not all pyrethroids exhibit significant effects on chloride channels, and the contribution of this interaction to the overall toxicological profile depends on the specific chemical structure and subtype of the pyrethroid involved. In summary, while voltage-gated chloride channels are not the primary targets of pyrethroids, their modulation can influence the severity and nature of pyrethroid-induced neurotoxicity, highlighting the multifaceted mechanisms underlying the toxicological effects of these insecticides [33]. Figure 3 exhibits the route of administration and toxicity caused by pyrethroids.

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6. HARMFUL EFFECTS OF PYRETHROIDS ON HUMAN HEALTH

The toxicity of pesticides refers to their capacity to cause harm to living organisms, including humans, wildlife, and entire ecosystems [34]. Among synthetic pesticides, pyrethroids have gained widespread use due to their potent insecticidal activity and relatively low acute toxicity to mammals. However, emerging research indicates that both acute and chronic exposure to pyrethroids can lead to significant adverse health effects in humans. The degree of toxicity depends on two critical factors: the dose (quantity of pesticide exposure) and the duration (frequency and length of exposure) [34]. These factors determine whether toxic effects manifest as acute poisoning incidents or chronic health conditions that develop over months or years of repeated exposure. Pyrethroids, despite being considered safer than organophosphates and carbamates, exhibit concerning neurotoxic, reproductive, developmental, and systemic effects that warrant careful examination. Figure 4 exhibits the harmful effects of pyrethroids on human health.

6.1. Neurological Effects of Pyrethroid Exposure

6.1.1. Mechanisms of Neurotoxicity

Pyrethroids primarily target the nervous system by interacting with voltage-gated sodium channels (VGSCs) in neuronal membranes. These compounds bind to the α-subunit of sodium channels, delaying their inactivation and causing prolonged depolarization of nerve cells [35]. This disruption leads to repetitive nerve firing, excessive neurotransmitter release, and, in severe cases, neuronal apoptosis. Type I pyrethroids (e.g., permethrin) induce tremors and hyperexcitation (T-syndrome), while Type II pyrethroids (e.g., deltamethrin) cause choreoathetosis and salivation (CS-syndrome) due to their differential effects on sodium channel kinetics [35].

6.1.2. Acute Neurological Symptoms

Acute exposure to high concentrations of pyrethroids, often occurring in occupational settings or accidental ingestions, produces immediate neurotoxic effects. Common symptoms include headache, dizziness, paresthesia (abnormal skin sensations described as tingling or burning), nausea, vomiting, and muscle fasciculations [35]. In severe poisoning cases, victims may experience seizures, loss of consciousness, and coma, particularly with Type II pyrethroids, which cause more pronounced neuronal depolarization. These acute effects typically result from temporary dysfunction of the nervous system and often resolve after the toxin is metabolized and excreted. However, repeated exposures can lead to longer-lasting neurological damage.

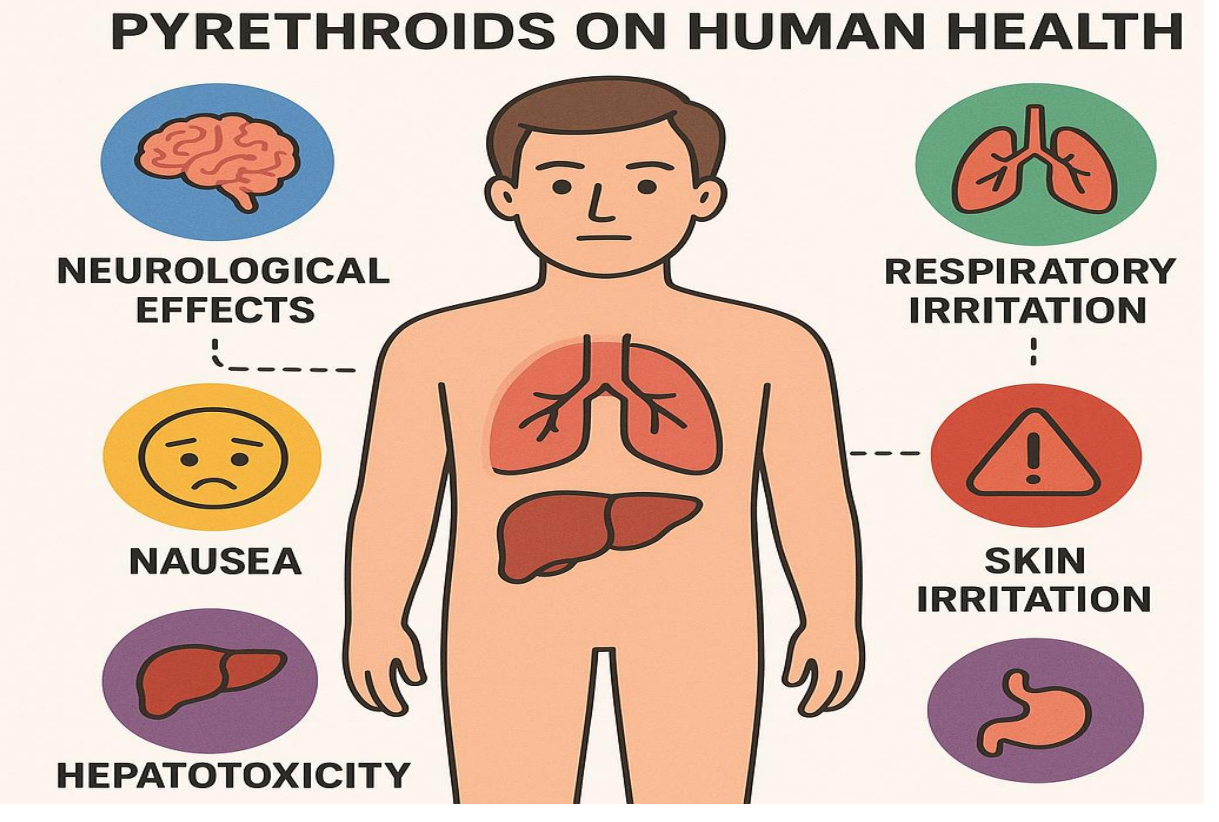

Fig. 4. Harmful Effects of Pyrethroids on Human Health.

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6.1.3. Chronic Neurodevelopmental and Neurodegenerative Effects

Chronic low-level exposure to pyrethroids, even at doses considered "safe" by regulatory standards, has been linked to persistent neurodevelopmental impairments, particularly in children. Epidemiological studies have demonstrated that prenatal exposure to pyrethroids correlates with reduced cognitive function, lower IQ scores, and increased incidence of attention deficit hyperactivity disorder (ADHD) in children [36]. Animal studies have further elucidated the mechanisms behind these effects, showing that pyrethroids induce oxidative stress in neural tissues, trigger neuroinflammation through microglial activation, and disrupt mitochondrial function, all of which contribute to neurodegeneration [37]. These findings raise concerns about the long-term consequences of pyrethroid exposure, especially during critical windows of brain development.

6.2. Reproductive and Endocrine-Disrupting Effects

6.2.1. Impact on Male Reproductive Health

Pyrethroids have been identified as endocrine-disrupting chemicals (EDCs) capable of interfering with the hypothalamic-pituitary-gonadal axis, which regulates reproductive function. In males, chronic exposure has been associated with decreased sperm concentration, reduced sperm motility, and increased sperm DNA fragmentation [38]. These effects stem from multiple mechanisms, including direct antagonism of androgen receptors, inhibition of steroidogenic enzymes (e.g., 17β-hydroxysteroid dehydrogenase), and induction of oxidative stress in testicular tissues. Studies on occupational workers exposed to pyrethroids have reported alterations in testosterone and luteinizing hormone levels, further supporting their role in reproductive toxicity [38].

6.2.2. Effects on Female Reproductive Health

In females, pyrethroid exposure has been linked to menstrual cycle irregularities, reduced fertility, and adverse pregnancy outcomes. Animal studies demonstrate that certain pyrethroids can disrupt estradiol synthesis and interfere with ovarian follicle development. Additionally, their ability to cross the placental barrier raises concerns about fetal exposure during critical developmental periods. Epidemiological evidence suggests that pregnant women with higher urinary levels of pyrethroid metabolites have an increased risk of preterm birth and intrauterine growth restriction [38].

6.3. Developmental Toxicity and Pediatric Risks

6.3.1. Prenatal and Early-Life Exposure Consequences

The developing fetus and young children are particularly vulnerable to pyrethroid toxicity due to their immature metabolic systems and rapid neurological development. Prenatal exposure has been associated with reduced birth weight, smaller head circumference, and delayed psychomotor development in infants [39]. These effects likely result from pyrethroid-induced endoplasmic reticulum stress in developing neurons, which disrupts protein folding and triggers apoptotic pathways. Furthermore, the blood-brain barrier in fetuses and neonates is more permeable to pyrethroids, allowing greater accumulation in neural tissues compared to adults.

6.4. Long-Term Cognitive and Behavioral Outcomes

Longitudinal studies tracking children exposed to pyrethroids during early development have identified persistent deficits in memory, learning ability, and executive function. A 2020 cohort study found that children with higher prenatal pyrethroid exposure scored significantly lower on cognitive assessments at age 6 compared to controls [36]. Behavioral abnormalities, including increased aggression and social withdrawal, have also been reported in animal models following developmental exposure. These findings suggest that pyrethroids may contribute to the rising prevalence of neurodevelopmental disorders in human populations.

6.5. Occupational and Environmental Exposure Risks

Agricultural workers face the highest risk of pyrethroid exposure due to frequent handling during crop spraying and pest control operations. Field studies have documented elevated rates of neurological symptoms (e.g., dizziness, tremors), respiratory irritation, and psychological distress (e.g., anxiety, depression) among farmworkers regularly exposed to pyrethroids [40]. Poor adherence to personal protective equipment (PPE) guidelines and inadequate safety training exacerbate these risks in many developing countries where regulatory oversight is limited.

The general population is exposed to pyrethroids through several environmental routes, with dietary intake being one of the most common pathways. Residues of these insecticides frequently remain on fruits, vegetables, and grains even after washing, leading to ingestion through contaminated food. Indoor exposure also poses a significant risk, as household insecticide sprays, mosquito coils, and pet flea treatments containing pyrethroids contribute to inhalation and dermal contact in residential settings. Additionally, airborne particles from agricultural spray drift or contaminated dust can lead to inhalation exposure, particularly in rural areas near treated fields. Children are especially vulnerable to these exposure routes due to their frequent hand-to-mouth behaviors and higher food consumption relative to their body weight. The widespread presence of pyrethroids in the environment is further

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confirmed by biomarker studies, which have detected pyrethroid metabolites in over 70% of urine samples from the general U.S. population, highlighting the pervasive nature of human exposure to these chemicals [40].

6.6. Vulnerable Populations and Risk Mitigation

Certain population groups face heightened vulnerability to pyrethroid exposure due to biological and physiological factors. Pregnant women are particularly at risk because pyrethroids can cross the placental barrier, potentially affecting fetal development. Infants and children represent another vulnerable group due to their still-developing nervous systems and higher metabolic rates relative to body weight, which may enhance their susceptibility to neurotoxic effects. Elderly individuals experience increased risk because of age-related declines in detoxification capacity, while immunocompromised patients face greater danger due to their impaired ability to counteract the oxidative stress induced by pyrethroids.

To mitigate these risks, several strategies can be implemented. Agricultural reforms that promote integrated pest management (IPM) techniques can help reduce reliance on chemical sprays while maintaining effective pest control. Consumer education initiatives should focus on proper usage of household insecticides and thorough washing of produce to minimize exposure. Regulatory agencies must continue reevaluating safety thresholds for pyrethroids, incorporating emerging neurotoxicity data to ensure adequate protection for vulnerable populations. These combined approaches can help balance the benefits of pyrethroid use with necessary protections for at-risk groups.

While pyrethroids remain valuable tools in pest control, growing evidence of their neurological, reproductive, and developmental toxicity necessitates a reevaluation of exposure risks, particularly for vulnerable populations. The disconnect between their perceived safety and emerging health effects underscores the need for more stringent regulatory standards, advanced protective measures for occupational workers, and increased public awareness about exposure prevention. Future research should prioritize longitudinal studies on chronic low-dose effects and investigate potential therapeutic interventions to mitigate pyrethroid-induced toxicity in affected individuals.

7. ORGAN TOXICITY OF PYRETHROID INSECTICIDES: HISTOPATHOLOGICAL EVIDENCE

7.1. Liver Histopathology and Pyrethroid-Induced Hepatotoxicity

Histopathological examinations of liver tissues from animal studies provide compelling evidence of pyrethroid-induced hepatotoxicity. Control groups consistently show normal hepatic architecture with intact lobular organization, healthy hepatocytes, and absence of pathological changes. However, animals exposed to pyrethroids through various delivery methods - including burning mosquito coils, liquid insecticide vapors, and mat-based repellents - demonstrate significant liver damage [41].

The most severe hepatic alterations occur in animals exposed to mosquito coil smoke, which induces marked intracytoplasmic accumulation of toxic metabolites, hydropic degeneration characterized by cytoplasmic vacuolization, and severe coagulative necrosis. These changes reflect profound cellular injury and compromised liver function. Histological sections reveal extensive hyaline droplet formation within hepatocytes, indicating protein reabsorption dysfunction, along with pronounced hyperemia suggesting vascular damage and impaired blood flow [41].

Comparative analysis shows differential toxicity patterns among exposure methods. Mat-based pyrethroid formulations primarily trigger inflammatory responses, with significant lymphocyte and macrophage infiltration in portal triads and hepatic parenchyma. This suggests an immune-mediated component to the hepatotoxicity. In contrast, liquid insecticide vapors produce more extensive necrotic changes, particularly in centrilobular regions where metabolic activation of toxins occurs. The zone-specific necrosis pattern implicates cytochrome P450-mediated bioactivation of pyrethroids as a key mechanism of liver injury [41].

The observed fatty degeneration (steatosis) in all exposure groups indicates mitochondrial dysfunction and impaired lipid metabolism. Electron microscopy studies corroborate this, showing swollen mitochondria with cristae disruption in pyrethroid-exposed hepatocytes. These ultrastructural changes correlate with biochemical evidence of oxidative stress, including depleted glutathione levels and elevated lipid peroxidation markers [41]. The cumulative histopathological evidence demonstrates that pyrethroid exposure, particularly through inhalation routes, causes dose-dependent liver damage through multiple mechanisms including oxidative stress, metabolic activation to reactive intermediates, and inflammatory cascades.

7.2. Cardiac Histopathology and Cardiovascular Effects

The cardiovascular system shows significant vulnerability to pyrethroid toxicity, as evidenced by histopathological changes in cardiac muscle tissue. Control animals maintain normal myocardial architecture with uniform cardiomyocyte striations, intact intercalated discs, and absence of vascular abnormalities. However, pyrethroid-exposed groups exhibit dose-dependent cardiac damage with distinct pathological features [42].

The most pronounced cardiac effects occur in animals exposed to mosquito coil smoke, showing severe myocardial atrophy with reduction in cardiomyocyte diameter, indicative of chronic toxicity. Histological sections reveal extensive vascular congestion and hyperemia, reflecting microcirculatory disturbances and potential ischemia. Lymphocytic infiltration appears predominantly in

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perivascular regions, suggesting an inflammatory response to pyrethroid exposure. These changes correlate with functional studies showing prolonged QT intervals and arrhythmias in electrocardiographic recordings from exposed animals [42].

Antioxidant intervention studies provide mechanistic insights into pyrethroid cardiotoxicity. Animals treated with antioxidant AA (ascorbic acid) after exposure show partial improvement, with reduced vascular congestion but persistent myocardial atrophy. This suggests that oxidative stress contributes to but doesn't fully explain the cardiac damage. In contrast, treatment with antioxidant E307 (a tocopherol-based compound) shows better preservation of myocardial structure, implicating lipid peroxidation as a major pathway in pyrethroid-induced cardiac injury [42].

Comparative analysis reveals route-dependent toxicity patterns. Inhalation exposure causes more severe cardiac effects than dermal or oral routes, likely due to direct access to circulation through pulmonary absorption. The right ventricle shows particular vulnerability, possibly due to its thinner wall and greater exposure to circulating toxins. Histochemical staining demonstrates accumulation of pyrethroid metabolites in cardiac tissue, with preferential localization in mitochondrial-rich areas, explaining the observed energy metabolism disturbances [42]. These findings highlight the need for cardiac monitoring in cases of pyrethroid exposure, particularly among occupationally exposed populations.

7.3. Renal Histopathology and Nephrotoxic Effects

The kidneys demonstrate significant histopathological alterations following pyrethroid exposure, reflecting their role in toxin elimination and consequent vulnerability. Control animals show normal renal architecture with intact glomeruli, patent tubules, and unremarkable vasculature. In contrast, exposed animals develop multiple renal lesions that vary by exposure method and duration [43].

The most severe nephrotoxicity occurs with mosquito coil smoke exposure, producing extensive glomerular necrosis with collapse of capillary tufts and thickening of Bowman's capsule. Tubular damage appears particularly pronounced in proximal segments, showing cytoplasmic degeneration with loss of brush borders, vacuolization, and hyaline cast formation. Vascular changes include marked congestion and dilation of peritubular capillaries, suggesting microcirculatory impairment. These findings correlate with functional studies showing elevated serum creatinine and blood urea nitrogen levels [43].

Comparative analysis reveals exposure-specific patterns. Liquid insecticide vapors primarily affect tubular function, evidenced by extensive hyaline droplet accumulation indicating impaired protein reabsorption. Mat-based formulations produce milder changes, primarily limited to vascular congestion and focal tubular necrosis. The differential toxicity likely reflects variations in metabolite profiles produced through different exposure routes [43].

Antioxidant intervention studies demonstrate partial protection against pyrethroid nephrotoxicity. Animals treated with AA/E307 combinations show preserved glomerular structure and reduced tubular damage, particularly in mat-based exposure groups. However, complete protection isn't achieved, suggesting additional mechanisms beyond oxidative stress. Electron microscopy reveals mitochondrial swelling in renal tubular cells, supporting the role of energy metabolism disruption in pyrethroid nephrotoxicity [43].

Immunohistochemical studies show increased expression of kidney injury molecule-1 (KIM-1) in damaged tubules, confirming the regenerative response to injury. The persistence of these markers in chronic exposure models suggests potential for long-term renal dysfunction. These findings have important implications for populations with repeated pyrethroid exposure, particularly in agricultural and pest control occupations where renal function monitoring may be warranted [43].

8. INTEGRATED ANALYSIS OF ORGAN TOXICITY MECHANISMS

The histopathological evidence across multiple organ systems reveals consistent patterns of pyrethroid toxicity. A primary mechanism involves oxidative stress generation through several pathways: (1) direct redox cycling of pyrethroid metabolites, (2) mitochondrial dysfunction with reactive oxygen species (ROS) overproduction, and (3) depletion of endogenous antioxidants like glutathione. These effects are particularly pronounced in metabolically active tissues like liver, heart, and kidneys [41-43].

Another unifying feature is the route-dependent toxicity, with inhalation exposure causing more severe damage than other routes. This likely reflects both the efficiency of pulmonary absorption and the generation of unique metabolites through lung metabolism. The combustion products from mosquito coils appear particularly toxic, suggesting that pyrolysis may generate additional harmful compounds beyond the parent pyrethroids [41].

The differential susceptibility of organ systems provides insights into pyrethroid toxicokinetics. The liver shows early and severe damage due to its role in xenobiotic metabolism, while cardiac and renal effects may manifest later as circulating metabolites accumulate. This temporal pattern suggests that standard acute toxicity assessments may underestimate potential harm from chronic, low-level exposures [42, 43].

The partial protection afforded by antioxidants supports oxidative stress as a key mechanism, while the incomplete reversal indicates additional pathways. These may include: (1) direct membrane disruption by lipophilic pyrethroids, (2) interference with ion channels (particularly in excitable tissues), and (3) epigenetic modifications altering gene expression patterns. Further research is needed to elucidate these non-oxidative mechanisms [41-43]. These findings have important implications for risk assessment and management. Current safety evaluations focusing primarily on acute neurotoxicity may need expansion to include

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chronic organ toxicity endpoints. The identification of particularly vulnerable populations - including those with pre-existing liver, heart or kidney

9. FUTURE DIRECTIONS

The growing body of evidence on pyrethroid neurotoxicity underscores the need for targeted research to address critical knowledge gaps. Future studies should prioritize elucidating the differential sensitivity of mammalian sodium channel isoforms (e.g., Nav1.3 in developing brains vs. Nav1.6 in adults) to pyrethroids, which could explain age-specific vulnerabilities. Advanced in vitro models, such as human-induced pluripotent stem cell (iPSC)-derived neurons, may provide deeper insights into developmental neurotoxicity mechanisms. Additionally, the role of pyrethroids in epigenetic modifications—such as DNA methylation and histone acetylation—in neurodegenerative pathways warrants exploration, as these effects could underlie long-term cognitive impairments. Another key area is the cumulative impact of mixed pyrethroid exposure, as humans are often exposed to multiple compounds simultaneously. Synergistic or additive effects on ion channels and neurotransmitter systems remain poorly understood. High-throughput screening and computational modeling could help predict these interactions and refine risk assessment frameworks. Furthermore, epidemiological studies should investigate low-dose chronic exposure in vulnerable populations, including pregnant women and children, to establish safer exposure thresholds. Developing mitigation strategies is equally urgent. Biodegradable pyrethroid alternatives, such as biopesticides (e.g., neem extracts or Bacillus thuringiensis toxins), and nanotechnology-based delivery systems could reduce environmental persistence and non-target toxicity. Pharmacological interventions targeting oxidative stress and neuroinflammation—such as antioxidants (e.g., N-acetylcysteine) or calcium channel blockers—may alleviate pyrethroid-induced neurotoxicity and should be tested in preclinical models. Regulatory policies must evolve to incorporate neurodevelopmental endpoints in safety evaluations, mirroring the EPA's guidelines for organophosphates. Global harmonization of pyrethroid regulations, particularly in developing nations where usage remains high, is essential to minimize health disparities. Public awareness campaigns on safer handling practices and biomarkers of exposure (e.g., urinary 3-phenoxybenzoic acid) could empower at-risk communities. The interdisciplinary collaboration among toxicologists, neuroscientists, and policymakers will be pivotal in translating research into actionable solutions, ensuring both agricultural efficacy and public health safety.

10. CONCLUSION

Pyrethroid insecticides, while effective in pest control, pose significant neurotoxic risks to humans and non-target organisms. Their primary mechanism involves disrupting voltage-gated sodium channels, leading to prolonged neuronal excitation and secondary effects on calcium and chloride channels. The dichotomy between Type I (tremor-inducing) and Type II (CS-syndrome) pyrethroids reflects their structural differences and varying toxicological profiles. Despite their lower acute toxicity in mammals compared to insects, chronic exposure—especially during critical developmental stages—is linked to cognitive deficits, endocrine disruption, and organ damage. The heightened sensitivity of developing brains to pyrethroids, attributed to the expression of susceptible sodium channel isoforms like Nav1.3, underscores the need for stringent exposure guidelines for pregnant women and children. Beyond neurotoxicity, pyrethroids contribute to environmental persistence and bioaccumulation, necessitating sustainable alternatives. While regulatory measures have restricted certain compounds, the continued use of pyrethroids in agriculture and household products demands vigilant monitoring. Future research should prioritize elucidating the long-term effects of low-dose exposure, interactions in mixed-pesticide scenarios, and the potential for epigenetic alterations. Innovations in biopesticides and targeted drug therapies may offer safer solutions. In summary, a balanced approach is essential—one that acknowledges the agricultural benefits of pyrethroids while mitigating their health risks through advanced research, robust regulatory frameworks, and public education. Only through interdisciplinary efforts can we ensure the safe use of these compounds without compromising neurological and environmental health.

DECLARATIONS

Ethical Approval

We affirm that this manuscript is an original work, has not been previously published, and is not currently under consideration for publication in any other journal or conference proceedings. All authors have reviewed and approved the manuscript, and the order of authorship has been mutually agreed upon.

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Conflicts of Interest

The authors declare that they have no financial or personal interests that could have influenced the research and findings

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presented in this paper. The authors alone are responsible for the content and writing of this article.

Authors' contributions

All authors contributed equally to this work.

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ABOUT THE AUTHORS

Mohammad Zaid Khan is a research scholar at Aligarh Muslim University, working under the guidance of Prof. Shahid Bin Zeya. His Ph.D. research focuses on "Systematic studies on some Indian genera of the family Mymaridae (Hymenoptera: Chalcidoidea) with molecular analysis of some taxa". He has qualified several prestigious exams, including DBT-JRF 2024, GATE 2022 & 2023, along with multiple national-level Ph.D. entrance tests. His work blends classical taxonomy with molecular tools to explore insect biodiversity in India.

Faiqua Haque is a Research Scholar at Aligarh Muslim University, pursuing a Ph.D. under the supervision of Prof. G. G. H. A. Shadab. The topic of her research work is "Evaluation of toxic effects of potent Copper based chemotherapeutic drug entity: An *in vitro* and *in vivo* investigations and its amelioration by natural antioxidant". Her area of research is Molecular toxicology and Genotoxicity. She obtained her Master of Science Degree from the Department of Zoology, Aligarh Muslim University, Aligarh in 2020 and is also the recipient of the prestigious Gold Medal for academic achievement both in M.Sc. and B.Sc.

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