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REVIEW ARTICLE

Pyrethroid based pesticides – chemical and biological aspects

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ABSTRACT

Human and animal welfare primarily depends on the availability of food and surrounding environment. Over a century and half, the quest to identify agents that can enhance food production and protection from vector borne diseases resulted in the identification and use of a variety of pesticides, of which the pyrethroid based ones emerged as the best choice. Pesticides while improved the quality of life, on the other hand caused enormous health risks. Because of their percolation into drinking water and food chain and usage in domestic settings, humans unintentionally get exposed to the pesticides on a daily basis. The health hazards of almost all known pesticides at a variety of doses and exposure times are reported. This review provides a comprehensive summation on the historical, epidemiological, chemical and biological (physiological, biochemical and molecular) aspects of pyrethroid based insecticides. An overview of the available knowledge suggests that the synthetic pyrethroids vary in their chemical and toxic nature and pose health hazards that range from simple nausea to cancers. Despite large number of reports, studies that focused on identifying the health hazards using doses that are equivalent or relevant to human exposure are lacking. It is high time such studies are conducted to provide concrete evidence on the hazards of consuming pesticide contaminated food. Policy decisions to decrease the residual levels of pesticides in agricultural products and also to encourage organic farming is suggested.

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Pesticides; pyrethroids; allethrin; cypermethrin; permethrin; fenvalerate; deltamethrin; λ-cyhalothrin; neurotoxicity; reproductive toxicity; oxidative stress; apoptosis; epigenetics; carcinogenicity

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1. Introduction

1.1. Literature review methodology

This review is a compilation of scientific material on the physical, chemical and biological aspects of pesticides to benefit the researchers working in the area of pesticide toxicology. Thus, it is to be noted that this is not a systematic review prepared keeping a specific aspect in focus. Information required to prepare this review was collected by searching multiple sources (PubMed, Google Scholar, Google and SCOPUS. The review was prepared by consulting different kinds of scientific material that are related to pesticide chemistry and toxicity. The methodology used to collect scientific material and the inclusion and exclusion criteria adopted in selecting the requisite material to compile this review is presented in Supplementary Table 1. The inclusion criteria was to select research articles (animal, human and

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in vitro studies), book chapters, commentaries, reports of Government organizations (Directorate of Plant Protection, Quarantine (DPPQ), India, Environmental Protection Agency (EPA), USA and World Health Organization (WHO)) and review articles related to pesticide chemistry and toxicity from 1960 to 2020. Overall, 130 animal studies, 37 human studies, 17 *in vitro* studies, 7 books and book chapters (7), 1 case report, 2 commentaries, 49 reports and 60 review articles were included to present this review. Details of the scientific material consulted to prepare this review was classified and given in Supplementary Tables 2–7. Figures and tables were prepared with the information available in other review articles and reports posted on the website of Directorate of Plant Protection, Quarantine and Storage (DPPQS 2020). Exclusion criteria adopted was to avoid consulting general articles and blogs, personal opinions, topics on discussion forums, reports in non-English, multimedia reports, newspaper reports, and reports in nonscientific material.

1.2. Historical perspective

Botanical derivatives as pesticides have been used for many centuries and are known for their ecofriendly nature (Thacker 2002; Isman 2006). The oldest herbal knowledge *Ebers Papyrus* described more than 800 medical recipes which included a number of pesticides as ingredients. Sulfur and arsenic were used as pesticides for pest management from the times of Romans. Nicotine sulfate, calcium arsenate and sulfur were in use in late 1800s for crop protection.

The major breakthrough in the development of pesticides started during World War II with the production of environmentally persistent first-generation synthetic pesticides namely, the organochlorines; and prominent among them were aldrin and dichlorodiphenyltrichloroethane (DDT). The second-generation organophosphate pesticides such as malathion were discovered between 1950 and 1955 followed by triazine weedicides during 1955–1960 and their usage reached its peak by 1961. Owing to the public attention toward excessive usage of pesticides and the health hazards elegantly described in the famous book "Silent Spring", the use of pesticides decreased drastically by 1962 (Carson 1962). Following this, a new method of integrated pest management (IPM) came into existence in which biological predators or parasites were used to control pests. Albeit the population of pests reduced significantly, IPM methods did not display substantial effect akin to chemical pesticides. During 1970–1980s, pyrethroids, sulfonylureas, synthetic fungicides and other chemical pesticides were introduced. DDT was completely banned in USA followed by restrictions on usage of endosulfan, dieldrin and lindane in early 1970s. An international treaty derived at Stockholm Convention held in 2001 to which 179 nations were signatories, resolved to completely ban the use of twelve persistent organic pollutants including DDT (SCPOP 2001). On the same lines, European Union (EU) supported to ban on the use of nicotinoids in 2013.

1.3. Usage and exposure

Pesticides, including synthetic pyrethroids are among the extremely useful as well as harmful agents to human welfare because of their widespread use (Thatheyus and Selvam 2013; Chrustek et al. 2018). The multiple benefits of pesticides are presented in Table 1. They are used to avert crop loss thereby alleviating the global problem of hunger (Peshin et al. 2009). Approximately, 1/3rd of agriculture production depends on pesticide use and thus has become indispensable. Despite pesticide usage, crop loss due to pests and diseases are around 40% and it is anticipated that it could be double in absence of pesticides (Popp et al. 2013). Only a minute quantity (0.3%) of the pesticide sprayed on the crop reaches the target site, while the rest of it leads to contamination of surrounding environment (Banaszkiewicz 2010; Jayaraj et al. 2016). Most of the pesticides are heat stable, polar and water soluble, which makes it difficult to reduce their lethality. The global usage of different chemical pesticides, that include insecticides, weedicides, fungicides and bactericides were projected for the year 2020. It is estimated that about 34,71,780 metric tons will be used globally in 2020 (Zhang 2018). Based on these projections, the percent use of different pesticides is presented in Figure 1. Worldwide, weedicidal pesticides are consumed at higher percentage (40%) than other types of pesticides with China ranking as the top consumer (Zhang et al. 2011). In India, The Directorate of Plant Protection, Quarantine and Storage (DPPQS), an apex agriculture institute funded by Government of India, provided the statistics on the projected consumption pattern of different pesticides for the year 2019–2020 (Figure 2) (DPPQS 2020).

Albeit the fact that pesticides improved the living standards of human health by controlling vector borne diseases, according to World Health Organization (WHO), indiscriminate usage of pesticides mainly in developing countries, causes approximately 3,000,000 poisonings and 220, 000 deaths every year. Infants, children, agriculture workers and

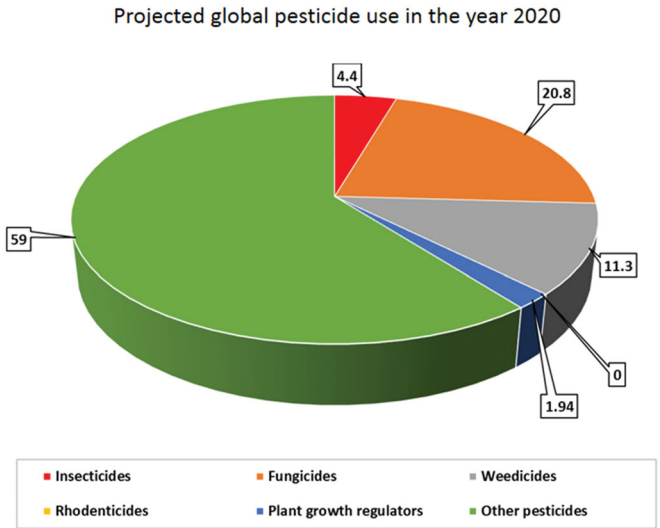

Figure 1. Projected use of pesticides globally. The global consumption of different pesticides were predicted by Zhang et al. (2018). The percent of each pesticide was calculated using its particular fraction out of the total pesticide amount.

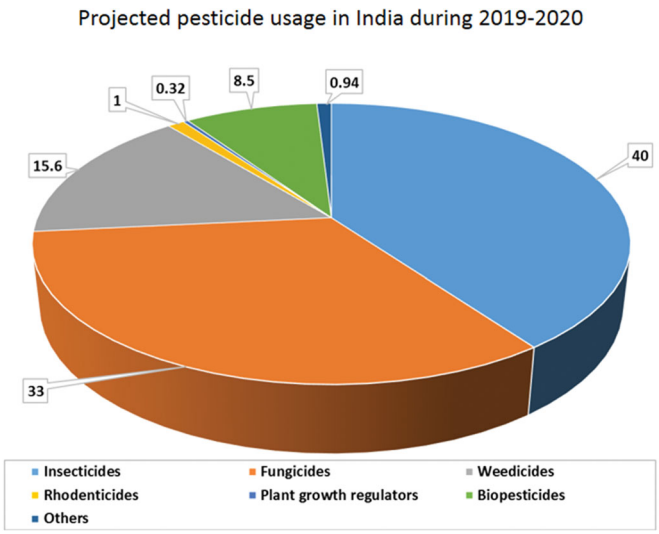

Figure 2. Pesticide usage in India during 2018–2019. The percent of each pesticide was calculated using the data provided by the Directorate of Plant Protection, Quarantine and Storage at http://ppqs.gov.in/statistical-database. (DPPQS 2020). The consumption of both indigenous and imported pesticides were combined to calculate the percentages.

pesticide applicators are more susceptible to pesticide toxicity than general population (Osman 2011; Liu and Schelar 2012). Pesticides enter into the ecosystem when the water soluble compounds are released into the aquatic systems, while the fat soluble compounds enter into animal tissues by bio amplification (Peshin et al. 2009; Mahmood et al. 2016). Excessive usage of pesticides led to their entry into the food chain and thus causing respiratory, carcinogenic, neurological, reproductive and endocrine abnormalities (Banaszkiewicz 2010; Mahmood et al. 2016). Consumption of pesticide contaminated food is the major gateway for their entry into human body, apart from accidental ingestion, inhalation and dermal exposure (Mahmood et al. 2016). The effects of pesticides on human health are highly variable and are classified as acute or short term (symptoms appears immediately or within hours) and chronic or long term (symptoms appear after months or years) (Kaur et al. 2019).

2. Classification of pesticides

Pesticides are broadly classified based on their origin i.e. natural (biological) or chemically synthesized. Based on the chemical structure and target of action, they are divided into five major categories namely, insecticides, weedicides, fungicides, rodenticides and fumigants and other minor categories like molluscicides and nematicides (Figure 3).

2.1. Natural pesticides

These are also referred to as biopesticides and a variety of them such as botanically derived compounds, antibiotics from microbes, pheromones of insects, microbial organisms, entomophagous nematodes, etc (Copping and Menn 2000). The most popular among them are of botanical origin that include crude extracts or purified compounds derived from different plants. Botanical pesticides have been used for centuries to protect stored food items, repelling household pests and also as fragrances (Isman 2006). Pyrethrum, azadirachtin nicotine, sabadilla, ryania, fluoroacetate, carboxin and Cry proteins of *B. thuringiensis* are used as insecticides (Oguh et al. 2019), whereas laminarine, fennel oil, lecithine are known to exhibit fungicidal properties. Citronella and pine oil derived products are used as repellents and herbicides, respectively (Isman 2006). Thus, plant protection products (PPPs) based on botanicals were developed to serve as pesticides. The target organ of the botanical based natural pesticides are diverse. The insecticides nicotine, sabadilla and pyrethrum act on the nerve cells, rotenone targets mitochondrial electron transport (Bomford and Isman 1996), ryania is a stomach poison (Oguh et al. 2019), azadirachtin is an inhibitor of the synthesis of ecdysteroids (Sieber and Rembold 1983), fluoroacetetate promotes citric acid accumulation (Clarke 1991), carboxin inhibits dehydrogenation of succinic acid to fumaric acid (Shievly and Mathre 1971). Biopesticides are known to have very low toxicity on mammalian physiology and are also cost effective and hence are increasingly being recognized throughout the world for plant protection in an eco-friendly manner.

2.2. Synthetic pesticides

Among the synthetic pesticides, insecticides rank the highest in terms of toxicity followed by fungicides and weedicides. Insecticides include organochlorines (OCs), organophosphates (OPs), carbamates, pyrethroids (PYs) and neonicotinoids (NEs).

2.2.1. Organochlorines (OCs)

OCs are synthetic chlorinated hydrocarbons classified as highly persistent organic pollutants (POPs) and widely used in agriculture and mosquito control. The overall statistics indicate that 40% of all pesticides used belong to OCs (Gupta 2004; FAO 2005). Most of the developed countries have banned use of OCs as they are non-biodegradable and persist in the environment (Aktar et al. 2009). The representative compounds that are highly used in this class are DDT, hexachlorocyclohexane (HCH), aldrin and dieldrin (Gupta 2004; FAO 2005). Based on the mechanism of toxicity and symptoms, OCs are divided into two subclasses namely DDT- and chlorinated alicyclic-type. Chlorinated alicyclic type is not well defined as DDT type. DDT type insecticides cause acute toxic effects in animals by preventing the deactivation or closing of sodium gates of axons, thereby resulting in hyperexcitation of the nervous system (Coats 1990). DDT is stored mainly in fat tissue and its metabolite DDE displays endocrine disruptive potential and carcinogenesis (Turusov et al. 2002). DDT as such causes liver cancer (Innes et al. 1969). Other health effects reported for OCs are impaired embryonic development and lipid metabolism, alterations in hematological, hepatic and endocrine functions (Mnif et al. 2011).

2.2.2. Organophosphates (OPs)

OPs or esters of phosphoric acid are ecologically good alternatives to OCs as they are not persistent in the environment.

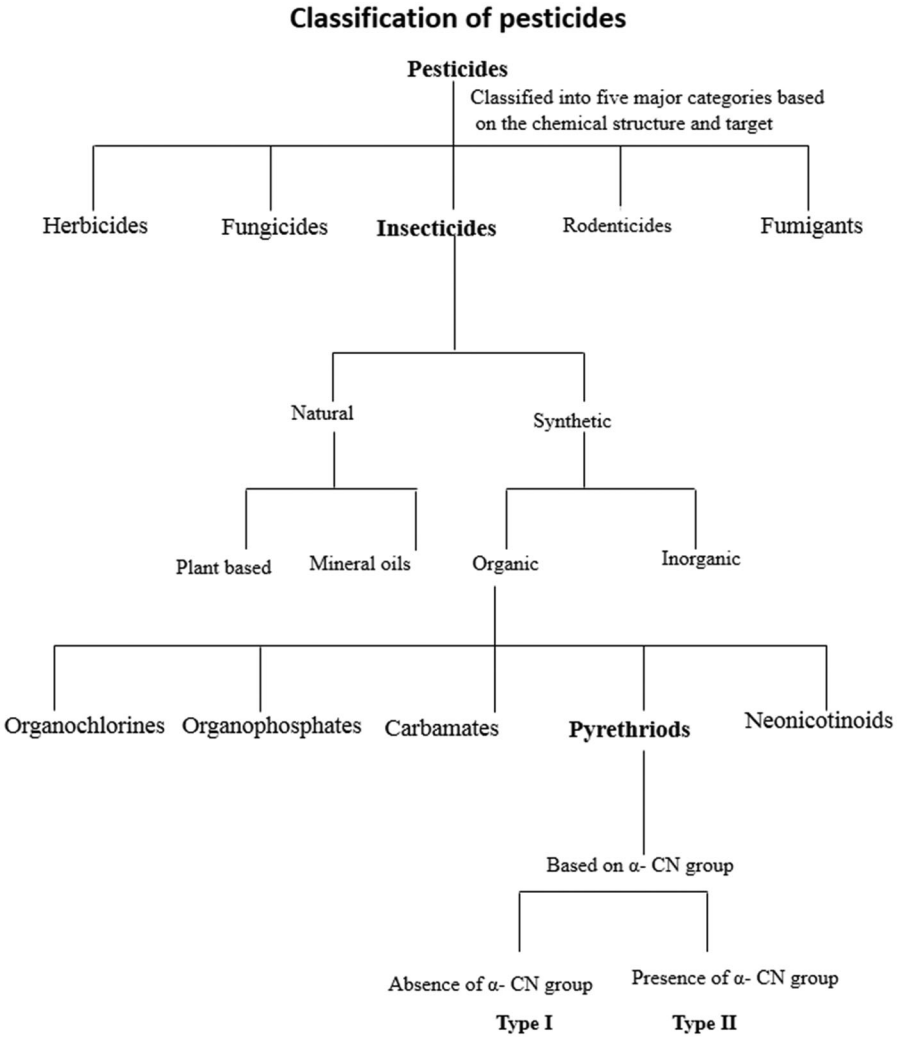

Figure 3. Classification of pyrethroids.

The most common of this class is glyphosate, a weedicide. The other OPs include malathion, parathion, dimethoate and chlorpyrifos. Global usage of organophosphate insecticides is more than 30% and according to Environmental Protection Agency (EPA) reports, more than 50% of total OPs are used in many crops, particularly cotton and corn in USA (Edwards 2006). In insects and mammals, OPs affect neuromuscular transmission by interfering with acetylcholinesterase (AChE) in cholinergic synapsis via phosphorylation of this enzyme resulting in excess accumulation of acetylcholine (Ach). This leads to death due to asphyxia, loss of respiratory control and over stimulation in cholinergic pathways (Reigart and Roberts 2013). Apart from neurotoxicity, they are also associated with aberrations in insulin secretion, metabolism, mitochondrial function and endocrine function (Nicolopoulou-Stamati et al. 2016).

2.2.3. Carbamates (CAs)

CAs are derived from carbamic acid and the first one among this class, carbaryl, was introduced in 1956 as a lawn and garden insecticide. Its broad-spectrum insect control activity and low toxicity to mammals allowed it to be a preferred choice. CAs are less persistent in the environment unlike OPs and OCs and are rapidly detoxified in animal tissues. The mode of action of CAs is similar to that of OPs as both are inhibitors of acetylcholinesterase (AChE). While CAs inhibit AChE activity by phosphorylation resulting in the formation of a reversible complex, OPs form an irreversible complex (Darvesh et al. 2008). Since CAs are considered to be safer than OPs, as they exhibit reversible action on AChE and do not cause severe poisoning in cholinergic pathway (Silva et al. 2013), they are proposed as therapeutic drugs (physostigmine derived from *Physostigma venenosum*) for neuromuscular disorders such as myasthenia gravis.

2.2.4. Pyrethrins and pyrethroids (PYs)

Pyrethrum is a natural resin extracted from dried flowers of pyrethrum daisy, *Chrysanthemum* (or *Tanacetum*) *cinerariaefolium*. This resin contains six esters of chrysanthemic and pyrethric acids. Those incorporated with pyrethrolone, form pyrethrins I and II and display insecticidal activity. Pyrethrins form 80% of global insecticide market (Isman 2006). The modern synthetic pyrethroids that are stable in the sunlight are derived from natural pyrethins and account for about one-sixth of global insecticidal sale with a turnover of US$1.4 billion.

Table 1. Pyrethroids and their applications.

		Applications		
Pyrethriod	Target vectors	Domestic / medicinal	Agricultural	Reference
Allethrin	Mosquitoes, ants, flies and other crawling insects	Shampoos and pet sprays, mosquito coils and nets, disinfestation agent in gardens, public places and households	N/A	(Gray 1985)
S- bioallethrin	Houseflies, cockroaches and mosquitoes	Disinfestation agent in gardens, public places and households	N/A	(WHO 2005a)
Bifenthrin	Cockroaches, houseflies and beetles,	N/A	Beans, cereals, corn, cotton, field and grass seed, melons, oilseed rape, potatoes, peas, raspberries, watermelons	(Tomlin 1994; Metcalf 1995; HSDB 2001; ATSDR 2003)
Permethrin	Beetle, bollworm, bud-worm, fleas, lice, moths, mosquitoes, termites and ants	Pet sprays and shampoos, disinfestation agent in gardens, public places and households, treatment of scabies and head lice.	Cotton, tomatoes, wheat, maize, onion and alfalfa	(EPOCRATES 2009; Krieger 2010)
Phenothrin	Wasps, water bugs, ticks, lice, flies, mosquitoes and honey bees	Major component of aerosol insecticides	N/A	(Caroline 2003; EPA 2008; NPIC 2011)
Resmethrin	Adult mosquitoes, houseflies, bees	Disinfestation agent in residential and industrial settings, animal houses, food handling establishments	N/A	(NPIC 2009)
Bioresmethrin	Mosquitoes and houseflies	Disinfestation agent in animal houses, public health settings and households	N/A	(Metcalf 1995; HSDB 2001)
Tefluthrin	Beetles, houseflies, mosquitoes moths, weevils	N/A	Corn, maize, sugar beet, sweet corn	(Tomlin 1994; Metcalf 1995; HSDB 2001)
Tetramethrin	Hornets, roaches, ants, wasps and fleas, cockroaches, mosquitoes	Aerosol, emulsifier in mosquito coils, disinfestation agent in public health, home and garden use	N/A	(IPCS 1989; ATSDR 2003)
Cyfluthrin	Cockroaches, houseflies, mosquitoes, rape winter stem weevil and aphids	Disinfestation agent in green houses	Ornamentals, hops, cotton, citrus, ground nuts, sweet corn, oilseed rape, pears, potatoes, rice, sugar beet, sugarcane, tobacco, different vegetables and cereals	(Metcalf 1995)
Cyhalothrin	Beetles, houseflies, ked, lice, mosquitoes and bedbugs	Disinfestation agent in animal houses and public places	N/A	(ATSDR 2003)
Cypermethrin	Flies, mosquitoes, moths and cockroaches	Disinfestation agent in animal houses and residential setups	Onions, pears, peaches, cotton and sugar beets	(ATSDR 2003)
Deltamethrin	Caterpillars cicadas, coding moths, weevils, whitefly	Disinfestation agent in animal houses, forestry, households and storage items	Cereals, coffee, cotton, figs, fruits maize, oilseed rape, olives, potatoes, soybeans, sunflowers, tea, tobacco, and different vegetables	(ATSDR 2003)
Fenvalerate	Cockroaches, beetles, flies, and mosquitoes	Disinfestation agent in ornamental plants and forestry	Cucurbita, corn, cereals, apples, Sunflower, tobacco, vegetables and sweet corn	(ATSDR 2003)
Esfenvalerate	Moths	Disinfestation agent in ornamental plants and forestry	Wheat, different vegetables, groundnuts, soybeans, sunflower, apples, tobacco	(ATSDR 2003)
Fenpropathrin	Mealybug, lace bugs, mites, aphids and beet armyworm	Disinfestation agent in ornamental plants and forestry	Citrus, cotton, pome, tomatoes, vegetables and vines	(ATSDR 2003)
Flucythinate	Whiteflies, leaf worms, sucking insects, beetles, boll-worms	N/A	Pineapples, bananas, strawberries, olives, coffee, cocoa, vegetables, soybeans, cereals, maize, alfalfa, sugar beet, sunflowers, tobacco, cotton, citrus fruit	(Mehler 1989; Meister 1992; EXTOXNET 1993)
Flumethrin	Cattle ticks, ticks and fleas, lice, psoroptic, chorioptic and sarcoptic munge	N/A	N/A	(ATSDR 2003)
Fluvalinate	White-flies, leafhoppers, moths, spider mites	Disinfestation agent in ornamental plants and forestry	Cereals, tobacco, vegetables and cotton	(ATSDR 2003)
Tralomethrin	Members of arachnida like spider, mites, ticks, harvestmen, and scorpions, Aphids, beetles, cockroaches, moths, weevils	Disinfestation agent for wood protection, public health, stored grain, animal houses and residential setups	Cereals, coffee, cotton, fruit, maize, oilseed rape, rice, soybeans, tobacco, vegetables	(HSDB 2001; ATSDR 2003)

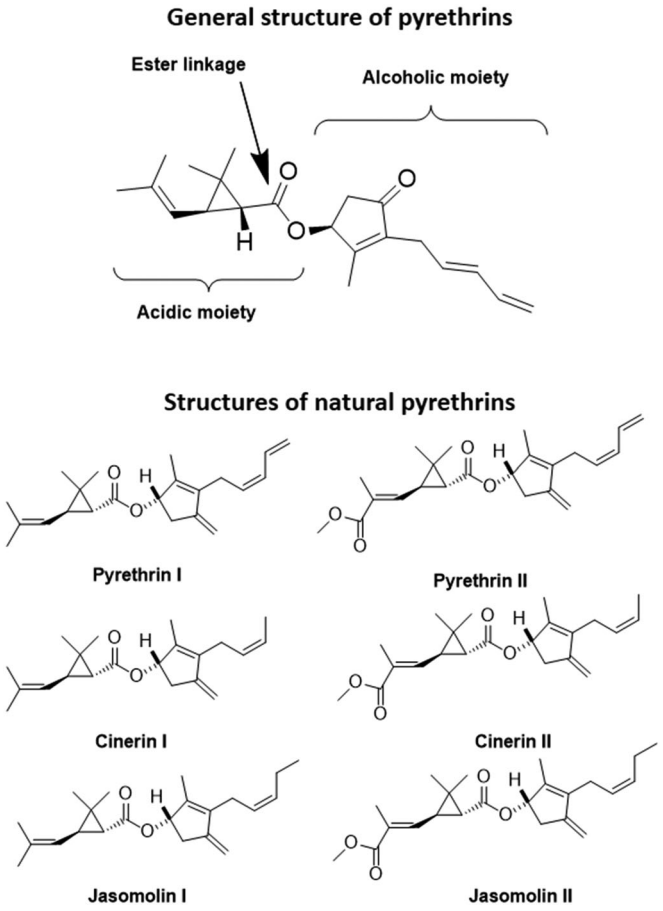

Figure 4. Chemical structure of pyrethrins.

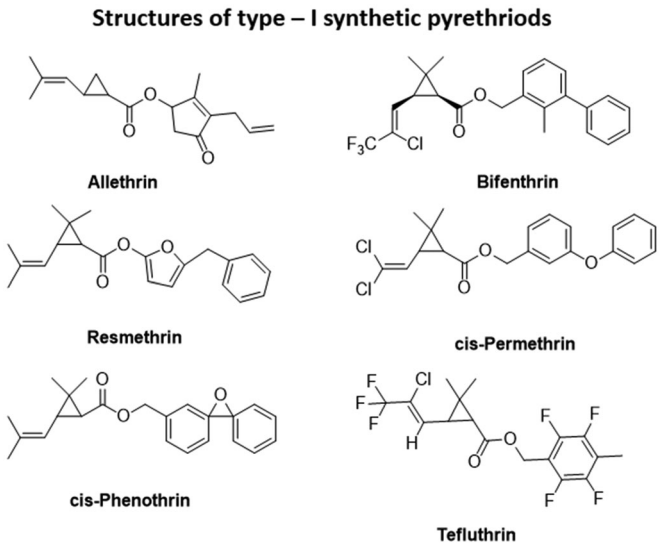

Figure 5. Chemical structure of type-I synthetic pyrethroids.

3. Pyrethroids

The first synthetic pyrethroids, allethrin and bioallethrin were developed in 1949. Resmethrin, the first generation synthetic pyrethroid was developed from naturally occurring pyrethrins by altering their structure to increase stability in sunlight and insecticidal activity in 1962. Bioresmethrin from resmethrin was produced in 1967 followed by commercial exploitation during late 1960s. Two new pyrethroids, cypermethrin and deltamethrin were also developed as potent insecticides (Khambay 2002). By 1983, pyrethroids were applied to crops in over 33 million hectares annually and constituted to 25.1% of global insecticide market (Casida and Quistad 1998). In late 1980s, World Health Organization (WHO), recommended use of pyrethroids including deltamethrin and permethrin owing to the less environmental persistency and toxicity to humans and other mammals. Pyrethroids such as cypermethrin and deltamethrin were used in long lasting insecticidal nets (LLINs) for malaria control programme of WHO (Khambay 2002).

3.1. Chemistry, classification and properties

A naturally occurring pyrethrum extract of chrysanthemum flower contains six types of compounds, namely, pyrethrins I, cinerins I, josmolins I, pyrehtrins II, cinerins II and josmolins II. The chemical structures of these compounds are shown in Figure 4. The first three are esters of chrysanthemic acid whereas the latter three are esters of pyrethric acid. Pyrethrin composition in pyrethrum extract is 45–55% with the proportion of pyrethrin I and II in the ratio of 0.2:2.8, whereas the ratio of pyrethrins: cinercins: jasmolins is 71:21:7. Pyrethrin I contributes to insecticidal activity, while pyrethrin II provides rapid knock-down (Elliott 1976). Chemically, natural pyrethrins contain an acid moiety, cyclopropane carboxylic acid and an alcohol moiety i.e. cyclopentenolone. The diversified pyrethroids are produced by adding specific functional groups to the moieties of natural pyrethrins. The structures of type I and type II pyrethroids differ with respect to position of α-cyano and other functional groups (Figures 5 and 6). Till date, 42 different pyrethroids with varying chemical structure or relative composition of stereoisomers are available. Except deltamethrin, all commercially available pyrethroids exists as complex mixture of isomers rather than a single compound because of the presence of multiple asymmetric carbons in cyclopropane ring. Owing to the presence of two chiral or asymmetric centers at carbon- 1 and 3 of acid moiety, pyrethrin I produces two pairs of diastereomers indicated as cis and trans that depends on the orientation of functional group on these positions with respect to cyclopropane ring or similar structure applied to replace this ring. In the synthetic compounds, a total of eight stereo-enantiomers are possible due to the presence of three asymmetric centers; one and two on alcohol and acid moiety, respectively (Shafer et al. 2005). In the natural pyrethrins, acidic moieties are specifically in the 1 R, trans (absolute) configuration. Esters with R configuration at cyclopropane C-1 of these chrysantmic acid isomers are more insecticidal whereas those isomers with enantiomeric 1S configuration are not insecticidal albeit displaying identical physical properties. This stereospecificity extends to compounds such as fenvalerate with 2S configuration on noncyclopropane acid moiety that is structurally congruent with 1 R cyclopropane carboxylates, confers insecticidal property (Soderlund et al. 2002). Although both cis and trans show insecticidal activity, cis isomer is relatively more potent (Ray and Forshaw 2000). Pyrethrins acquire insecticidal properties from ketoalcoholic esters of pyrethric

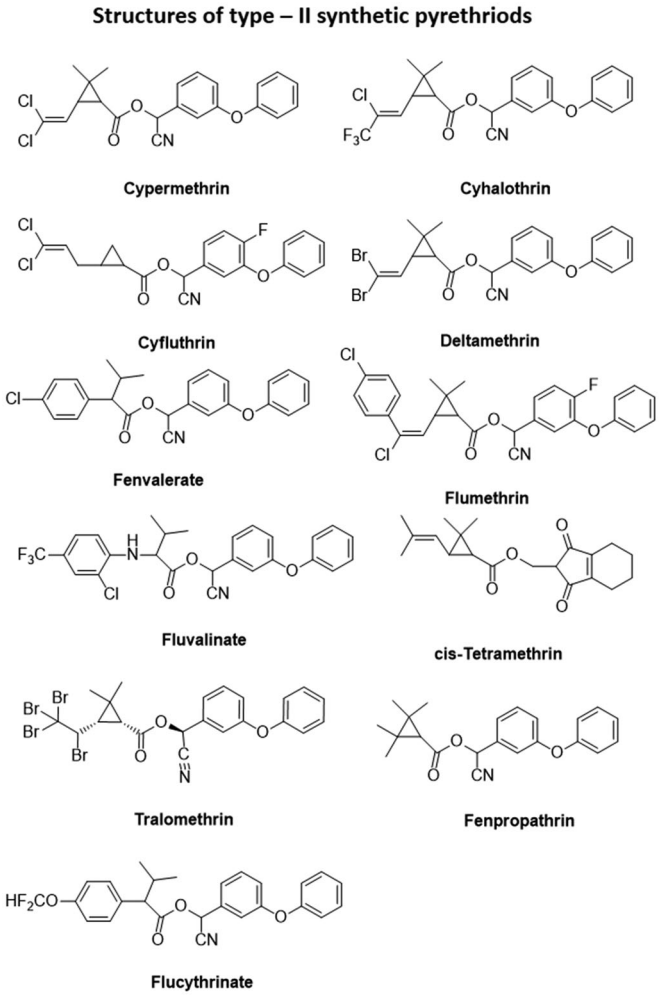

Figure 6. Chemical structure of type-II synthetic pyrethroids.

acid and chrysanthemic acid (Matsuo 2019) and due to strong lipophilic nature of these acids, pyrethrins easily penetrate and paralyze the insect nervous system (Lushchak et al. 2018). Pyrethroid pesticides are categorized into two groups, type I and type II based on behavioral toxicity and on the presence or absence of α- cyano group in their structures. Most of them are placed in category class I and II based on their acute toxicity in rodents (Table 2). Allethrin was the first candidate of type I synthetic pyrethroid identified. Other known type I pyrethroids are permethrin, resmethrin, bifenthrin, d-phenothrin and tetramethrin. So far, identified Type II pyrethroids are cypermethrin, deltamethrin, cyhalothrin (lambda), cyfluthrin and fenvalerate (esfenvalerate). Type I pyrethroids do not have the α-cyano group and hence are less toxic, whereas Type II pyrethroids that contain α- cyano group are highly toxic. Because of the unstable nature of these pyrethroids to sunlight, there was a need to generate next generation type compounds to overcome these problems (Ujihara 2019). Based on the photostability, pyrethroids are divided into two groups viz first generation and second generation. The first-generation photo labile synthetic pyrethroids are the derivatives of chrysanthemic acid esters, produced by substitutions to alcohol moiety. Examples include resmethrin, tetramethrin, phenothrin which are similar to natural pyrethrins and these are susceptible to photolysis easily. Second generation synthetic pyrethroids (permethrin, cypermethrin and deltamethrin) with high potency and photostability were produced by systemic changes in both acid and alcohol moieties. The physical properties of pyrethroids are low vapor pressure, low Henry's law constants, larger octanol- water ratio coefficients (K_{ow}), sparingly soluble in water, enantiomers with identical physical properties and diastereomers with different physical properties (Laskowski 2002).

3.2. Routes of exposure, absorption, metabolism and excretion

Several hazardous chemicals and other environmental pollutants, including pesticides are being released into the environment through different routes - agriculture fields, industrial waste and various anthropogenic activities. The main routes for human exposure to pesticides are physical contact, ingestion and inhalation (Maroni et al. 1999), whereas spills at storage houses also contribute to a certain extent (Hudson et al. 2014). Inhalation is the one of the predominant routes of exposure to pesticides (Walters et al. 2009). Since pyrethroids are being used in various domestic applications including household products, impregnated cloths, repellents and shampoos, they can also be absorbed through skin (Rossbach et al. 2010; Glorennec et al. 2017) and can also exposed through floor wipes and floor dust (Lu et al. 2009; Morgan 2012). Children are more prone to exposure of pyrethroid based products during treatment of scabies and lice (Menegaux et al. 2006). The oral absorption rate of pyrethroids is higher than skin penetration rate (Kaneko 2011). The rate of oral absorption of pyrethroids may also depend on the type of vehicle in which target compound is mixed. Most pyrethroids or their metabolites are not accumulated in any tissues or organs as they are metabolized within 16–24 h after absorption. However, some of them are detected in fat tissues due to high lipophilicity (Kaneko 2011). The acid and alcohol moiety of pyrethroids are completely excreted through urine after few days of oral administration whereas carbons derived from α-CN groups are incompletely excreted and display longer bio-retention in skin and stomach (Ruzo et al. 1978; Crawford et al. 1981). After cleavage of ester bond, α-CN groups are metabolized into thiocyanate and the slow and incomplete excretion of this thiocyanate may be due to its distribution in extracellular fluid and binding with serum albumin (Ohkawa et al. 1979; Kaneko et al. 1981). Based on several studies carried out in rodents, it is evident that the metabolism of more than 30 pyrethroids involve oxidation, hydrolysis of ester bond (phase I) and conjugation (phase II) to generate hydrophilic and lipophilic forms (Hodgson 2010). The hydrophilic conjugates are in the form of glucuronides, sulfates and amino acid conjugates; and they are excreted rapidly into urine due to their hydrophilicity. In some cases, the lipophilic conjugate found in fat tissues have more bio-retention than hydrophilic conjugates.

Table 2. Classification of pyrethroids based on their toxicity.

	Oral LD_{50} in rat (mg/ kg b.w.)			Oral LD_{50} in mice (mg/ kg b.w)			
Pyrethriod	Male	Female	Toxicity Category	Male	Female	Toxicity category	Reference
Allethrin	1100	685	II	500	630	II	(Meister 1992)
S- bioallethrin	709	1042	II	285	250	II	(Miyamoto 1976; WHO 2005b)
Bifenthrin	70.1	53.8	II	43.5	42.5	I b	(Miyamoto 1976; USEPA 1988)
Permethrin	430	470	II	540–2690		II	(IPCS 1979b)
Phenothrin	>5000		III	354–405		II	(IPCS 1980)
Resmethrin	6091	4639	III	690		II	(USEPA 2006)
Bioresmethrin	N/A			480–10000		III/U	(USEPA 2006)
Tefluthrin	21.8	34.6	II	45.6	56.5	I b	(ECHA 1985)
Tetramethrin	>2000		III	1060–2000		II	(ECHA 2002)
Cyfluthrin	250	N/A	II	291	609	II	(EMEA 2001)
Cyhalothrin	79	56	II	19.9	19.9	I b	(EXTOXNET 1996)
Cypermethrin	187–326	150–500	II	82		II	(IPCS 1995)
Deltamethrin	74–122	77–97	II	21–34		I b	(EXTOXNET 1995)
Fenvalerate	451		II	200–300	100–200	II	(IPCS 1979a)
Esfenvalerate	458		II	87.2		II	(IPCS 2002)
Fenpropathrin	54	48.5	I b	67	58	II	(IPCS 1975)
Flucythinate	81	67	II	76		II	(EXTOXNET 1993, 1995, 569)
Flumethrin	41		I b	>20	>20	I b	(IPCS 1984)
Fluvalinate	218–365	194–353	II		N/A		(FAN 2005)
Tralomethrin	1250	1070	II		N/A		(PubChem)

Pyrethroids cause lesser acute toxicity in mammals due to their rapid metabolism (Soderlund et al. 2002). Depending on the chemical structure, several sites of acid and alcohol moieties undergo oxidation. Trans form of isomer is oxidized more than cis form. Similarly, 4th position of phenoxy ring is more prone to oxidation than other positions (Casida and Ruzo 1980). It is also observed that more extent of ester hydrolysis occurs in trans isomer and primary alcohol derivatives when compared to corresponding cis secondary alcohol derivatives. The metabolism of pyrethroids, primarily in humans and rat, involve oxidation and ester hydrolysis mediated by cytochrome p450 isoforms and carboxylesterases respectively (Yang et al. 2009; Kaneko 2011). The components involved in the metabolic machinery of pyrethroids is shown in Table 3. The metabolism of bifenthrin, S-biollehtrin, resmethrin, β-cyfluthrin, cis-permethrin and trans-permethrin were well studied in hepatic microsomes of rat and human. The rate of hepatic clearance for most of the pyrethroids except trans-permethrin was more in rat microsomes than in the human counterparts. Bifenthrin, S-bioallethrin and cis-permethrin are metabolized by oxidative process in rat and human microsomes, while Bioresmethrin and cypermethrin are metabolized by hydrolytic process in human hepatic microsomes, but by both hydrolytic and oxidative process in rat hepatic microsomes. Six rat specific cytochrome P450 isoforms (CYP1A1, CYP1A2, CYP2C6, CYP2C11, CYP3A1 and CYP3A2) and four human specific isoforms (CYP2C8, CYP2C9, CYP2C19 and CYP3A4) are implicated in the metabolism of most pyrethroids. Deltamethrin and esfenvalerate are metabolized by rat specific CYP1A1, CYP2C6, CYP2C11 and CYP3A2, and human specific CYP2C8, CYP2C19 and CYP3A5. The cleavage of ester bond by hydrolysis is catalyzed by carboxylesterases and liver has the highest hydrolase activity. These enzymes are also observed in kidney, lung and small intestine (Satoh and Hosokawa 2006). The biotransformation and enzymatic reactions of synthetic pyrethroids in mammals are extensively reviewed (Mikata et al. 2012).

3.3. Epidemiology of exposure

The plasma half-life of pyrethroids is less than 8 h (Kim et al. 2008) and some high lipophilic compounds like permethrin remain in tissues up to 24 h (Kaneko 2011). The commonly detected pyrethroid metabolites in urine and the detection methods used to estimate them are presented in Table 4. Pyrethroid metabolites (cis-DCCA, trans-DCCA and 3-PBA) were analyzed in the urine of Chinese pregnant women, infants and children by gas chromatography-mass spectrometry (GC-MS) (Qi et al. 2012; Wu et al. 2013; Chen et al. 2016). Urinary pyrethroid metabolites (cis-DCCA, trans-DCCA, and 3-PBA) were detected in the school children of occupational agriculture families in northern Thailand by isotope dilution high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) after solid-phase extraction (Panuwet et al. 2009). 3-phenoxybenzoic acid (3-PBA) was detected in the 24-h urine samples of Italian healthy adults who were subjected to non-occupational exposure to pesticides (Saieva et al. 2004). 3-PBA was detected in the urine of middle and elderly aged general population of Japan (Ueyama et al. 2009). Metabolites of permethrin were detected in the body fluids among US military personnel, adult occupationally exposed- and general population (Proctor et al. 2018; Maule et al. 2019). Permethrin exposure and urinary time course excretion of permethrin metabolites were measured in agriculture workers working in corn production in Canada (Ferland et al. 2015). Thirteen pyrethroids were detected in human breast milk samples in Brazil, Colombia and Spain wherein pyrethroid application for malaria control was implemented (Corcellas et al. 2012). They were also detected in eggs laid by home reared chicken and also those from commercial farms in Rio De Janeiro (Parente et al. 2017). Bioavailability of 17 different pyrethroids including bifenthrin, cypermethrin, cyhalothin, deltamethrin and permethrin were detected in meat and the dietary exposure to these insecticides in Brazilian citizens (Dallegrave et al. 2018). Exposure of

Table 3. Molecular components involved in metabolism of pyrethroids.

	Metabolic activity				
	Hydrolysis by carboxylases / esterases		Oxidation by CYP P450 isoform		
Pyrethriod	Rat	Human	Rat	Human	Reference
Allethrin	Unknown	Unknown	CYP2C11, 3A1 and 3A2	CYP2C8 and 2C19	(Scollon et al. 2009)
S- Bioallethrin	Unknown	hCE1, hCE2	CYP CYP1A1,2A1,2C6 CYP2C11, 3A1 and 3A2	CYP2C8, CYP2C9, 2C19 and CYP3A4	(Scollon et al. 2009; Yang et al. 2009)
Bifenthrin	Unknown	hCE1 and hCE2	CYP1A1, 2C6, 2C11 and 3A1	CYP2C9 and 2C19	(Nishi et al. 2006; Scollon et al. 2009; Yang et al. 2009)
Permethrin	Unknown	hCE1 and hCE2	CYP1A1, 1A2, 2C6, 2C11 and 3A1	CYP1A1, 1A2, 2C9, 2C19 and 3A4	(Nishi et al. 2006; Scollon et al. 2009; Yang et al. 2009)
Phenothrin	Unknown	Unknown	Unknown	Unknown	–
Resmethrin	rat CES 1	hCE1	CYP1A1, 2C6, 2C11 and 3A1	CYP, 2C8, 2C9 and 2C19	(Crow et al. 2007; Nakamura et al. 2007; Scollon et al. 2009)
Bioresmethrin	rat CES 1	hCE1	CYP1A1, 2C6, 2C11 and 3A1	CYP, 2C8, 2C9 and 2C19	(Crow et al. 2007; Nakamura et al. 2007; Scollon et al. 2009)
Tefluthrin	Unknown	Unknown	Unknown	Unknown	–
Tetramethrin	Unknown	hCE1, hCE2	Unknown	3A4 only	(Yang et al. 2009)
Cyfluthrin	Unknown	Unknown	CYP1A1, 2C6, and 3A1	CYP2C8, 2C9 and 2C19	(Scollon et al. 2009)
Cyhalothrin	Unknown	Unknown	CYP1A1, 2C11, 2D1 and 3A1	CYP2C19 and 3A4	(Scollon et al. 2009)
Cypermethrin	Unknown	Unknown	CYP1A1, 2A1, 2C6, 2C11, 3A1, and 3A2	CYP1A2, 2C8, 2C19, and 3A4	(Scollon et al. 2009)
Deltamethrin	Hydrolase A and B	hCE1 and hCE2	CYP1A2, 1A1, 2C6, 2C11 and 3A2	CYP2C8, 2C19 and 3A5	(Anand, Bruckner et al. 2006; Crow et al. 2007; Godin et al. 2007)
Fenvalerate	Unknown	Unknown	Unknown	Unknown	–
Esfenvalerate	Hydrolase A and B	hCE1 and hCE2	CYP1A1, 2C6, 2C11 and 3A2	CYP2C8, 2C9, 2C19 and 3A5	(Godin et al. 2007)
Fenpropathrin	Unknown	Unknown	Unknown	Unknown	–
Flucythinate	Unknown	Unknown	Unknown	Unknown	–
Flumethrin	Unknown	Unknown	Unknown	Unknown	–
Fluvalinate	Unknown	hCE2	Unknown	Unknown	Yang et al. 2009
Tralomethrin	Unknown	Unknown	Unknown	Unknown	–

Table 4. Metabolites of pyrethroids detected in human urine.

	Metabolites			
Pyrethriod	Common	Specific	Suitable detectable methods	Reference
Allethrin	3- PBA	CDCA, MPCA and allethrolone	GLC/GC/ECD/FPD/ modified ELISA	(Yoshida 2013; Glorennec et al. 2017; Morgan et al. 2018)
S- bioallethrin	3- PBA	CDCA and allethrolone	GC/MS	
Bifenthrin	–	CTFCA and MPBA	GC/MS/FID	
Permethrin	3- PBA	Cis and trans- DCCA	UHPLC/MS/ GC/MS	
Phenothrin	3- PBA	MPCA	GC/MS	
Resmethrin	3- PBA	MPCA	HPLC/UV, GC/MS	
Bioresmethrin	3- PBA	MPCA	GC/MS	
Tetramethrin	–	MPCA	GC/MS	
Cyfluthrin	–	Cis and trans- DCCA and 4 –F-PBA	UHPLC/MS	
Cyhalothrin	3- PBA	TFP- Acid	GC/MS	
Cypermethrin	3- PBA	Cis and trans- DCCA	GC/ECD	
Deltamethrin	3- PBA	Cis- DBCA	GC/MS	
Fenvalerate	3- PBA	–	UHPLC/MS/ HPLC/ GC/NPD	
Esfenvalerate	3- PBA	–	GC/MS	
Fenpropathrin	3- PBA	TMCA	GC/MS	
Flumethrin	–	4 –F-PBA	GC/MS	
Fluvalinate	3- PBA	-	GC/MS	
Tralomethrin	3- PBA	-	GC/MS	

children to pyrethroid pesticides in United States is prevalent (Morgan 2012). Urinary metabolites of pyrethroids were analyzed from morning spot samples of 245 young children from France (Glorennec et al. 2017). Pyrethroids metabolites were analyzed in urine samples of German urban population (Heudorf and Angerer 2001). Biological monitoring was carried out for pyrethroidal exposure and urinary metabolites were analyzed by GC-MS in the agricultural workers who applied insecticides and other pesticides in Germany (Hardt and Angerer 2003). In Egypt, α-cypermethrin and its urinary metabolites were detected in agricultural workers (Singleton et al. 2014). Exposure to pyrethroids was associated with increased cardiovascular deaths in U.S. adult population (Bao et al. 2020). In the Indian context, residual levels of

pyrethroids were detected in many of the food items such as cereals, fruits, vegetables and milk products (ICAR 2013, 2014). The sum concentrations of 11 pesticides in the urine collected from a small group of people from an Indian town (Mettupalayam) was found to be 14.2 ng/ml (Li and Kannan 2018). Thus, there is ample epidemiological evidence to indicate that exposure to pyrethroids is prevalent globally irrespective of whether the affected population have directly used the pesticides or not.

3.4. Mechanism of action

Most of the synthetic pesticides including insecticides primarily target the components of nervous system (Field et al. 2017). The primary insecticidal activity of pyrethroids is to disturb the nerve membrane of insect by delaying the closure or inactivation or long-term opening of voltage-sensitive sodium channels (VSSC) that leads to more sodium ions crossing the membrane and depolarizing the neural membrane beyond the normal extent (Figure 7). Some of the pyrethroids also act on voltage-gated chloride and calcium channels as secondary target sites (Soderlund 2012; Costa 2015). The action of pyrethroids on voltage- sensitive sodium channels (VSSC) is stereospecific (Lund and Narahashi 1982) and stereoisomers which disturb VSSC function also have strong insecticidal or toxicological activity (Ray and Forshaw 2000). Perturbations in the activity of acetylcholinesterase activity and sodium gated channels was reported (Rao and Rao 2002; Field et al. 2017). The immediate signs of pyrethroidal intoxication in insects are tremors and hyperexcitation followed by paralysis (Narahashi 1971). First systemic description for the signs of intoxication of pyrethroids in rats exposed to biolallethrin and resmethrin through either oral or intravenous route were documented (Verschoyle and Aldridge 1980). Pyrethroids are less toxic for mammals and birds than fishes and insects due to rapid detoxification and less intestinal absorption in homoeothermic organisms (Skolarczyk et al. 2017). The acute neurotoxicity, metabolism, toxicity and actions of pyrethroid are well characterized and reviewed (Verschoyle and Aldridge 1980; Soderlund et al. 2002; Shafer et al. 2005). Pyrethroids bind to α subunit of VSSC and the presence of α subunit (Na $_v$1.2) is enough to generate their effects on sodium channel function in mammalian cells (Trainer et al. 1997; Smith and Soderlund 1998). Co-expression of β subunit with Na $_v$1.2 further increased their sensitivity of this channel compared with α subunit (Na $_v$1.2) alone, indicating that β subunit modulates the interactive affinity of pyrethroids with the channel (Smith and Soderlund 1998). Any mutations in the α-subunit of insects and mammals changes the sensitivity of VSSC to pyrethroids (Smith et al. 1997; Vais et al. 2000; Lee and Soderlund 2001; Wang et al. 2001). The differential sensitivity of VSSC to pyrethroids is demonstrated (Tatebayashi and Narahashi 1994). The relative sensitivity of sodium channels of dorsal ganglion neurons (tetrodotoxin sensitive (TTX-S) and resistant (TTX-R)) to tetramethrin is interesting (Tatebayashi and Narahashi 1994). The TTX-S and TTX-R arise from several different VSSC α subunits. During neurodevelopment, VSSCs show differential expression patterns and embryological form of VSSCs are replaced by adult form. In rodents, elevated expression of embryological form of Na $_v$ 1.3 (Albrieux et al. 2004) is replaced by Na $_v$ 1.2 during postnatal period (Felts et al. 1997) and the expression of Na $_v$ 1.2 at immature node of Ranvier is replaced with Na $_v$ 1.6 during myelination process (Boiko et al. 2001).

Type II pyrethroids modulate the action of GABA-gated chloride channels, voltage dependent chloride channels, ATPase and voltage-gated calcium channels, calcium dependent release of neurotransmitters and PKC-dependent protein phosphorylation (Lawrence and Casida 1982; Enan and Matsumura 1993; Forshaw et al. 1993; Shafer and Meyer 2004; Soderlund 2010). Most of the type II pyrethroids are associated with dopaminergic transport *in vivo,* but the mechanism is not clear (Bloomquist et al. 2002). Long term exposure to cypermethrin causes nigrostriatal degeneration which leads to oxidative stress (Singh et al. 2011; Singh, Tiwari, Upadhyay, et al. 2012).

3.5. Degree of toxicity

In toxicology, the general assumption is that the severity of pathogenesis is directly related to the dose of the toxicant and is referred to as monotonicity. However, in many instances the severity of pathogenesis would be inversely proportional to the dosage of the toxicant, an effect called as nonmonotonicity. Classical examples are endocrine disruptive chemicals (EDCs), pesticides and few heavy metals that exert severe effects even at low doses and the same severity may not be anticipated at higher doses (Vandenberg et al. 2012; Beausoleil et al. 2013; Zoeller and Vandenberg 2015; Hill et al. 2018; Badding et al. 2019). Thus, toxicological studies associated with EDCs have challenged the traditional concepts in the field of toxicology, such as "dose makes the poison".

Pyrethroids are 2250 times more toxic to insects than higher organisms because of the smaller size, low body temperature and excess expression of sensitive sodium channels with small structure (Bradberry et al. 2005). They also act on aquatic organisms to disturb mitochondrial membrane function and ion channels of the neural membranes (Burridge and Haya 1997; Carcamo et al. 2017). Based on the acute toxicity of hazardous chemicals and their LD_{50} values, they are classified into five classes as per WHO and GHS guidelines (Table 5). Similarly, based on the acute toxicity (LD_{50} values) in the rat, synthetic pyrethroids are classified as moderately hazardous (class II) for which the oral LD_{50} values are between 50 and 500 mg/kg bw (solids) or 200–2000 mg/kg body weight (liquids). To sustain the degree of toxicity and stability, commercial formulation of pyrethroids are mixed with synergistic compounds such as piperonylbutoxide (PBO), MGK-264, N-octyl bicycloheptene dicarboximide, sulfoxide, petroleum distillates and sesame oil (Goshman 1985).

Based on the information from limited number of studies, it is evident that the age-related toxicological magnitude of both Type I and II pyrethroids show large variations than other pesticides. Type II pyrethroid, deltamethrin, has been

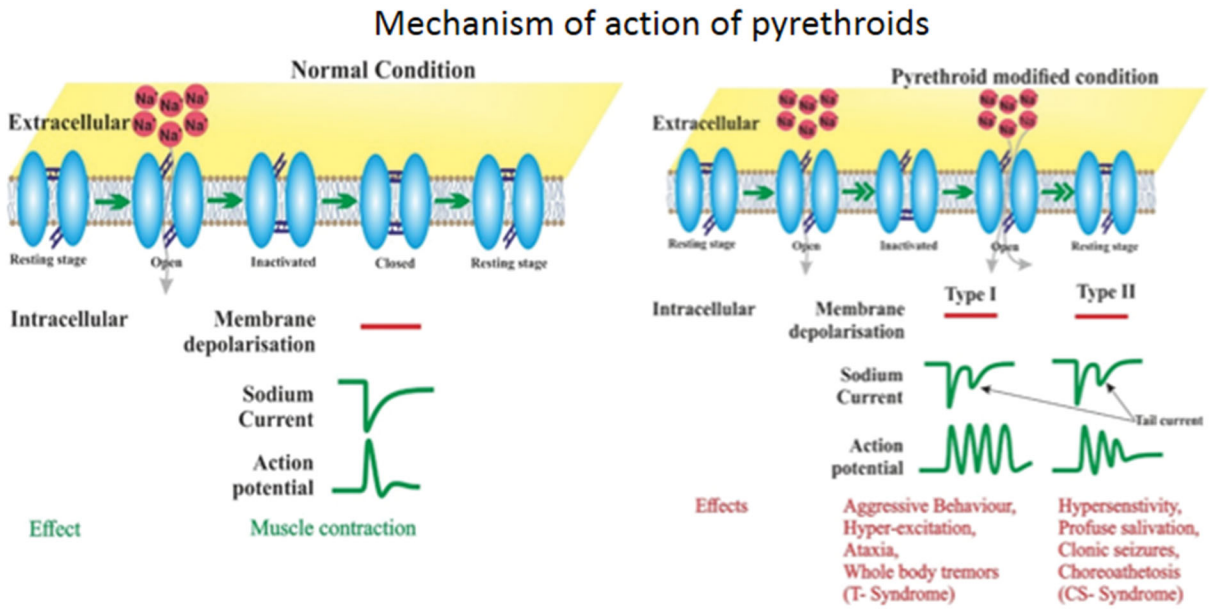

Figure 7. Molecular mechanism of action of pyrethroids on nervous system. Under normal conditions, VSSCs are in resting state (closed). An extracellular stimulus results in opening of VSSCs to allow influx of Na^+ ions. Entry of Na^+ creates an action potential, which diminishes when the VSSCs revert to resting state. The downstream effect of action potential generates many physiological responses such as muscle contraction. The toxic action of type-I or type-II pyrethroids results in continued opening of VSSCs to allow prolonged influx of Na^+ influx and persistent action potential. The consequences of the action of type-I or type-II pyrethroids leads to development of T- and CS-syndrome respectively. (Figure redrawn based on a previously reported model (Shafer et al. 2005).

Table 5. WHO and GHS classification of pesticides based on their oral LD_{50} values (EPA 2004; WHO 2004).

WHO				GHS			
LD_{50} for rat (mg/kg b. w)	Toxic category	Description	Symbol / Single word	LD_{50} for rat (mg/kg b. w)	Toxic category	Description	Symbol/ Single word
< 5	Ia	Extremely hazardous	POISON	≤5	1	Highly toxic	DANGER
5–50	I b	Highly hazardous	POISON	5–50	2	Highly toxic	DANGER
50–2000	II	Moderately hazardous	WARNING	50–300	3	Moderately toxic	DANGER
2000–4999	III	Slightly hazardous	CAUTION	300–2000	4	Slightly toxic	WARNING
5000 or more	U	Unlikely to present acute hazard	CAUTION	2000–5000	5	Relatively non- toxic	WARNING

shown to exhibit 16-fold acute lethality in young rats than their adult counterparts due to lower metabolic rates (Sheets et al. 1994). But, two type I pyrethroids, cismethrin and permethrin, did not exhibit any age related toxicity (Sheets 2000). The acute toxicity of type II pyrethroid, cypermethrin and type I pyrethroid, permethrin is 17-fold and 6-fold in younger age groups (PND 8) than in adult age groups respectively (Cantalamessa 1993). The LD_{50} values for cypermethrin during oral toxicity were 14.9, 27.1, 49.3 and 250 mg/kg in 8-, 16-, 21- day old and adult rats, respectively. The acute oral LD_{50} doses for cypermethrin in 18-, 21- and 72 day- old rats were 18, 73 and 439 mg/kg, respectively. It indicates that the acute lethality of cypermethrin is about 17-24 times higher in neonates than adult rats. An interesting observation is that permethrin enhances the mRNA expression pattern of c-fos in cultured mouse cerebellar granule cells and significantly suppress the c-fos expression in cerebella of neonatal mice in a dose dependent manner (Imamura et al. 2002). Another important aspect related to dose and degree of toxicity is the metabolic ability of the experimental animals being used. The metabolism of deltamethrin by plasma/hepatic carboxylesterases and hepatic microsomes is higher in adult rats than postnatal day 10 rats (Anand, Kim, et al. 2006). Equal concentration of deltamethrin was observed in the brain tissue of weaning and adult rats that were administered with 12 mg/kg and 80 mg/kg respectively (Sheets et al. 1994). Children aged 5 months to 17 years are more prone to exposure to one or more pyrethroids present in food, air and floor dust as indicated by the presence of pyrethroid metabolites in the urine samples (Morgan 2012). Because of these complexities, deciding on a dose in toxicological studies need to include the LD_{50} value and age of the experimental animals.

4. Health hazards of pyrethroids

Several studies have reported the health effects associated with synthetic pyrethroids in laboratory animals as well as in humans (general population and agriculture workers). They are summarized in Figure 8.

4.1. Reproductive toxicity

Insecticides being endocrine disruptive chemicals (EDC) can affect reproductive system and the target organs primarily being the testis and ovary. Damage to accessory glands and aberrations in endocrine function are also reported (Moline et al. 2000). Effects of pyrethroids associated with female

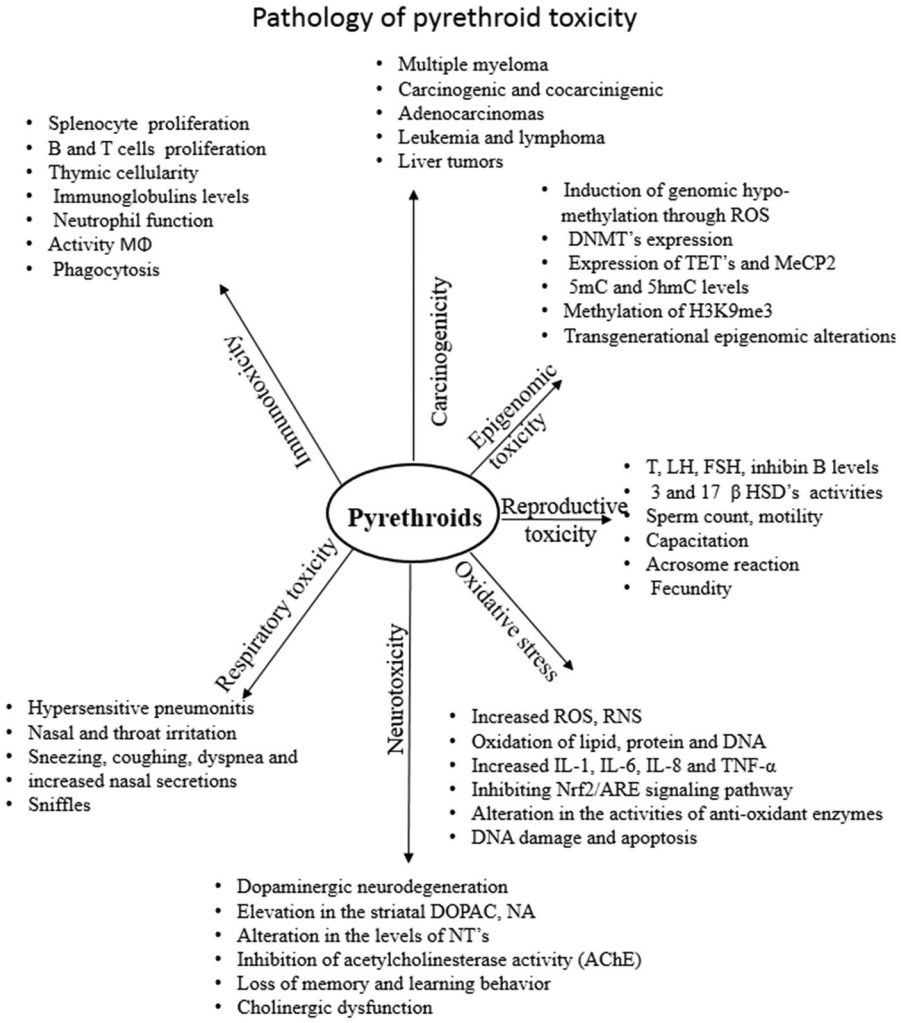

Figure 8. Pathology of pyrethroid toxicity. The potential health hazards of pyrethroids are depicted. The functional, biochemical and molecular events that may occur in each of the pathology are indicated.

reproductive system are reviewed (Marettova et al. 2017). Oral administration of cypermethrin to female mice caused disruption in the ovarian activity of the offspring which led to infertility associated with delay in the onset of puberty and irregular estrous cycles (Al-Hamdani and Yajurvedi 2017). Permethrin, when administered orally, altered the absolute and relative wet weights of uterus in rats without affecting vaginal weight and did not exert any estrogenic or anti-estrogenic effects (Kunimatsu et al. 2002; Kim et al. 2005). Permethrin also affected the fertility in female rats when administrated orally at the dose 250 mg/kg b.w during 6–15th of day pregnancy (Marettova et al. 2017). Cypermethrin caused adverse effects on ovary and uterus in rats that include loss of follicular cells and oocytes and altered enzyme activities of acid phosphatase, alcoholic phosphatase and 3 β-HSD (Grewal et al. 2010; Sangha et al. 2013). Cypermethrin decreased the progesterone concentration in luteal cells in *in vitro* (Gill et al. 2011). The effects of cypermethrin and its products on the reproductive system of dairy animals is extensively reviewed (Sharma et al. 2018). Fenvalerate toxicity to pregnant rats was associated with impairment of female reproductive development in the offspring, reduced fecundity and ovulation number due to impairment in corpora luteal count (Guerra et al. 2011). Vacuolization, loss of mitochondrial cristae and expansion of endoplasmic reticulum in corpus luteum cells was reported during fenvalerate induced toxicity (He et al. 2006). Inhibition of rat ovarian follicular growth *in vitro* was reported for fenvalerate (Fei et al. 2010). Histological abnormalities and decreased implantation sites were observed in female albino rats treated with deltamethrin (Lemos et al. 2011). Exposure to bifenthrin is associated with increased risk of ovulatory abnormalities in rat (Liu et al. 2011). Bifenthrin interferes with endocrine signaling and reduces reproductive ability (Brander et al. 2016). Permethrin and tetramethrin altered the absolute and relative wet weights of ovaries and exhibited endocrine disruption (Kim et al. 2005).

Pyrethroids reduced the semen quality and damaged sperm DNA which correlates with the levels of urinary metabolites in humans (Meeker et al. 2008). An association between levels of urine pyrethroid metabolites (3- phenoxybenzoic acid (3-PBA), cis and trans- 2,2- dichrorovinyl-2,2-dimethycyclopropane carboxylic acid (cis-DCCA and trans-DCCA) with serum levels of testosterone, LH, FSH and inhibin B was evident in adult men (Meeker et al. 2009). Permethrin and Cyfluthrin bind to androgen receptor on the skin cells and

peripheral benzodiazepine (PBZ) receptors to stimulate production of testosterone in men (Ramadan et al. 1988; Eil and Nisula 1990; Ferdinand et al. 2012). Exposure to permethrin caused embryo loss in pregnant rats (Spencer and Berhane 1982). λ-Cyhalothrin delayed the Leydig cell development during puberty in rat (Li, Fang, et al. 2018). Adult male mice treated with deltamethrin affected sperm quantity, quality, impairment of libido, decreased testosterone and inhibin B levels and severe alterations in the seminiferous tubules of testis (Ben Slima et al. 2017). Oral administration of deltamethrin alone and in combination with dimethoate during gestation caused a decrease in testicular weights and sperm function in male offspring (Ben Slima et al. 2012). Significant reduction in body and organs weights, sperm parameters, serum testosterone, semen plasma fructose, sialic acid content of epididymis, activities of 3 β and 17 β- hydroxysteriod dehydrogenases and severe alterations in the histology of testis in male Swiss albino mice treated with 3–6 mg/kg b.w of deltamethrin for 45 days were evident (Desai et al. 2016). Oral administration of deltamethrin during pregnancy and lactation resulted in changes in reproductive behavior and physiology of male offspring without any maternal toxicity (Andrade et al. 2002). Exposure to 3.83 mg/kg b.w of cypermethrin in male rats for 14 days caused reproductive toxicity and significantly decreased the weights of testis and epididymis, testicular sperm headcounts, sperm motility and live sperm counts, sex hormones, activities of anti-oxidant enzymes and increased sperm abnormalities (Sharma et al. 2014). Cypermethrin decreased the motility and increased the DNA damage in human spermatozoa *in vitro* (Zalata et al. 2014). Cypermethrin reduced the expression of androgen receptor both in *in vivo* as well as *in vitro* due to its inhibitory effect on IL-6, which stimulates the expression of this receptor and also disrupted steroidogenesis (testosterone production) by down regulating the expression of steroid acute regulatory protein (StAR) in testis of male mice (Wang et al. 2010). Sprague–Dawley rats treated with 7.5, 15, 30 and 60 mg/kg b.w of cypermethrin for 15 days showed significant decrease in the sperm production, number of Leydig and Sertoli cells, changes in the levels of sex hormones in the plasma (Li, Pan, et al. 2013). Cypermethrin acted as an endocrine disrupting chemical by directly targeting the Leydig cells and interfered with the maintenance of steroidogenesis (Li, Pan, et al. 2013). Cypermethrin decreased glutathione peroxidase activity and induced degenerative changes in the prostate epithelium and oxidative stress in rats (Hashem et al. 2015). Maternal exposure to fenvalerate during critical period (prenatal and postnatal) of sexual differentiation caused significant decreases in the weights of ductus deferens, seminal vesicle and also plasma testosterone levels in adult male offspring (Moniz et al. 1999). Fenvalerate affected male and female reproduction in rats and mice through alterations in calcium transport (Xiao et al. 2006; Arena et al. 2008; Song et al. 2008).

We reported that allethrin exposure through oral or inhalation routes caused oxidative stress and disruption in the transcription of genes involved in the germ cell development in male rats (Madhubabu and Yenugu 2012). Further, we also demonstrated that decreased p53 gene expression and increased phosphorylation of MAPK (p42/p44) during allethrin toxicity contributes to deregulation of cell cycle in the male reproductive tract of rat (Madhubabu and Yenugu 2014). Oral administration of 25- 150 mg/kg b.w allethrin to rats affected testosterone levels, sperm count, daily sperm production and the mRNA expression of factors associated with steroidogenesis and spermatogenesis (Madhubabu and Yenugu 2017). We showed that allethrin induced apoptosis was associated with voltage gated calcium channel mediated intracellular calcium release (Madhubabu and Yenugu 2014). Our recent studies were on the effects of long-term oral exposure to a mixture of pyrethroids at a concentration that is relevant to the residual amounts present in average Indian diet (Ravula and Yenugu 2019). Such an exposure affected fertility, lipid profile, antioxidant status, histopathological alterations in the reproductive organs and the expression of a variety of genes involved in spermatogenesis, steroidogenesis and germ cell reprogramming rat (Ravula and Yenugu 2019, 2020).

4.2. Immunotoxicity

Pyrethroid based pesticides have been demonstrated to have a variety of effects on the immune system. Exposure of female mice to single dose of 5–25 µl of permethrin equivalent to 220–1100 mg/kg body weight caused inhibition in the proliferation of splenic T cells by 32% at higher concentration, whereas during an *in vitro* exposure, the inhibition was 72% with 25 µM and 86% with 100 µM (Prater et al. 2002). In the same study, it was also demonstrated that dose dependent decrease in the thymic cellularity by 52 and 80% were observed in mice exposed to 15 and 25 µl of permethrin, respectively. Permethrin induces hypocellularity, DNA damage and respiratory burst in immune cells in a rodent experimental model (Gabbianelli, Falcioni, Cantalamessa, et al. 2009; Gabbianelli, Falcioni, Nasuti, et al. 2009). Beta-cypermethrin and 3- phenoxybenzoic acid (3-PBA) were associated with cytotoxicity, apoptosis, immunotoxity and expression of mRNA of pro-inflammatory cytokines in RAW 264.7 cells (Wang, He, et al. 2017). They also induced immunotoxicity in human promyelocytic leukemia cells (HL-60) by reducing cell viability and inhibiting granulocytic cell differentiation (He et al. 2018). Cis-bifenthrin induced immunotoxicty in RAW 264.7 cells involves activation of apoptosis, oxidative stress and reduction in the transcription levels of IL-1β, IL-6 and TNF-α (Wang, Gao, et al. 2017). Reduction in the proliferation of chicken B and T cells and myelotoxicity on human hematopoietic progenitor cells have been demonstrated (Mandarapu and Prakhya 2015; Ambwani et al. 2018). In male rats, cyhalothrin altered the activity of macrophages, decreased nitric oxide production and phagocytosis (Righi and Palermo-Neto 2005; Righi et al. 2009; Mandarapu and Prakhya 2015). Cypermethrin altered levels of immunoglobulins, rate of lymphocyte transformation and neutrophil phagocytosis in rats (Liu et al. 2006). Deltamethrin and imiprothrin displayed potential immunotoxic effects upon inhalation in young male rats (Emara and Draz 2007). Exposure of albino Wistar rats to low (1 mg/kg) and high (5 mg/kg) doses

of λ-cyhalothrin caused immunotoxicity that involved suppressed total serum immunoglobulin concentrations, hemagglutinin titer, hemolysis of sheep red blood cells (SRBCs), phagocytic function of neutrophils and macrophages and decreased percentage of CD4+ and CD8+ without affecting CD4/CD8 ratio (Ibrahim 2016). Exposure of male Wistar rats to a mixture of pesticides resulted in hematotoxicity and immunotoxicity (Aroonvilairat et al. 2018). Exposure to pyrethroids decreased immunity in humans and animals characterized by decreased concentration of IgG, macrophages, interleukin 2 (IL-2), interleukin 8 (IL-8), interleukin 12 (IL-12), interferon γ (INF-γ) and inhibition in the proliferation of peripheral blood leukocytes (Skolarczyk et al. 2017). Cyhalothrin decreased the intensity of macrophage mediated phagocytosis in BALB/c mice (Quinteiro-Filho et al. 2009). A significant decrease in the B lymphocytes and increase in the micronuclei of lymphocytes and reticulocytes as well as increased chromosomal aberrations and DNA damage were reported in farmers exposed to pyrethroids, compared to control and organic farmers; who did not use pesticides in the field (Costa et al. 2014). Significant reduction of proinflammatory cytokine levels (IL-2, IL-8, IL-12p70 and IFN-γ) in plasma of healthy human population exposed to α- cypermethrin suggested that exposure to pyrethroids may reduce the host defenses against infection and cancer (Costa et al. 2013).

4.3. Respiratory toxicity

Unlike the extensive reports available on the effects of pyrethroid based insecticides on different organ systems, the toxicological effects on respiratory system are not well reported. Symptoms associated with respiratory illness were observed in laboratory animals and children exposed to pyrethroids. It is shown that acute and repeated inhalation of cyfluthrin, induced stimulation of upper respiratory tract nociceptors in pregnant and normal rats (Pauluhn 2018). A cohort study on association between pesticide exposure and respiratory illness reported that prenatal exposure to piperonyl butoxide (PBO), which is used in the formulation of pyrethroid insecticides, may be associated with childhood cough (Liu, Jung, et al. 2012). The association of deltamethrin with low respiratory toxicity in rats was reviewed (Chrustek et al. 2018). A survey on experiences relevant to illness of pyrethroid exposure in California revealed that cyfluthrin and lambda- cyhalothrin are associated with respiratory irritant symptoms (Spencer and O'Malley 2006). Symptoms associated with acute respiratory problems among people exposed to pyrethrins was reported (Hudson et al. 2014). According to a five year survey of Washington State Department of Health and Oregon Public Health Division on pesticide poisoning, out of 407 cases, 52% cases were related to respiratory illness and 40% were related to neurological illness (Walters et al. 2009). Hypersensitive pneumonitis (characterized by shortness of breath, nonproductive cough and pleuritic chest pain) was reported and diagnosed in women exposed to indoor pyrethrum based insecticides (Carlson and Villaveces 1977). Signs of respiratory irritation (shortness of breath, cough and cognition) were reported in office workers who entered into a building that had been sprayed with cypermethrin formulation (Lessenger 1992). Nasal irritation and throat irritation were reported in workers who sprayed lambda cyhalothrin indoor (Moretto 1991). Few major respiratory symptoms like sneezing, coughing, increased nasal secretions and dyspnea were reported in those who used pyrethroidal insecticides to treat seedling of conifer (Kolmodin-Hedman et al. 1982). During packing of insecticides, sniffles and sneezes were reported when exposed to deltamethrin and fenvalerate (He et al. 1988).

4.4. Carcinogenicity

The International Agency for Research on Cancer (IARC) classified pyrethroid based pesticides as carcinogens though few studies demonstrated that they are not carcinogenic (Sankpal et al. 2012). Pesticides are identified as carcinogens by WHO through IARC (Peto 2001). Exposure to pesticides was associated with cancers of the prostate, pancreas, rectum, colon, lung, blood, bladder, skin and brain (Weichenthal et al. 2010). In an agriculture health study to determine the possible occurrence of cancer in the pesticide (permethrin) applicators, a correlation was not evident (Rusiecki et al. 2009). On the contrary, a correlation was observed in another study conducted on pesticide applicators in North Carolina, USA, wherein permethrin was associated with multiple myeloma risk (Alavanja et al. 2014). Permethrin association with prostate cancer in pesticides applicators is characterized by modifications in the chromosome 8q24 region (Koutros et al. 2010). However, permethrin is listed under group 3 (not classifiable as to its carcinogenicity to humans) as per the classification given in IARC monographs (IARC 2020). The urinary metabolites of pyrethroids, cis and trans 3-(2,2-dichlorovinyl)-2,2- dimethyl cyclopropane carboxylic acid (cis-DCC, trans-DCCA) and 3-phenoxybenzioc acid (3-PBA) are associated with acute lymphoblastic leukemia (ALL) in children (Ding et al. 2012). Maternal exposure to permethrin during pregnancy is a high risk for leukemia in the offspring (Ferreira et al. 2013). Cypermethrin displays both tumor initiating (carcinogenic) and promoting (co-carcinogenic) potential in rodent models (Shukla et al. 2002). Delatmethrin induced lymphomas in mice and thyroid tumors in rat (Cabral et al. 1990). Liver tumors were observed in mice treated with fenvalerate besides micro granuloma in spleen and lymph nodes (Cabral et al. 1990). Long term dermal exposure to deltamethrin causes initiation of skin tumors in both the sexes of Swiss albino mice and failed to show tumor promoting potential (Shukla et al. 2001). Imiprothrin, a type I pyrethroid, was associated with lung adenocarcinomas in both the sexes of rat and mice at higher doses (Yamada et al. 2019). Recently, a study concluded that imiprothrin should not be classified as carcinogen as it does not induce proliferation or morphological changes in mouse Club cells (Kawamoto et al. 2020). However, permethrin increased club cell proliferation (Yamada et al. 2017). Permethrin also induced tumors in liver of both male and female CD1 mice and lung of CD1 female mice and not in rats when treated at the doses equivalent to the dietary levels (Ishmael and Litchfield 1988). An *in vitro*

study suggested that exposure to permethrin and malathion induced gene aberrations in *Igh, Kmt2a, Etv6* and *Runx1* and frequency of cells with aneuploidy (gain and loss of chomosomes 18 and 12) (Navarrete-Meneses et al. 2017). A hospital based case study reported that exposure to pyrethroids based pesticides increased the risk of childhood brain tumors (Chen et al. 2016). Cyhalohrin, was associated with increase in Ehrlich ascitic tumor growth in isogenic BLAB/c mice following intraperitoneal administration of 5.0×10^6 tumor cells (Quinteiro-Filho et al. 2009).

4.5. Neurotoxicity

Pesticide exposure associated neurotoxicity of the central nervous system (CNS) and brain are demonstrated in humans and in experimental model systems. Though pyrethroids are less toxic in mammals, their primary mode of action on the nervous system is by delaying the closure or prolonged opening of voltage-gated sodium channels (Soderlund 2012; Hansen et al. 2017). Further, calcium and chloride channels are known to be the secondary targets for pyrethroid mediated neurotoxicity (Breckenridge et al. 2009). Several studies implicated pyrethroids in multiple neurological disorders. Cypermethrin induced motor deficit and short term toxicity in CNS by crossing blood brain barrier (Liao et al. 2011; Singh, Tiwari, Prakash, et al. 2012; Singh, Tiwari, Upadhyay, et al. 2012). Pyrethroids are associated with pathogenesis of Parkinson's disease (PD) (Baltazar et al. 2014; Johnson and Bobrovskaya 2015). Cypermethrin administration to normal and hemiparkinsonian rats, at lower dose (15 mg/kg/day), decreased the number of tyrosine hydroxylase immunopositive (TH-IP) dopamine (DA) neurons in the substantia nigra (Mun et al. 2005). It also induced neurotoxicity through altering the levels of gamma-aminobutyric acid (GABA) (Manna et al. 2005). After series of exposures from short to long-term and low to high doses, the neurotoxicity of cypermethrin relevant to dopaminergic neurodegeneration was reported (Singh, Tiwari, Prakash, et al. 2012; Singh, Tiwari, Upadhyay, et al. 2012). It decreased the motor activity without affecting memory and movement co-ordination in female mice (Nieradko-Iwanicka and Borzecki 2008). Both cypermethrin and deltamethrin interfered with the function of GABA gated chloride channels in insects (Costa 2015; Taylor-Wells et al. 2015). Neonatal exposure to permethrin and cypermethrin increased spontaneous locomotor activity, altered the striatal monoamine levels and increased oxidative stress in rats (Nasuti et al. 2007). Fenvalerate caused brain impairment during development of zebra fish (Gu et al. 2010). Postnatal exposure of deltamethrin caused long-term behaviour and cognitive deficit in Sprague–Dawley rats (Pitzer et al. 2019). Prenatal exposure to deltamethrin increased the levels of striatal 3,4-dihydroxyphenylacetic acid (DOPAC) and noradrenaline (NA) without affecting the levels of dopamine (DA), ratio of DOPAC/DA, serotonin (5-HT), 5-hydroxyinolacetic acid (5-HIAA), ratio of homovallinic acid (HVA)/DA as well as 3-methoxy-4-hydroxyphenyl-glycol (MHPG) in male and female rats (Lazarini et al. 2001). Perinatal exposure of rats to fenvalerate did not alter the levels of striatal monoamines in the offspring (Moniz et al. 1999). A recent study reported that both cyfluthrin and α-cypermethrin acted as potential developmental neurotoxic compounds in SH-SY5Y cells (Martínez et al. 2020). Permethrin exposure induced oxidation of lipid, protein and causes DNA damage as well as depletion of GSH in striatum of treated rats (Nasuti et al. 2014). Cypermethrin was associated with induction of alterations in the enzymes involved in the xenobiotic metabolizing cytochrome P450 and neurotransmitter biosynthesis in the brain regions of rat offspring during development (Singh, Mudawal, et al. 2016). Similarly, gestational exposure to cypermethrin caused dose-dependent induction of cytochrome P450 mRNA and its protein isoforms (2D1 and 3A1) and neurotransmitter receptors (GABAAα1, CHRM2, DA-D2, and 5-HT2A) in brain regions of rat offspring (Singh et al. 2015). Prenatal exposure to deltametrhin in rats induced ontogenic changes in xenobiotic metabolizing cytochrome P450 isoforms in brain and liver of offspring (Johri et al. 2006). Exposure to pyrethroid based mosquito repellents was associated with significant decrease in cholinergic receptor binding, inhibition of acetylcholinesterase activity (AChE), loss of memory and learning behavior in rat offspring during prenatal and early postnatal period (Sinha et al. 2006). λ-cyhalothrin was associated with neurobehavioral toxicity; cholinergic dysfunction and enhanced oxidative stress in developing rats (Ansari et al. 2012).

4.6. Oxidative stress, inflammation and apoptosis

Irrespective of the target tissue, pyrethroid toxicity is associated with oxidative stress and disruption in the antioxidant status. Oxidative stress from reductive state to oxidative state leading to oxidation of biomolecules (lipids (lipid peroxidation (LPO); proteins (carbonylation) and nucleic acids (8-OHdG) and perturbations in activities of antioxidant enzymes and levels of antioxidants such as glutathione, ascorbate and tocopherol. A balance between production of reactive oxygen/nitrogen species (ROS/RNS) and their elimination by antioxidant defense mechanisms through detoxifying enzymes (glutathione-S- transferase (GST), glutathione peroxidase (GPX), superoxide dismutase (SOD) and catalase (CAT)) are compromised.

Metabolism of pyrethroids by various isoforms of cytochrome P450 (for oxidation) and carboxylesterases (for hydrolysis) generates reactive oxygen species and thus oxidative stress (Wang et al. 2016). Deltamethrin altered the levels of lipid peroxidation and antioxidant defense system in rat liver following 16 weeks of exposure to low and higher doses (Tuzmen et al. 2008). α- cypermethrin increased in the levels of malondialdehyde and nitric oxide in neuroblastoma cell line (SH-SY5Y) in dose dependent manner and also altered the expression of genes involved in apoptosis, autophagy and necrosis (Romero et al. 2017). Deltamehtrin exposure induced oxidative stress in mouse oocytes by changing the expression of catalase and superoxide dismutase (Jia et al. 2019). On the contrary, no alteration in the levels of reduced glutathione and its detoxifying enzymes were observed in Wistar rats treated with 64.9 mg/kg b.w of deltamethrin (Anitha et al. 2019). Deltamethrin induced toxicity in

vertebrates and invertebrates was associated with oxidative stress, generation of reactive oxygen species and altered metabolism (Lu et al. 2019). Our studies demonstrated that allethrin (125 μM) induced cytotoxicity is associated with generation of reactive oxygen species, increased lipid peroxidation, altered detoxifying enzymatic status in Leydig cell carcinoma cells (LC540) and isolated primary Leydig cells of rat and also increased apoptosis by modulating p53 mRNA and PARP-1 protein levels (Madhubabu and Yenugu 2014). Increased lipid peroxidation, osmotic fragility, decreased protein content and activities of catalase and superoxide dismutase were observed in erythrocytes treated with different concentrations of λ-cyhalothrin in combination with chlorpyrifos *in vitro* (El-Demerdash 2007; Deeba et al. 2017). β-cyfluthrin induced oxidative stress in human erythrocytes *in vitro* was by decreasing catalase and superoxide dismutase activities (Sadowska-Woda, Wójcik, et al. 2010). There were significant increase in the levels of kidney lipid peroxides and protein carbonyls and renal morphology abnormalities in rats treated with λ-cyhalothrin (Fetoui et al. 2010). Bifenthrin was also associated with oxidative stress in human erythrocyte (Sadowska-Woda, Popowicz, et al. 2010). The activity of glutathione-S-transferase was reduced in liver, brain and testis of New Zealand White male rabbits treated with cypermethrin (el-Demerdash et al. 2003). Our studies demonstrated that antioxidant status was altered in many organs of male Wistar rats treated with a mixture of five pyrethroids (allethrin, cypermethrin, cyhalothrin, fenvalerate and deltamethrin) at the low doses (0.6266 μg/kg body weight; equivalent to one-twenty fifth of that is present in Indian staple foods; cereals and different vegetables (Ravula andYenugu 2019). Exposure to deltamethrin is associated with inflammation, oxidative stress, DNA damage and apoptosis in different organs of common carp (Arslan et al. 2017). Cypermethrin induced oxidative stress and the concomitant translocation of NRF2 from cytosol to nucleus by increasing mRNA expression of *Nrf2* and *Ho-1* (Zhou et al. 2016). Bifenthrin induces inflammatory and oxidative stress markers, such as NRF-2, COX-2, mPGES-1 and nuclear factor kappa B (NF-kappa B) in primary microglial cells and organotypic hippocampal slice cultures, besides altering the anxiety behavior in adult rats (Gargouri et al. 2018). It was found that deltamethrin increased the expression of Nrf2 mRNA and protein levels in PC12 cells and its activation is associated with its downstream factors, heme oxygenase-1 (HO-1) and glutamate cysteine ligase catalytic subunit (GCLC) (Li, Wu, et al. 2013). λ-cyhalothrin induced the expression of genes related to cytochrome P450 enzymes, oxidative stress and apoptosis in the liver of rats (Martínez et al. 2018). Cypermethrin exposure caused neurotoxicity associated with apoptosis and oxidative damage in primary cortical neurons of C57BL/6 mice by inhibiting Nrf2/ARE signaling pathway (Zhou et al. 2019). Fenpropathrin, induced testicular damage that was associated with oxidative stress and DNA damage and apoptosis (Mohamed et al. 2019). Cypermethrin induces oxidative stress resulting in apoptosis of goat spermatogonial cells (Bhardwaj et al. 2018). Our studies also demonstrated that allethrin induced toxicity in the male reproductive tract involved alteration of oxidant-antioxidant ratio (Madhubabu and Yenugu 2012; Madhubabu and Yenugu 2014; Madhubabu and Yenugu 2017).

4.7. Epigenomic toxicity

Environmental factors, including various toxins, plastic materials, specific dietary products and pesticides alter the epigenetic inheritance and may influence multiple generations (Denham 2018; Elmhiri et al. 2018). The major epigenetic modifications that can be transmitted paternally are DNA methylation, histone modification and noncoding RNA (ncRNAs). The association between pyrethroid toxicity and genetic reprogramming via epigenetic modifications has been emerging in the last decade and it continues to be an active area of investigation because of increased exposure to pesticide residue either through occupational or domestic or food consumption mode. Limited studies conducted till date indicate aberrations in epigenetic regulation associated with pyrethroid toxicity. Permethrin exposure induces genomic hypomethylation through generation of ROS and also up regulates the expression of DNMTs in both sexes of rats (Bordoni et al. 2015). Elevated pesticide residue levels in the blood were associated with global DNA methylation (Rusiecki et al. 2008; Kim et al. 2010; Collotta et al. 2013). Neonatal exposure to low doses of permethrin causes increased expression of genes encoding TET and MeCP2 proteins involved in the epigenetic mechanism, elevated 5mC and 5hmC levels and reduction in the methylation levels at H3K9me3 in the promoter regions of both *Th* and *Nurr1* in stratum of male Wistar rats (Bordoni et al. 2019). Similarly, another study showed increased protein levels of DNMT1 and DNMT3a in the stratum of adolescent rats treated with permethrin (Fedeli et al. 2017). Sub-lethal dose of lambda-cyhalothrin exerted transgenerational effect on reproduction and development in the offspring of leaf beetle and also affected antennae symmetry (Müller et al. 2017). Exposure to deltamethrin and corticosterone simultaneously affected the methylation status of glucocorticoid receptor gene, *Nr3c1* in the midbrain of C57/BL6N male mice (Vester et al. 2020). Paternal exposure to fenvalerate influenced the reproductive function in offspring by altering the methylation status of angiotensin I converting enzyme (*Ace*), forkhead box O3 (*Foxo3a*), huntingtin-associated protein 1 (*Hap1*), nuclear receptor subfamily 3 (*Nr3c2*), promyelocytic leukemia (*Pml*), and prostaglandin F2 receptor negative regulator (*Ptgfrn*) (Xia et al. 2013). Impaired levels of cerebral cytochrome P450s (CYP1A and 2B1) through alterations in the H3 acetylation and DNA methylation in their promoter regions was observed in the offspring of rats prenatally exposed to cypermethrin (Singh, Agrahari, et al. 2016).

5. Conclusions and future prospects

Food and health demand of humans are always on an exponential phase throughout the world. To accomplish the gap in demand, indiscriminate use of pesticides in agriculture and health protection is practiced. The huge gap between the quantum of pesticides applied and the actual amount that

reaches the target site resulted in percolation of the excess pesticides into the environment to contaminate soil, water and air and thus entering into the food chain. A historical perspective of the development of pesticides indicate the emergence of pyrethroid based ones as preferred choice. The synthetic pyrethroid based pesticides display diverse chemical structures and development of sensitive analytical methods have enabled to detect the levels of these compounds and their metabolites in the body fluids. Epidemiological, demographic, physiological, biochemical and molecular studies indicated the prevalence of pyrethroid based pesticide exposure, contamination and health hazards that range from simple nausea to cancer. Though the primary target of pyrethroids is the nervous system, it is evident that they can be toxic to reproductive, immune and respiratory systems. At the molecular level, they cause oxidative stress and alterations in epigenetic status to contribute to the development of cancers in most of the organ systems.

Whilst majority of the studies on the toxic effects of pyrethroid based pesticides were conducted by using dosages that were either lethal or sub-lethal, reports on the implications when exposed to doses that are relevant to human settings are rare. Exposure to pesticides happens unintentionally on a daily basis in general population through consumption of food that contains residual levels of these chemicals and also through gadgets used for pest control in domestic settings. Animal experimentation wherein toxicity studies are carried out using the exact doses of pesticides to which humans are exposed and durations that mimic human life time will generate substantial information on the health risks. Such studies will be of potential benefit to public health and to generate policies at all levels to mitigate the impending dangers caused by the double-edged swords of this century i.e. the pesticides. Technologies that can deliver pesticides more precisely to the target, processing protocols to reduce the residual levels of pesticides in food and encouraging organic farming with subsidies are the need of the day.

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Declaration of interest

The authors declare no conflicts of interest. The authors are not affiliated with Directorate of Plant Protection, Quarantine (DPPQ) and none of the employees of this institution were contacted to prepare this review and thus are not contributors of this review. All the statements made in this review are the opinions of the authors as understood from the available literature. The evaluators (Prof. Senthilkumaran Balasubramanian and Prof. Vijay Kumar Kutala) provided inputs to improve the overall presentation and thus did not contribute to the actual preparation and presentation of the manuscript and hence they were not included as authors. The evaluators are aware of this agreement.

Supplemental material

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