

Biomarkers of Type II Pyrethroid Toxicity: A Review

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ABSTRACT

Presently, the most commonly used pesticides exhibiting neurotoxic effects are synthetic pyrethroids, especially the Type II pyrethroids (e.g. deltamethrin, cypermethrin, cyfluthrin, cyhalothrin, and fenvalerate). Although the toxicity of these substances to humans and other mammals is generally modest, their effects on the environment and human health are nonetheless concerning, particularly in light of their ability to interfere with the operation of the nervous system. The purpose of this review is to investigate the biomarkers linked to Type II pyrethroid-induced toxicity in rats, a crucial animal model for evaluating the effects of pesticides and other environmental toxicants. Among the biomarkers discussed are biochemical signs of oxidative stress (like glutathione depletion and lipid peroxidation), neurochemical changes (such as changes in sodium channels and acetylcholinesterase activity), genotoxic markers (such as chromosomal aberrations, nuclear abnormalities, and the micronucleus test), hematological changes, hepatotoxicity biomarkers, and reproductive toxicity biomarkers. Additionally, because these biomarkers shed light on the functional effects of exposure, behavioural indicators including motor coordination and cognitive performance are also discussed. Early identification, risk assessment, and management of pyrethroid toxicity all depend on an understanding of these indicators. This review article summarizes the state of current knowledge regarding the biomarkers of type II pyrethroid induced toxicity in rats and provides a thorough framework for further investigation and regulatory assessment.

Keywords: Synthetic pyrethroids, biomarkers, Oxidative stress, acetylcholinesterase, neuro-behavioural toxicity, hepatotoxicity, genotoxicity, hematological alterations, reproductive toxicity.

1. INTRODUCTION

During past several decades human species has made tremendous progress, but these advancements have come with major environmental concerns such the widespread use and discharge of pesticides,

fertilizers, heavy metals, pharmaceuticals and several other contaminants. Pesticides are frequently employed to control the bug infestation and weeds in fields, as well as a range of pests and disease-carrying organisms (such as rats, mice, ticks, and

mosquitoes) in workplaces, homes, shopping centres and public areas. By lowering vector-borne illnesses and shielding crops from pests, pesticides improve human welfare. The most often used pesticides for industrial, residential, and agricultural pest management are insecticides.

Nevertheless, certain pesticides like synthetic pyrethroids, which are analogues of natural pyrethrin, remain in the environment and cause multiple negative impacts on organisms that are not their intended targets.^[1] Most of the commercial domestic insecticides utilized are synthetic pyrethroids because of their quick insect knockdown action, minimal harm to mammals, and rapid breakdown in the environment.^[2]

Synthetic pyrethroids have their source from naturally occurring pyrethrins, which are obtained from the pyrethrum of dried *Chrysanthemum* flowers.^[3] Ketoalcoholic esters of chrysanthemic and pyrethroic acids, which are highly lipophilic and may quickly enter insect pest bodies to cause toxicosis, are responsible for insecticidal effects of pyrethrins. However, the pyrethrins found in nature are highly photosensitive and break down within some duration before the body of insects accumulate enough of them to kill them. Over the past 20 years, there have been intriguing advancements in the modification of structure, stereochemistry, and formulations to create thousands of contemporary pyrethroids with chemical and biological characteristics appropriate for use in agriculture. These changes include adding a cyano group to the alcohol moiety and halogenating the pyrethrin molecule's cyclopropane side chain ^[4], combination of optical and geometric isomers, as well as formulations of the technical grade compound with solvents and carriers that contain 85% or more of the active components.

Alpha-cyano pyrethroids are known as type II pyrethroids, while non-cyano pyrethroids are classified as type I pyrethroids. Only the

α -cyano substituent is responsible for the toxic nature of type II pyrethroids, making them more powerful neurotoxins than type I (non-cyano) pyrethroids. Due to their comparatively minimal threat to mammals and birds, synthetic pyrethroid pesticides, particularly type II compounds are widely utilized in pest management worldwide.^[5]

Despite being deemed "safer," synthetic pyrethroids can't be considered as innocuous because reports have shown that they are hazardous to a variety of exposed creatures.^[6,7] Ingestion of food carrying pesticide residues, inhalation of dust and contaminated air, and skin contact are some of the ways that the general public is exposed to pyrethroids.^[8] There are certain studies that show samples of human milk and urine contain pyrethroids and their metabolites.^[9] Thus, pyrethroids directly endanger human health. The male reproductive system, liver, kidneys, and neurological system have all been reported to be negatively impacted by pyrethroids.^[10] Therefore, it is essential to assess the present state of the several biomarkers that are used to identify the harmful effects of type II synthetic pyrethroids.

A change in the way the body responds that could be connected to exposure to or the negative effects of environmental pollutants is called a biomarker. The reaction of being exposed to any kind of contaminant or chemical, toxicant, or other foreign particle is shown by biomarkers. It is possible to assess biomarkers at the molecular, cellular, community, or ecological level. Through morphological, anatomical, histopathological, hematological, physiological, and biochemical profiles, these biomarkers can significantly indicate the harmful effects of the toxicant on the exposed organism, including toxicities on its neurology that result in changed behaviour.^[1,5]

This review article aims to provide an overview of the biochemical and physiological biomarkers caused by type II pyrethroid toxicity in rats, pinpointing the characteristics that have been proven to be

unmistakable biomarkers of these pesticides.

Table 1. Common Type II Synthetic Pyrethroids

Type II Pyrethroid	Applications	Major Human Exposure Routes	Primary Target Organs (Experimental Evidence)	Toxic Effects
Deltamethrin	Agriculture, household insecticides, malaria vector control (Narahashi, 2009 ^[11] ; Saillenfait et al., 2015) ^[8]	Oral (food residues), dermal, inhalation (Barr et al., 2010 ^[9] ; Saillenfait et al., 2015) ^[8]	Brain, liver, kidney, testes (Zhang et al., 2021 ^[12] ; Zhu et al., 2020) ^[7]	Oxidative stress, neurotoxicity, hepatotoxicity, nephrotoxicity, reproductive toxicity (Zhu et al., 2020) ^[7]
Cypermethrin	Crop protection, veterinary medicine, household pest control (Saillenfait et al., 2015 ^[8] ; Cycoń & Piotrowska-Seget, 2016) ^[13]	Oral, dermal, inhalation (Barr et al., 2010 ^[9] ; Saillenfait et al., 2015) ^[8]	Liver, kidney, brain, testes (Soliman et al., 2015 ^[14] ; Ullah et al., 2019) ^[1]	Oxidative stress, endocrine disruption, reproductive toxicity, neurotoxicity (Ullah et al., 2019 ^[1] ; Zhu et al., 2020) ^[7]
Fenvalerate	Agricultural insecticide for cereals, cotton and vegetables (Laskowski, 2002 ^[15] ; Cycoń & Piotrowska-Seget, 2016) ^[13]	Oral and dermal exposure (Saillenfait et al., 2015) ^[8]	Liver, brain, reproductive organs (Misra & Sharma 1997 ^[16] ; Arena et al., 2008) ^[17]	Hepatic injury, oxidative stress, neurotoxicity, reproductive toxicity (Misra & Sharma 1997 ^[16] ; Arena et al., 2008) ^[17]
Lambda-cyhalothrin	Agriculture, household pest control, public health vector management (Saillenfait et al., 2015 ^[8] ; He et al., 2008) ^[18]	Oral, dermal, inhalation (Barr et al., 2010 ^[9] ; Saillenfait et al., 2015) ^[8]	Brain, liver, kidney (Fetoui et al., 2010 ^[19] ; Zhu et al., 2020) ^[7]	Neurotoxicity, oxidative stress, hepatotoxicity, nephrotoxicity (Fetoui et al., 2010 ^[19] ; Zhu et al., 2020) ^[7]
β-Cyfluthrin	Agriculture and structural pest management (Saillenfait et al., 2015) ^[8]	Oral, inhalation, dermal (Saillenfait et al., 2015) ^[8]	Brain, liver, kidney (Breckenridge et al., 2009) ^[20]	Neurotoxicity, oxidative damage, liver dysfunction (Breckenridge et al., 2009) ^[20]

2. Type II Pyrethroids: Sources and Exposure

The presence of α -cyano (α -CN) group in the Type II pyrethroids confers them greater insecticidal potency, environmental persistence, and neurotoxicity. Common Type II pyrethroids include deltamethrin, cypermethrin, cyfluthrin, fenvalerate, esfenvalerate, λ -cyhalothrin, cyhalothrin, fenpropathrin, and cyphenothrin (**Table 1**).

2.1 Sources of Exposure:

The extensive use of Type II pyrethroids has made human exposure to these compounds almost inevitable. They are ubiquitously present, being used in domestic settings, agriculture, in mosquito coils and vaporizers, aerosols, termite control

formulations, veterinary ectoparasite treatments, and public health vector-control programs. As a result the residues of pyrethroids have been detected in several food items like fruits and vegetables, milk, meat, surface water and household dust.^[21,22]

2.2 Routes of Human Exposure:

Humans are generally exposed to Type II pyrethroids through oral, dermal and inhalational routes. The general population is most commonly exposed orally by consuming contaminated food and water. Severe poisoning characterized by seizures, nausea, vomiting, respiratory problems have been reported following accidental ingestion of concentrated formulations.^[23] The

exposure of agricultural workers and pesticide applicators mainly occurs dermally, the lipophilic nature of pyrethroids make them penetrate the skin. Local symptoms such as burning, itching, tingling, numbness, and paresthesia are common following dermal contact. Inhalational exposure occurs during pesticide spraying, indoor fogging, aerosol application, and occupational handling. Inhaled pyrethroids are rapidly absorbed through the respiratory tract and may produce respiratory irritation together with systemic neurological symptoms in cases of high exposure. [24]

Children constitute a particularly vulnerable population because of their frequent contact with contaminated floors, household dust, and treated surfaces, coupled with immature detoxification systems and ongoing neurological development. Prenatal exposure through placental transfer and postnatal exposure through breast milk have also been reported, raising concerns regarding developmental neurotoxicity. [25]

3. Biomarkers of Pyrethroid Toxicity:

3.1 Oxidative Stress and antioxidant enzyme activity:

The imbalance of oxidation and antioxidation caused by the production of excess reactive oxygen species (ROS) and free radicals, such as hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{\bullet -}$), hypochlorous acid ($HOCl$), hydroxyl radical ($HO^{\bullet}$), and hydroperoxyl radical ($HOO^{\bullet}$), as well as Reactive Nitrogen Species (RNS), like peroxyxynitrite, and nitric oxide synthase (NOS)-catalyzed nitric oxide (NO), [26,27] is known as oxidative stress.

The extensive and indiscriminate use of pyrethroids has contaminated many environmental areas, increasing the likelihood that they will bioaccumulate in food items. [28] Because they are lipophilic, they can bioaccumulate in membranes and develop ROS, which causes oxidative damage in animals. [29,30]

Reactive oxygen species induced lipid peroxidation is a prevalent indicator of

oxidative stress by toxicants. The characteristics of biological membranes can be altered by lipid peroxides, which can ultimately lead to cellular membrane damage. [31] Malondialdehyde (MDA), a byproduct of lipid peroxidation brought on by free radicals, is the most often used parameter for lipid peroxidation. [5]

It has been observed that the harmful effects of cypermethrin (CYP), a type II synthetic pyrethroid are caused by the generation of ROS. CYP causes oxidative stress in animal models, as evidenced by elevated oxidative stress indicators and decreased antioxidant activity. [32] Malondialdehyde (MDA), lipid hydroperoxides (LOOH), and advanced oxidized protein products (AOPP) were among the oxidative stress markers that increased in the kidney and liver of rats after 14 days of oral CYP treatment. This resulted in a reduction of glutathione and antioxidant capacity. While catalase and glutathione peroxidase activities declined, superoxide dismutase activity rose. Lipid peroxidation brought on by CYP caused damage to the liver and kidney tissues. The cytochrome P450 microsomal mechanism metabolizes CYP while producing oxidative stress at the same time. [33] Because CYP is lipophilic, it can readily penetrate the lipid bilayer and compromise the integrity of cells. [34] Bhushan *et al.*, 2013 [35] have documented histological changes in liver tissue of CYP-exposed animals.

Deltamethrin generates ROS and RNS, which results in oxidative stress injury. According to an *in vitro* study, deltamethrin has the capacity to harm rat primary hepatocytes through oxidative stress by causing cell death and the formation of ROS at doses of 1 and 5 μM . [36] According to studies, rats exposed to deltamethrin (0.6 mg/kg b.w.) experience neurotoxicity, with NO generation playing a major role in this toxic impact. The oxidative damage and neurotoxicity of deltamethrin were revealed to be significantly correlated by the study of Galal *et al.*, (2014) [37]; Ogaly *et al.*, (2015) [38].

In both aquatic and terrestrial animals antioxidant status is impacted by deltamethrin, it affects both antioxidant enzymes (glutathione S-transferase (GST), glutathione peroxidase (GPx), catalase (CAT), superoxide dismutase (SOD) and glutathione reductase (GR) and non-enzymatic antioxidants (reduced thiols, ascorbic acid (AsA) and glutathione (GSH)). As indicators of oxidative damage, metallothioneins and CYP450 enzymes are essential for detoxification. Vitamin E and glutamine are two antioxidant components included in dietary supplements that can help reduce the damage caused by deltamethrin-induced oxidative stress.^[39]

Following the administration of lambda-cyhalothrin, oxidative stress in the liver, concentrating on hepatic ROS concentrations and antioxidant enzymes SOD, GR, GPx, and GST were evaluated in a study. The antioxidant enzyme SOD, which is mostly found in the mitochondrial matrix, and the GR enzyme, which is engaged in glutathione's oxidation-reduction (redox) cycle, were found to be elevated in the results, although ROS and SOD levels were unaffected. GPx activity dropped 1.33 times, while GST activity, a crucial detoxifying enzyme that catalyzes the association of different electrophiles, dropped 1.47 times. Rats given various pyrethroid treatments also showed similar results.^[40]

In a similar study, exposure of rats to lambda-cyhalothrin, for a period of 3 weeks caused a significant increase in protein carbonyl levels and kidney MDA levels as compared to controls. The activities of antioxidant enzymes; catalase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase and superoxide dismutase were also found to be significantly decreased due to lambda-cyhalothrin exposure.^[19]

Proteins, lipids, DNA, and antioxidant enzymes can all suffer significant damage from oxidative stress. One of the most widely utilized biomarkers of protein oxidation is protein carbonyl content (PCC).^[41] Numerous medical conditions,

such as diabetes, inflammatory bowel disease, arthritis, and Alzheimer's disease, have been linked to PCC accumulation.^[42]

3.2 Apoptotic Biomarkers:

Programmed cell death, also known as apoptosis, is a highly controlled physiological process that eliminates damaged or malfunctioning cells while preserving tissue homeostasis. There is growing evidence that apoptosis plays a significant role in the toxicity of Type II pyrethroids, especially in the reproductive organs, liver, kidney, and neurological system. Deltamethrin, cypermethrin, lambda-cyhalothrin, and fenvalerate are examples of Type II pyrethroids that cause excessive oxidative stress, mitochondrial dysfunction, calcium overload, and neuroinflammation. These factors together trigger intrinsic and, to a lesser extent, extrinsic apoptotic pathways.^[4,43-45] As a result, proteins linked to apoptosis have become useful biomarkers for evaluating pyrethroid-induced cellular damage.

➤ **Caspase-3:** Caspase-3 is the key executioner caspase that mediates proteolytic cleavage of proteins during apoptosis, leading to chromatin condensation, DNA fragmentation, membrane blebbing and the formation of apoptotic bodies. Studies show increased caspase-3 activity in the brain, liver, kidneys, and testes of rodents exposed to deltamethrin and cypermethrin, indicating substantial apoptotic cell death.^[44,46,47]

➤ **Caspase-9:** Caspase-9 initiates the mitochondrial apoptotic pathway. Oxidative stress induced by Type II pyrethroids disrupts mitochondrial membrane integrity, causing cytochrome c release into the cytoplasm. Cytochrome c binds apoptotic protease activating factor-1 (Apaf-1), forming the apoptosome, which activates caspase-9, leading to caspase-3 activation.^[4,45,47] Thus, elevated caspase-9 expression indicates early mitochondrial-mediated apoptosis.

- **Bax and Bcl-2:** The B-cell lymphoma-2 (Bcl-2) family of proteins influences mitochondrial membrane permeability and apoptosis susceptibility. The pro-apoptotic protein Bax increases mitochondrial outer membrane permeability, while the anti-apoptotic protein Bcl-2 inhibits cytochrome c release. Type II pyrethroid exposure raises Bax expression and lowers Bcl-2 expression, resulting in a higher Bax/Bcl-2 ratio, a known biomarker for apoptotic commitment. [46-49] Elevated Bax/Bcl-2 ratios are linked to neuronal degeneration, hepatocellular injury, renal tubular damage, and germ cell apoptosis.
- **Cytochrome c:** Cytochrome c is vital for the mitochondrial electron transport chain and, during oxidative stress, it translocates from mitochondria to the cytosol, triggering apoptosome formation and activates downstream caspases. Elevated levels of cytosolic cytochrome c were observed after exposure to deltamethrin and cypermethrin, serving as indicators of mitochondrial dysfunction and apoptosis. [4,45,49]
- **Poly ADP-ribose Polymerase (PARP):** PARP-1 is a nuclear enzyme essential for DNA repair and genomic stability. During apoptosis, caspase-3 cleaves PARP, disrupting DNA repair and promoting cell death. Elevated levels of cleaved PARP have been observed in pyrethroid toxicity models, signifying irreversible apoptotic damage. [45,47]
- **p53:** The tumor suppressor protein p53 is activated by oxidative DNA damage and cellular stress, leading to the transcription of pro-apoptotic genes like Bax and suppression of anti-apoptotic genes such as Bcl-2, promoting mitochondrial apoptosis. Elevated p53 levels have been observed in neuronal and hepatic tissues after exposure to Type II pyrethroids, serving as a key biomarker connecting oxidative stress with apoptotic signalling. [47,48]
- **DNA fragmentation:** DNA fragmentation is a key event in apoptosis, activated by reactive oxygen species from pyrethroid exposure, leading to chromosomal DNA cleavage. It is assessed through terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL), DNA ladder, and comet assays. Increased TUNEL-positive cells have been found in various organs, including the hippocampus and liver, in animals exposed to Type II pyrethroids, indicating significant apoptotic cell death. [46,49]

Table 2. Apoptotic Biomarkers of Type II Pyrethroid Toxicity

Biomarker	Role in apoptosis	Effect following exposure to pyrethroids	Significance	References
Caspase-3	Executioner caspase	Increases	Final apoptosis mediator	[44,46,47]
Caspase-9	Initiator caspase	Increases	Indicates activation of mitochondrial apoptotic pathway	[4,45,47]
Bax	Pro-apoptotic protein	Increases	Promotes release of cytochrome c	[46-49]
Bcl-2	Anti-apoptotic protein	Decreases	Reduced cell survival	
Bax/Bcl-2 ratio	Maintains balance between survival and apoptosis	Increases	Indicates apoptotic commitment	
Cytochrome c	Mitochondrial electron transport protein	Cytosolic release increases	Indicates mitochondrial membrane damage	[4,45,49]
PARP (cleaved)	DNA repair enzyme	Increases	Indicates irreversible apoptosis	[45,47]
p53	DNA damage response protein	Increases	Promotes apoptosis following oxidative stress	[47,48]
DNA fragmentation	End-stage apoptotic event	Increases	Confirms apoptotic cell death	[46,49]

3.3 Alterations in Sodium channels:

Synthetic pyrethroids are neurotoxins, their main target of toxicity being receptor site of voltage gated sodium channels.^[50] By attaching themselves to sodium channels and causing excitatory paralysis, they kill insects. Additionally, they alter the membrane potential, which makes nerve cells hyperexcitable in an unusually stable condition. These changes cause insects to undergo "knockdown," an incapacitating effect that is not fatal.^[51]

Long-term opening of voltage-sensitive sodium channels, which interferes with their gating properties associated with depolarization and recurrent firing, is the main way that pyrethroids cause neurotoxicity. Compared to type I pyrethroids, type II pyrethroids have been shown to maintain the channel open for a longer period of time. Pyrethroids may also impact voltage-gated calcium channels, Gamma-aminobutyric acid (GABA) receptors, chloride channels, and the mitochondrial electron transport chain in addition to sodium channels.^[52]

Type II pyrethroids with an α -cyano group cause neurotoxicity in rats by interfering with GABAergic neurotransmission and changing the expression of cytochrome P450 in the brain and liver.^[53,54] Cl flux is reduced and inhibitory neural input is eliminated by blocking GABA receptors, which has an indirect neuroexcitatory effect.^[55]

Research on the molecular mechanisms behind knockdown resistance (kdr), a primary type of insect resistance to pyrethroids, has significantly enhanced comprehension of the molecular interactions between pyrethroids and sodium channels.^[56] In a study by Du *et al.*, (2008),^[57] it was suggested that intracellular linker that connects domains II and III of the cockroach sodium channel, contains a residue G1111 and two positively charged lysines immediately downstream of G1111 that are specifically involved in the action of type II pyrethroids. G1111 deletion, which results from alternative splicing, decreased

sodium channel sensitivity to type II pyrethroids. These results provide a molecular understanding of how type II pyrethroids interact with the sodium channels.

Calcium and chloride channels are secondary targets of pyrethroid neurotoxicity.^[20] Taylor-Wells *et al.*, (2015)^[58] have documented that GABA-gated chloride channels are bound by type II pyrethroids, including deltamethrin and cypermethrin, which block them. Several studies have shown that it raises the risk of neurodegenerative illnesses because it blocks nerve impulses by changing the kinetics of ligand-gated ion channels and voltage-sensitive sodium channels (GABA receptors, nicotinic acetylcholine receptors, and glutamate receptors).^[59] Deltamethrin reduces AChE activity by decreasing the acetylcholine binding area at the aromatic, hydrophobic surface of AChE, most likely as a result of its lipophilic nature.^[60]

3.4 Acetylcholinesterase activity:

Inhibition of acetylcholinesterase, an enzyme that hydrolyzes the neurotransmitter acetylcholine, causes toxicity in humans and animals by causing acetylcholine to accumulate in synapses or neuromuscular junctions, which are biomarkers for environmental contamination. Acetylcholinesterase (AChE) release is variably modulated by deltamethrin (type II) in the cortical and hippocampal regions of Wistar rats. The most frequent neurotoxic effect of deltamethrin in exposed rats is acute neurotoxicity, which is mainly caused by suppression of AChE catalytic activity in central and peripheral neurons.^[61]

Acetylcholine (ACh), the main neurotransmitter in peripheral and central cholinergic systems, is regulated by the enzymes AChE and choline acetyltransferase (ChAT), which are critical for the cholinergic system operation. A study on beta-cyfluthrin reported detrimental effects on rats' spatial memory, indicating a connection between spatial memory and hippocampus choline acetyltransferase activity.^[6]

Kale *et al.* (1999) [62] too observed significant decreases in serum and erythrocyte AChE activity following treatment with fenvalerate and cypermethrin. Increased oxidative stress brought on by pyrethroids may be linked to the cholinergic dysfunction manifested by changes in AChE activity. [6]

Work by Singh *et al.*, (2014) [63] suggested that, neurotoxicity associated with cypermethrin may include reduced antioxidant defense, free radical formation, and inhibition of AChE activity. Exposure to cypermethrin in rats leads to overt cholinergic activity, such as salivation, muscle twisting followed by tremors, and water thirst, indicating impairment in AChE activity in brain.

3.5 Neurobehavioral alterations:

While type II pyrethroids cause Choreoathetosis with Salivation (CS)-syndrome, which is marked by a rise in pawing and burrowing activities, accompanied by tremors throughout the body and excessive salivation, and a "sinuous writhing" motion known as choreoathetosis, type I pyrethroids are known to cause T-syndrome of poisoning, which is characterized by tremors. [64]

In rats and mice, developmental exposure to deltamethrin has been shown to impair cognitive function. Early exposure to deltamethrin has been demonstrated to produce long-lasting effects on dopamine, apoptosis, learning and memory, acoustic startle, and locomotor activity. [65]

Acute clinical manifestations of neurotoxicity, including cognitive function, motor coordination, and sensory responsiveness [66,67] resulting from pyrethroid exposure, have been extensively documented by. [68] According to studies, pyrethroid exposure causes neurological illnesses like dementia, Parkinson's, and Alzheimer's, perhaps as a result of toxicity brought on by oxidative stress. Prolonged exposure to pyrethroid pesticides may have a negative impact on the central nervous system (CNS), resulting in a variety of subjective symptoms and a decline in

neurocognitive function. [69] Because the hippocampus, which is in charge of memory and learning, has been damaged as a result of pyrethroid treatment, discrimination index and spontaneous alternation have reduced thereby resulting in dementia in rats. [70]

According to a recent study, in adult male Wistar rats, repeated oral exposure to cypermethrin (5, 20, and 80 mg/kg/day for 30 days) was shown to dramatically impair learning and memory. In the Morris water maze, treated rats showed longer escape latency; in the elevated plus maze, they showed anxiety-like behavior; and in the Morris water maze, they showed decreased novel object identification and impaired passive avoidance memory. Pyrethroid exposure-induced neurotoxicity and cognitive impairment were linked to these behavioral abnormalities. [71] This reduction in learning capacity and memory caused by pyrethroids may be linked to oxidative stress and neurochemical alterations in hippocampus region of brain as reported by Sinha *et al.* (2006). [72]

The functional effects of pyrethroid exposure in adult rodents include decreased grip strength (pyrethrum, bifenthrin, S-bioallethrin, permethrin, β -cyfluthrin, cypermethrin, and deltamethrin), altered locomotor activity, impaired rotarod performance (deltamethrin and α -cypermethrin), decreased schedule-controlled operant responding (allethrin, permethrin, cis-permethrin, deltamethrin, cypermethrin, and fenvalerate), and altered startle reflexes, including increased acoustic startle (Type I pyrethroids) or decreased acoustic startle amplitude (Type II pyrethroids). [67,73]

Using the Elevated Plus Maze (EPM), Open Field Test (OFT), and neurochemical investigations, Ricci *et al.* (2013) [74] examined the neurobehavioral effects of deltamethrin in adult rats. Without impairing motor coordination, deltamethrin administration (1, 3, and 10 mg/kg) significantly increased anxiety-like behavior, as shown by decreased entry into

and time spent in the EPM's open arms. Altered striatal serotonergic neurotransmission were found by neurochemical analysis, indicating that deltamethrin-induced behavioral abnormalities are linked to disruptions in central neurotransmitter systems.

In a similar investigation, rats received a 5µg intracerebroventricular dosage of deltamethrin. Both spatial working memory impairment (spontaneous alternation task) and increased locomotor activity (open field) were noted. Alongside these changes, there was a decrease in tyrosine hydroxylase (TH) immunoreactivity in the dorsal striatum, ventral tegmental area (VTA), and substantia nigra pars compacta (SNpc). According to the findings, deltamethrin may disrupt the dopaminergic system, resulting in hyperactivity and cognitive changes. [75]

Syed *et al* (2016) [6], reported that exposure to beta-cyfluthrin impairs spatial memory and motor coordination. Rats who received treatment showed reduced levels of dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), epinephrine (EPN), and

serotonin (5-HT) in frontal cortex, corpus striatum, and hippocampus. Beta-cyfluthrin also decreased the activity of AChE in all regions of the brain. Additionally, there was a decrease in the expression of choline acetyltransferase in the hippocampus. Additionally, the antioxidant defense system was compromised; the treated rats showed clearly reduced levels of the antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT).

In a similar study, rats were given 20 mg/kg body weight of cyfluthrin orally for six days, mild movement incoordination and skeletal muscle contraction in the hind limbs was observed. Furthermore, in the brain regions: hypothalamus, midbrain, hippocampus, striatum, and prefrontal cortex, cyfluthrin at dose levels of 5, 10, and 20 mg/kg body weight resulted in a dose-related statistically significant drop in dopamine and its metabolites dihydroxyphenyl acetic acid and homovanillic acid (HVA) as well as in serotonin and its metabolite 5-HIAA. [76]

Table 3. Behavioral biomarkers associated with Type II pyrethroid toxicity

Behavioral biomarker	Behavioural tests used	Major behavioural manifestations	Mechanisms involved	References
Locomotor activity	Open-field	Hyperactivity (acute), hypoactivity (chronic), reduced exploration	Sodium channel dysfunction, altered dopamine and glutamate signalling	[66-68, 74,75]
Anxiety-like behavior	Elevated plus maze, light-dark box, open-field test	Anxiety, reduced open-arm exploration, increased freezing	Oxidative stress, neuroinflammation, altered GABA and serotonin levels	[71,73,74]
Learning and memory	Morris water maze, Y-maze, passive avoidance, novel object recognition	Impaired spatial learning, poor memory retention, reduced recognition	Hippocampal oxidative damage, cholinergic dysfunction	[65,70-72, 75]
Motor coordination	Rotarod, beam walking, grip strength, wire-hang	Tremors, impaired balance, reduced motor performance	Cerebellar dysfunction, neuronal hyperexcitability	[64,67,68]
Cognitive deficits	Barnes maze, T-maze, touchscreen tests	Deficits in attention, executive function, cognitive flexibility	Synaptic dysfunction, neuroinflammation, mitochondrial damage	[65,67,69,70]

3.6 Genotoxicity:

The most widely used indicators of genotoxicity are nuclear abnormalities (NA), chromosomal aberrations (CA), and the micronucleus test (MN). [5]

Pyrethrin has been reported to be genotoxic to human cultured lymphocytes, as demonstrated by the 8-hydroxy-2-deoxyguanosine (8-OHdG) biomarker and sister chromatid exchange (SCE) assay.

SCEs were significantly elevated by pyrethrin, in a dose-dependent manner. Therefore, pyrethrin exposure may be linked to DNA damage in addition to respiratory and neurological harm. The significant increase in the oxidative stress biomarker 8-OHdG suggests that this damage may be the result of oxidative stress brought on by pyrethrin.

In rats, cypermethrin, damaged astrocytes by altering Ca (++) and generating reactive oxygen species, which in turn triggered the production of P38 matrix metalloproteinase and JNK.^[77]

Another type II pyrethroid lambda-cyhalothrin has been shown to damage chromosomes in a dose-dependent manner along with an elevation in the number of micronucleated erythrocytes in bone marrow cells.^[78]

Taha *et al* (2021)^[41] demonstrated that rats given cypermethrin had the most brain DNA damage, which was followed by an increase in lipid peroxidation and the activation of antioxidant enzymes. After 28 days of oral exposure, elevated levels of 8-hydroxy-2-deoxyguanosine, a kind of oxidative stress caused by free radicals in nuclear and mitochondrial DNA, were seen in the liver and urine.

Sub-acute oral exposure of adult male Wistar rats to α -cypermethrin at daily doses of 2.186, 0.015, 0.157, and 0.786 mg/kg bw to for 28 days induced significant primary DNA damage in peripheral blood leukocytes, liver, kidney, and brain cells. The brain showed a substantial rise in both GPx activity and the quantity of thiobarbituric acid reactive species. All α -cypermethrin-treated groups showed an increase in GPx activity in their livers, but their blood GPx activity was much lower than that of the controls. The kidney and liver showed a decline in ChE activity as well. At nearly all tested doses, α -cypermethrin exposure caused considerable DNA damage in a variety of cell types, with the brain being the most vulnerable organ.^[79]

In yet another study, beta-cyfluthrin has been reported to cause DNA damage. Increase in the level of MDA and reduction in the activity of CAT and SOD was observed. The generation of free radicals and oxidative metabolites during intense hepatic metabolism may be the cause of the rise in genetic damage and MN development which serves as genotoxicity biomarkers.^[80]

3.7 Hematological alterations:

Blood parameters are essential for evaluating the health of the animal, determining systemic functions, and identifying hemolysis brought on by drugs or chemicals in a variety of environmental settings. Hematocrit (Hct), hemoglobin (Hb) concentration, and total erythrocyte counts (TEC) are essential components of a minimum hematological package; toxicological investigations have often included these measurements.^[81]

Rats given cypermethrin showed a significant drop in hemoglobin concentration starting at 1/9LD₅₀, which may have been caused by compromised bone marrow heme production. In rats, decreased erythropoietin was indicated by a drop in the RBC count and Hb concentration.^[82]

Another study reported that cypermethrin treated groups had higher WBC counts, which could have resulted from the body's immunological and defense systems being activated.^[83]

Pyrethroids may cause oxidative stress due to a higher concentration of lipid peroxidation products. Serum glutamate-oxaloacetate transaminase (SGOT) and serum glutamate-pyruvate transaminase (SGPT) activity were found to be elevated. Liver dysfunction is suggested by the rise in serum enzyme activity. Therefore, increased cell membrane permeability is often associated with hazardous substance-induced cellular damage. These findings demonstrated that CYP caused a rise in MDA and a fall in GSH levels, which may be related to oxidative stress brought on by cypermethrin in rat hepatocytes.^[82]

The serum of rats intoxicated with pyrethroids showed increased activity of the enzymes alkaline phosphatase (ALP), lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in addition to other compounds due to mixed pyrethroid toxicity. AST is linked to mitochondrial damage, while ALT is linked to overall hepatocellular dysfunction. In a study, elevated serum aminotransferase (AST and ALT) activity was observed, reflecting hepatic damage caused by mixed pyrethroid stress, which causes these enzymes to escape into the general circulation. The first explanation for the rise in serum ALP activity is pathophysiological alterations in the liver brought on by pyrethroid toxicity. Damage to hepatocyte membrane permeability causes this enzyme to leak into the bloodstream, changing the normal hepatocellular architecture [35,84]

Cypermethrin treated rats showed decreased packed cell volume (PCV), clearly caused by a drop in blood erythrocyte counts. The PCV value is crucial for assessing the impact of stressful conditions of animals and serves as a gauge of the animal's blood's ability to carry oxygen. The markers of macrocytic and hypochromic anemia are a decrease in mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular volume (MCV), this might be because that cypermethrin interferes with erythropoiesis. [85]

3.8 Hepatotoxicity:

The liver is a key organ for the metabolism of exogenous substances that are harmful to human health, such as metals, medications, and pesticides. [86] It has been well documented that pyrethroid insecticides, such as deltamethrin (DLM), cause oxidative injury to the liver by producing reactive oxygen species (ROS) and elevating lipid peroxidation. [87] The results of an investigation showed that DLM exposure significantly raised the levels of LDH, ALT, AST, and ALP in rat serum. The detrimental impact of DLM on the liver cell

membrane, which results in liver dysfunction, may be the cause of the rise in these enzymes. Furthermore, the enzyme's leaking into the bloodstream after hepatocellular necrosis explains the rise in serum LDH activity in rats administered DLM. [88]

A study by Bhushan *et al.*, (2013) [35] on beta-cyfluthrin and cypermethrin, following the determination of their respective oral LD₅₀s (416.98 mg kg⁻¹ and 354.8 mg kg⁻¹ body weight), assessed hepatotoxicity in Wistar rats after acute (0.1 of LD₅₀ for 1 day) and sub-acute (0.1 of LD₅₀ for 7, 14, 21, or 28 days) exposure. In the liver homogenate after pyrethroid stress, there was a rise in ALT, AST, LDH, total lipids, phospholipids, cholesterol, and free fatty acids. On the other hand, structural protein lysis and enzyme leakage into the bloodstream resulted in a decrease in hepatic proteins, glycogen, and ALP activity. Histological changes (cytoplasmic vacuolization, nuclear polymorphism, eccentric nucleus, sinusoidal dilatation, karyolysis and karyorrhexis,) were in agreement with biochemical findings. Rats injected with beta-cyfluthrin showed somewhat greater hepatocellular damage than rats treated with cypermethrin; this is most likely due to the fluorine atom in beta-cyfluthrin.

Two significant hepatic enzyme indicators of hepatotoxicity are Serum Glutamic Oxaloacetic Transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). Significant increases in SGOT and SGPT levels following lambda-cyhalothrin (LCT) administration at varying concentrations was observed in rats in a study by Ghosh *et al.*, (2016). [89] Reduced glutathione content and elevated hepatic malon-di-aldehyde (MDA) level indicated that LCT causes hepatic damage and pathogenesis by altering the antioxidant system and generating free radicals. Low synthesis or non-enzymatic oxidation of GSH to glutathione disulfide (GSSG) as a result of oxidative stress in the liver of rats treated with LCT may be the cause of the

decrease in cellular GSH concentrations. It was also demonstrated that rats given LCT had a markedly elevated blood bilirubin level. Hyper-bilirubinemia, a helpful sign of hepatic impairment, is shown by the elevated level of total bilirubin in treated female rats.^[89,90]

According to reports, fenvalerate changed the architecture of the hepatocytes in female rats and resulted in histological damage to the liver tissue.^[91] Another study by Mani *et al.*, (2004)^[92] shows that, rats were inhaled fenvalerate developed fatty acid degeneration and hepatic necrosis.

3.9 Reproductive Toxicity:

Several pyrethroids have been shown to cause testicular damage and negatively impact fertility and sperm qualities after repeated exposure.^[93,94]

Body weight, glutathione peroxidase (GPx) activity, blood total antioxidant capacity (TAC), serum testosterone level, and sperm count, motility, and viability percent were all greatly reduced in a group of Wistar rats given deltamethrin (DLM) at a dose of 0.6 mg/kg bwt. In addition to a considerable drop-in sexual activity, as evidenced by an increase in mount, intromission, or ejaculation latency and a decrease in mount or intromission frequency, the DLM-treated group also exhibited a significant elevated levels of malondialdehyde (MDA) concentration in blood and sperm abnormalities (%). Histological changes, which included a marked decrease in spermatogenesis and seminiferous tubule diameter, validated these harmful consequences.^[95]

According to another research, cypermethrin significantly decreased the amount of sperm produced daily by the testicles. A decrease and deformation of spermatogonia, spermatocytes, and an unorganized arrangement of spermatids were seen, along with atrophy and malformed seminiferous tubules. Cypermethrin treated groups exhibited ultrastructural alterations, including necrosis of spermatogonia spermatocytes and sertoli cells, aberrant nucleus morphology, and

damaged cellular connections.^[96,97] The weights of the testes and epididymis, testicular sperm head counts, sperm motility, live sperm counts, sex hormone levels, and sperm abnormalities all significantly decreased in male rats.^[98]

Work by Li *et al.*, (2022)^[99] suggested that cypermethrin exposure (12.5–50 mg/kg/day) showed endocrine-disrupting effects on the developing male reproductive system in pubertal Sprague–Dawley rats by inhibiting Leydig cell development, significantly lowering serum testosterone, increasing luteinizing hormone (LH) at the highest dose, and downregulating steroidogenic genes (Lhcgr, Star, Cyp11a1, and Cyp17a1). In a study, fenvalerate another synthetic pyrethroid, was given orally (0.2, 2.0, and 20 mg/kg body weight) to pregnant mice every day for the entire duration of their pregnancy. The findings demonstrated that the growth and development of the newborn offspring throughout nursing were significantly delayed by the mother's exposure to fenvalerate during pregnancy. Additionally, male offspring exposed to fenvalerate exhibited more anxiety-like behaviors. Also, female offspring showed significant impairments in spatial learning and memory. It was concluded that maternal exposure to fenvalerate during pregnancy caused a gender-dependent delay in growth and neurobehavioral development.^[100]

In a study of Ben Abdallah *et al.*, (2013)^[101] it has been documented that, Lambda-cyhalothrin dramatically decreased epididymal sperm count, motility, and viability while raising the proportion of morphologically aberrant spermatozoa. Along with significant histological changes in seminiferous tubules, it also causes oxidative stress in the testes, which was characterized by elevated lipid peroxidation and antioxidant enzyme depletion, indicating severe reproductive toxicity.

4. CONCLUSION

In order to evaluate the dangers to human and environmental health, it is essential to understand the biomarkers linked to the

toxic effects of pyrethroids, especially Type II pyrethroids, which are more commonly used insecticides. The significance of a number of biomarkers in tracking the toxicological effects of pyrethroid exposure is highlighted in this review.

Changes in acetylcholinesterase (AChE) activity, sodium channel activity and oxidative stress are important biomarkers of neurotoxic injury that have been found in rats exposed to Type II pyrethroids. Furthermore, hematological changes, developmental and reproductive toxicity, and hepatotoxicity indicators shed light on the physiological processes that underlie pyrethroid toxicity.

For more precise and trustworthy monitoring of pyrethroid exposure, particularly in non-target organisms, more study is required to improve these biomarkers. Standardization of the techniques for evaluating these biomarkers is also necessary, since this could improve the prediction of pyrethroid toxicity in diverse environmental settings. Improving safety regulations and reducing the health risks connected with pyrethroid use would need the development of more sensitive and specific biomarkers.

Declaration

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