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Systematic review on pyrethroid toxicity with special reference to deltamethrin

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Abstract
Pyrethroids are synthetic organic compounds synthesized from *chrysanthemum* flowers that are used extensively as household and commercial insecticides. The keto-alocoholic esters of chrysanthemic and pyrethroic acid being lipophilic are responsible for its insecticidal properties. Pyrethroids are broadly classified into first and second generation pyrethroids. The first generation (Type 1) pyrethroids are less toxic to mammals than the second generation (Type II) pyrethroids. Mainly Type II pyrethroids cause paresthesia, which is characterized by transient burning/tingling/itching sensation of the exposed skin. Also, it has been suggested that some pyrethroids cause developmental neurotoxicity, but available evidence has been judged to be insufficient. While some pyrethroids have been shown to cause tumors in rodent models, the tumor induction does not appear to reflect a common carcinogenic endpoint for this particular subset of compounds. Deltamethrin is an alpha-cyano pyrethroid insecticide used extensively in pest control. Although initially thought to be least toxic, a number of recent reports showed its toxicity in mammalian and non-mammalian laboratory and wildlife animal species. The article sheds light on deltamethrin induced various toxicities during acute and chronic exposure in different species.

Keywords: Pyrethroids, fenvalerate, cypermethrin, deltamethrin, Oxidative stress.

1. Introduction
Synthetic pyrethroids are considered to be less toxic to wildlife and biodegrade more efficiently than organochlorine. Deltamethrin and fenvalerate is considerably less harmful to the environment and most non-target organisms than other insecticides [1]. Like DDT, pyrethroids are used to spray inside the houses, to impregnate bednets, which protect populations from malarial mosquito bites. They are three times as expensive as DDT, but used in very low amounts for bednet spraying. Because of their consequent development of resistance by pests and their harmful effects on non-target organisms, WWF (World Wildlife Fund) does not recommend pyrethroid as a viable alternative to DDT and suggests more research work on the "possible hazards" of pyrethroids in human and aquatic organisms.

1.1 Pyrethrins
Pyrethrins are natural insecticides produced by certain species of the *chrysanthemum* plant. Pyrethrins containing dusts and extracts usually have an active ingredient content of about 30%. These active insecticidal components are collectively known as pyrethrins [2-3]. Two pyrethrins are most prominent, pyrethrin-I and pyrethrin-II (Table 1). The pyrethrins have another four different active ingredients, cinerin I and II and jasmolin I and II (Table 1). Pyrethrin compounds have been used primarily to control human lice, mosquitoes, cockroaches, beetles and flies. Some "pyrethrin dusts," used to control insects in horticultural crops, are only 0.3% to 0.5% pyrethrins, and are used at rates of up to 50 lb/acre. Other pyrethrin compounds are used in grain storage and in poultry pens and on dogs and cats to control lice and fleas [2-3]. The natural pyrethrins are contact poisons which quickly penetrate the nerve system of the insect. A few minutes after application, the insect cannot move or fly away (knockdown dose). But, a "knockdown dose" does not mean a killing dose [2-3]. The natural pyrethrins are swiftly detoxified by enzymes in the insect. Thus, some pests will recover. To delay the enzyme action so that a lethal dose is assured, organophosphates, carbamates, or synergists may be added to the pyrethrins. The biotransformation of pesticide is shown in Figure 1.

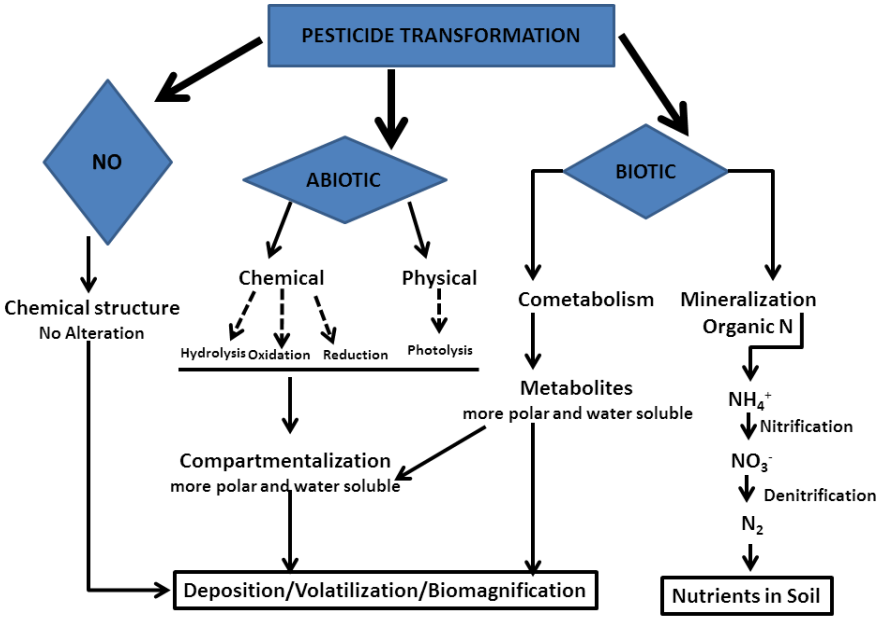


Fig 1: Biotransformation of pesticides

Table 1: Active ingredients of pyrethrin I and pyrethrin II

Pyrethrin I	$-CH=CH_2$	$-CH_3$
Pyrethrin II	$-CH=CH_2$	$-COOCH_3$
Cinerin I	$-CH_3$	$-CH_3$
Cinerin II	$-CH_2CH_3$	$-CH_3$
Jasmolin I	$-CH_2CH_3$	$-COOCH_3$

1.1.1 Advantages of using pyrethrins rapid

1. **Low mammalian toxicity:** They have a low mammalian toxicity. They are one of least toxic domestic insecticides available.
2. **Broad spectrum of insecticides:** Because they consist of a group of related compounds, they have a wider spectrum of activity against insect species than any other insecticide group.
3. **Lack of persistence:** Pyrethrins are degraded by the combination of sunlight and air, and therefore present little of the hazards which are usually associated with certain other classes of persistent insecticides.
4. **Repellency:** Pyrethrins are powerful insect repellents which in combination with low mammalian toxicity favours them in many applications.

1.2 Synthetic Pyrethroids

Semisynthetic derivatives of the *chrysanthemum*ic acids have been developed as insecticides. These are called pyrethroids and tend to be more effective than natural pyrethrins while they are less toxic to mammals. One common synthetic pyrethroid is allethrin. Pyrethroid pesticides interact with the γ- amino butyric acid (GABA) receptor – ionophore complex to cause neurotoxicity [2-3].

1.2.1 Advantages of Using Synthetic Pyrethroids

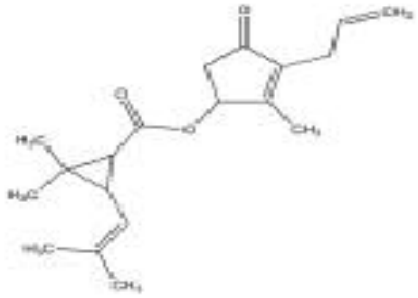
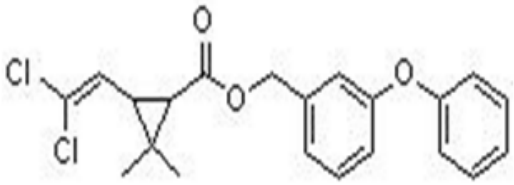
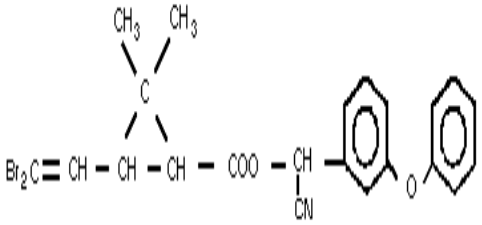
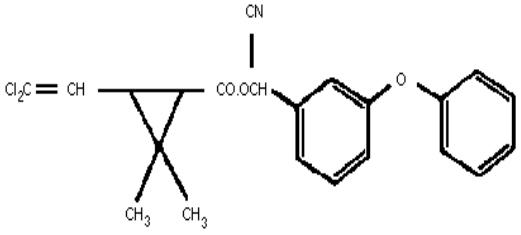
1. They have extremely high insecticidal activity at extremely low doses and are biodegradable in nature.
2. Their activity is most pronounced against lepidopterous pests and are also effective against beetles, leaf miners and bugs.
3. They maintain insecticidal activity over an extended period of time which helps in controlling overlapping generations of pests.
4. They have rain fastness i.e. they are not readily washed off from the plants by rain. The lipophilic character enables ready absorption on waxy layers of plant surface.
5. Synthetic pyrethroid treated crops give increased yields of better quality and in the case of cotton, the crop tends to mature early.
6. The movement from site of application is limited in air due to low volatility and in soil and plants due to low polarity.

Pyrethroid insecticides are highly toxic to insects and fish and have generally low toxicity to mammals, forming the basis of their favorable selectivity [4-5]. They can be divided into two major classes based on neurophysiological, toxicological, and pharmacological effects [6].

1.2.2 Types of Synthetic Pyrethroids

There are two different types of synthetic pyrethroids type I and II as shown in Figure 2. The major action and the chemical structure of Type I and Type II pyrethroids are shown in Table 2.

Table 2: Type I and Type II pyrethroids, chemical structures and their action, toxicity of Pyrethroids

Group	Name	Structure	Toxicity/Mode of action
Type I Pyrethroid	**Allethrin**		Allethrin is a pyrethroid, a synthetic compound that duplicates the activity of the pyrethrin plant. It has stomach and respiratory action and paralyzes insects before killing them (Casida *et al*., 1983)
	Permethrin		Permethrin makes the nervous system hypersensitive to stimuli from sense organs; permethrin-exposed nerves send a train of impulses. This excitation occurs because permethrin blocks the movement of sodium ions from outside to inside of the nerve cells (Casida *et al*., 1983)
Type II Pyrethroid	**Deltamethrin**		Deltamethrin's mode of action is thought to be mainly central in action, or at least originate in higher nerve centers of the brain. Death of insects seems to be due to irreversible damage to the nervous system occurring when poisoning lasts more than a few hours.
	Cypermethrin		The major target site of cypermethrin is the sodium channel of the nerve membrane. A sodium channel exposed to cypermethrin can remain open much longer, even up to several seconds (He, 1989).

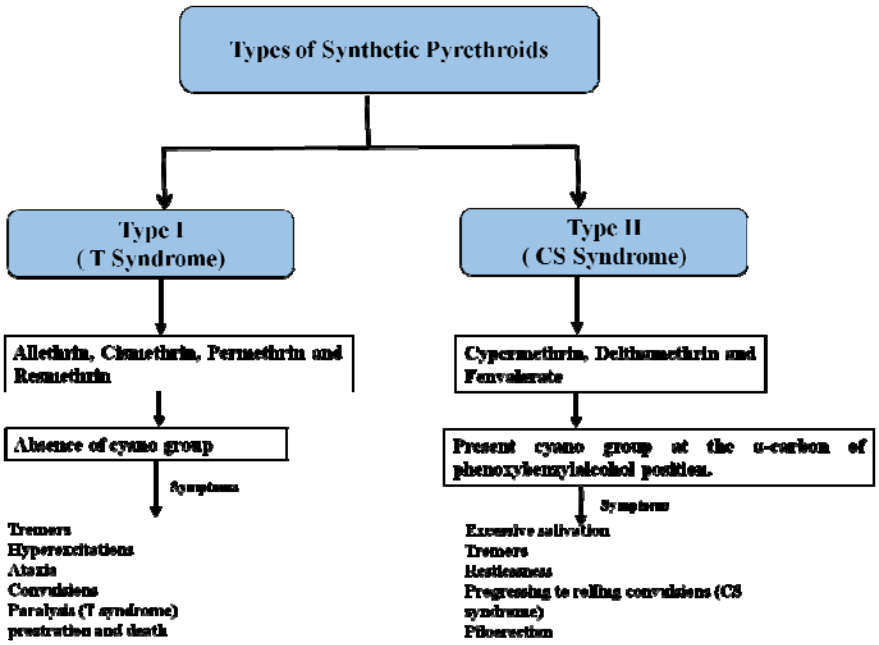


Fig 2: Types of synthetic pyrethroids type I and II

1. 3 Toxicity

1.3.1 Human toxicity

Pyrethroids are increasingly being used in public health and animal husbandry and are claimed to pose relatively low human toxicity. Pyrethroids are unlikely to be of acute toxicity for occupationally exposed subjects employing good work practices and safety precautions [7]. However, about two hundred cases of acute occupational pyrethroid poisoning resulting from inappropriate handling were first reported in China in 1982 [7]. The majority of the cases involved exposure to deltamethrin, followed by fenvalerate, cypermethrin and other pyrethroids (cyfluthrin, fenpropathrin). In an epidemiological survey conducted in China, the prevalence of mild acute pyrethroid poisoning in 3,113 spraymen was 0.38% [8]. However, Litchfield [9] and He *et al*., [7] reported fatal fenvalerate poisoning due to oral ingestion of 2g/kg bw dose [7, 9]. Sweden has banned fenvalerate for its use in forestry following health-related complaints from workers [10-11]. In addition to occupational exposure, the indoor application of pyrethroids led to their chronic exposure to unaware individuals. Adsorption of pyrethroids by small dust particles and various other surfaces makes them potential indoor toxicants [12]. Suspected pesticide-related illness and injury have been reported in Oregon since 1987 [12-13]. For incidents reported to the Pesticide Poisoning Prevention Programme in the years 2000-2002, the active pesticides associated with the largest number of pesticide illness were pyrethrins and synthetic pyrethroids (Table 3) [2-3]. The symptoms of intentional poisoning often start with epigastric pain, dizziness, headache, nausea, anorexia, fatigue, increased stromal secretion, muscular fasciculation and vomiting within 10 min-1h after ingestion. Additionally, in severe cases of intentional poisoning; convulsive attacks, disturbance of consciousness, dyspnea, cyanosis and pulmonary edema mainly occur [14].

Synthetic pyrethroids are lipophilic insecticides whose biological activity seems to be directly related to their chemical structure [15-16]. As a result, they interfere with lipid packing order that leads to disturbance in cell membrane bilayer [17, 18] and hence cause release of histamine from basophils and mast cells [15]. *Chrysanthemum* flower harvesters suffer from a special form of occupational allergy, namely '*Chrysanthemum* Pickers Allergy' and extracts of *chrysanthemum* flowers are also reported to cause anaphylactic and anaphylactoid reactions [18, 19]. Kolmodin-Hedman *et al*., [19] reported that fenvalerate and permethrin exposed workers were found to have contact dermatitis and asthma-like reactions. The initial symptoms of acute occupational pyrethroid poisoning are burning and itching sensations in the face or dizziness that usually develop 4-6 hours after exposure. Hypersensitivity reactions including wheezing, sneezing, shortness of breath and bronchospasm may be noted [19-21]. Death in these cases is however due to respiratory failure. Eye exposures may result in mild to severe corneal damage [10].

Le Quesne *et al*., [22] described transient facial sensory symptoms among 23 workers exposed to cypermethrin, fenpropathrin, fenvalerate and permethrin in the laboratory or in the field trials [21]. Sensations were noted as tingling, burning, like "coming in form the cold" nettle rash or sunburn but there were no abnormal neurological signs. Cutaneous paraesthesia is the most prominent health symptom known to accompany topical contact with the synthetic pyrethroids [23]. This is considered to be a result of repetitive firing of sensory nerve endings and should be a warning signal for overexposure. The paresthesia has been described as ranging from a mild itch to a stingling sensation, with progression to numbness in some cases and can be exacerbated by direct exposure to sunlight and upon contact with water [24]. The duration of symptoms varies, ranging from several hours to about 24 hours [25]. In 1941, workers with plant extract, pyrethrum noted a paraesthesia similar to but less intense than, that described by present day workers with the more potent synthetic pyrethroids [26]. Flannigan and Tucker [30] reported that permethrin caused the least pronounced and flucythrinate the most pronounced paraesthesia, whereas cypermethrin and fenvalerate were intermediate and approximately equal in effect.

Table 3: Reported pesticide-related illness associated with pyrethrins or pyrethroids, oregon in the years 2000-2002

Year	Total Cases	Cases Associated with Pyrethrins / Pyrethroids
2000	200	35
2001	213	35
2002	194	31

1.3.2 Toxicity in aquatic organisms

Pyrethroids have a devastating effect on aquatic invertebrates with most LC_{50} values less than 1.0 parts per billion (ppb). These LC_{50s} are similar to those for mosquito, black fly and tsetse fly larvae, for which pyrethroids are often used in vector control [27]. The most sensitive organisms are surface dwelling insects, mayfly nymphs and some of the large crustaceans; zooplankton and benthic organisms are also significantly affected by pyrethroids. Even at low (non-lethal) concentration, there are significant behavioral changes in aquatic invertebrates e.g. in their ability to respond to tactile stimuli, which may affect their survival. Lobster and shrimp are susceptible to all pyrethroids.

Pyrethroids are highly toxic to fish; about 40 percent of the LC_{50} values for fish are less than 1.0 ppb. Deltamethrin is the most toxic; allethrin is the least toxic; fenvalerate, permethrin and cypermethrin are intermediately toxic pyrethroids [28]. They can indirectly affect fish due to diminished and insecticide contaminated food supplies [28, 29].

Fenvalerate mainly affects the teleost nervous system. It also produces osmoregulatory imbalance, as judged by altered calcium uptake [31], abnormal sodium and potassium excretion rates, and elevated urine osmolality [32, 33]. Histological damage to gill surface by this insecticide is attributed to its high accumulation in gills, irritation due to elevated mucus secretion, increased ventilation volume, and decreased gill-oxygen uptake efficiency [32, 33]. Symptoms of fenvalerate poisoning in fish include loss of schooling behavior, swimming near the water surface, hyperactivity, seizures, loss of buoyancy, elevated cough rate, increased gill mucus secretions, flaring of the gill arches, head shaking and listlessness before death [34].

1.3.3 Toxicity in bees

Pyrethroids are toxic to insects including bees as they have a strong repellant action against them by affecting their feeding behavior [35]. This insecticide initially cause knockdown (the inability of the insect to maintain its normal position) followed by recovery or death.

Fenvalerate has some repellency action on bees, as a result of which it reduces bee's contact with plant surfaces; that lasts up to a day after application [27]. Since most intoxicated bees die in the field before contamination of their hive, the brood remains unexposed to insecticides.

1.3.4 Toxicity in birds

Birds are indirectly affected by pyrethroids, because of the threat to their food supply. Waterfowl and small insectivorous birds are the most susceptible [36]. They are more resistant to pyrethroids than are mammals, as judged by studies with Japanese quail and rats where as the basis for this resistance is not well understood [37].

Quail excreted fenvalerate more rapidly, had lower absorption and faster metabolism; the oral LD_{50} for quail was >4,000 mg/kg bw. versus 450 mg/kg bw. for rat, almost an order of 10 magnitude higher [38].

1.3.5 Toxicity in earthworms and other soil biota

Soil applications of pyrethroids have been shown to decrease the number of predatory mites and at high rates, pyrethroids caused significant reduction in earthworm populations [39].

1.3.6 Mammalian toxicity

The pyrethroids are potent neurotoxicants in vertebrates and invertebrates but acute toxicity in mammals is low. The low mammalian toxicity is because of their swift biotransformation and release from the organism in the form of non-active metabolites, mostly in urine [40].

1.4 Resistance to Synthetic Pyrethroids

The cotton bollworm, *Helicoverpa armigera*, is one of the most damaging cotton pests in China. Since early 1980s, pyrethroids had been used widely to control this insect. By the end of 1980s, *H. armigera* developed resistance to fenvalerate and deltamethrin in Asia, particularly from China, Pakistan and India as well as from West Africa [41, 42, 43]. Pyrethroid is failure to control cotton bollworm poses a critical problem to cotton growers due to the lack of new and effective insecticides. In addition to cotton bollworm, German cockroach, *Blattella germanica* codling moth, *Cydia pomonella,* yellow fever mosquito, *Aedes aegypti*, house fly, *Musca domestica*, *Anopheles minimus* and African *Anopheles funestus* also developed resistance against synthetic pyrethroids [44, 45-54].

1.5 Disadvantages of Using Pyrethroids

1. Synthetic pyrethroids are not systemic and do not have translaminar action, so they are not effective against sucking pests lime aphids and mealy bugs resulting in the resurgence of these pests.
2. Constant use of synthetic pyrethroids increase incidence of mites in crops like cotton, tea, vegetable etc.
3. With large scale use of synthetic pyrethroids incidence of *Alternaria* disease increased in cotton mostly is sandy soil.
4. The synthetic pyrethroids are highly toxic to fish. The lipophilicity of pyrethroids indicates that they will be absorbed strongly by the gills of fish even at very low concentration in water.

2. Deltamethrin

Pyrethroids were introduced as replacement for the persistent nature of the organophosphates and chlorinated pesticides. Pyrethroids, particularly deltamethrin are considered to be safe. But the studies on toxic effects of deltamethrin are very less. So there is a need to investigate deleterious toxic effects of deltamethrin and other pyrethroids to determine their impact in case of human exposure. Deltamethrin is used to control apple and pear suckers, plum fruit moth, caterpillars on brassicas, pea moth, aphids (apples, plums, hops), winter moth (apples and plums), codling and tortrix moths (apples). Control of aphids, mealy bugs, scale insects, and whitefly on glasshouse cucumbers, tomatoes, peppers, potted plants, and ornamentals. It also controls numerous insect pests of field crops. Formulations include emulsifiable concentrates, wettable powders and flowable formulations and granules. There are no known incompatibilities with other common insecticides and fungicides [55].

Deltamethrin has a rapidly disabling effect on feeding insects and for this reason there is hope that it may be useful to control the vectors of "non-persistent" viruses (viruses that can be passed on by the vector within a few minutes of starting to feed on the plant). The mode of action of deltamethrin is thought to be mainly central in action, or at least originates in higher nerve centers of the brain [56, 57]. Death of insects seems to be due to irreversible damage to the nervous system occurring when poisoning lasts more than a few hours [56-58]. Deltamethrin poisoning occurs through cuticular penetration or oral uptake. Deltamethrin has very broad-spectrum control and is considered the most powerful of the synthetic pyrethroids [56, 59, 60]. Technical deltamethrin has greater than 98% purity. Deltamethrin is chemically stable and exposure to breakdown products is therefore not an issue. It has a low vapour pressure (2.0×10−6 Pa or 1.5×10−8 mm Hg) and is considered to be ractically non-volatile; inhalation risks are thus likely to be low. It is lipophilic (log Po/w 5.43) and is readily soluble in organic solvents, but is virtually insoluble in water (<2 µg/l), forming suspensions rather than solutions [56, 59, 60].

2.1 Absorption, distribution, metabolism and excretion

Pyrethroids in general are lipophilic and would be expected to be readily absorbed, both orally and dermally. Deltamethrin is readily absorbed from the gastrointestinal tract after oral administration in rats and mice. Studies in rats have shown that deltamethrin, an ester, is rapidly metabolised by tissue esterases, which are widely distributed including in the gut wall and liver, and by liver microsomal oxidases [61, 62]. The principle routes of metabolism in rodents involve cleavage of the ester link to produce acid and alcohol moieties, oxidation of various parts of the molecule before or after cleavage of the ester link, and conjugation with sulfuric acid, glycine or glucuronic acid of the products of oxidation of both moieties. About 13–21% of unchanged deltamethrin is excreted in rat faeces and metabolites are readily excreted in urine and faeces within 2–4 days, with the exception of the cyano group, which is converted to thiocyanate and excreted more slowly (about 20% still retained mainly in skin and stomach after 8 days) [61, 62].

Metabolism in mice is similar to that in rats, but with less excretion of unchanged deltamethrin, less tissue retention of metabolites after 8 days, similar but not entirely identical urinary and faecal metabolites and differing ratios of faecal metabolites [61, 62]. Evidence of development of tolerance in rats on repeated dosing with deltamethrin suggests that the compound induces its own metabolism [63]. The routes of metabolism in man have not been well studied, but the limited evidence available suggests that they are likely to be similar to those in rodents. Absorption, distribution and excretion have been studied in three male human volunteers given ^{14}C-radiolabelled deltamethrin as a single 3 mg dose orally [2-3, 62]. Plasma Concentrations were maximal at 1–2 h after administration with an apparent elimination half-life in plasma of 10–11.5 h. Levels in blood cells and saliva were very low. Over 5 days, 10–26% of the dose was eliminated via faeces and 51–59% via urine, of which 90% of urinary excretion was within the first 24 h. Urinary half-life of 10–13.5 h was consistent with plasma half-life. The occurrence of the metabolite 3-(2, 2-dibromovinyl)-2, 2-dimethylcyclopropane carboxylic acid, in sprayers of deltamethrin confirms that hydrolysis of the ester occurs in man [63, 64].

Deltamethrin is poorly absorbed by the dermal route in rats, with only 3.6% of the amount applied to skin being absorbed and excreted in 24 h [2-3]. In view of its lipophilicity, the low absorption is surprising. There are no published data on dermal absorption in humans.

2.2 Acute toxicity

The acute toxicity from single doses of deltamethrin differs considerably, depending on the route of administration and the vehicle [3, 66]. The LD_{50} ranged from 30 to 140 mg/kg body weight (b.wt) in rats, with a minimum toxic dose of 10 mg/kg bw causing mild salivation [67] ; the LD_{50} ranged from 19 to 34 mg/kg bw in mice when deltamethrin was given orally in vegetable oil or polyethylene glycol [68]. However, when deltamethrin was given orally to rats in aqueous vehicles, no deaths were observed at doses up to 5000 mg/kg bw of an aqueous suspension of deltamethrin in carboxymethyl cellulose, or when given as a wettable powder at doses up to 15,000 mg/kg bw. No deaths were observed in dogs given up to 300 mg/kg bw in capsules. No deaths were observed after deltamethrin administration via the dermal route either in rats at doses up to 800 mg/kg bw in organic solvents or in rabbits up to 2000 mg/kg bw in polyethylene glycol. Administration via inhalation was similarly of low toxicity, with an LD_{50} in rats of 600 mg/m3 for dust; the LD_{50} exceeded 785 mg/m^3 when given as an aerosol or micronised powder. Clinical signs of acute poisoning in rodents are typical of a Type II pyrethroid [2, 3, 64] including choreoathetosis (writhing) and salivation (hence also known as CS-syndrome), motor inco-ordination, tremors, respiratory difficulties and convulsions, hyperactivity and hypersensitivity.

2.3 Human toxicity

Reports of acute deltamethrin human poisonings, other than from occupational exposure, are rare. In one case, 5 g deltamethrin ingested by a 13-year-old girl in a suicide attempt resulted in loss of consciousness, muscle cramps, myosis and tachycardia. Hospital treatment resulted in complete recovery within 48 h [2-3]. Ingestion of 1.75 g deltamethrin by a 23-year-old man caused no neurological defects. Other digestive and liver signs were attributed to the ingestion of the solvent, xylene in which deltamethrin was dissolved [3, 64]. Reported poisonings from occupational exposure have involved mainly skin symptoms such as burning and paraesthesia (numbness and tingling). An agricultural worker contaminated with liquid containing 5 g/l of deltamethrin developed paraesthesia of the legs, mouth and tongue, and diarrhoea. Tingling persisted for 24 h but had disappeared by 48 h [2-3, 64]. Repeated sprayings in cotton fields by unprotected workers in China in the 1980s resulted in 90% reporting skin sensations. Severe headache, dizziness, fatigue, nausea and anorexia, with transient EEG changes, were also reported in some cases, and muscle fasciculation and convulsions in one severe case. All made a complete recovery. In a review of 573 cases of acute pyrethroid poisoning reported in the Chinese medical literature, 325 involved deltamethrin. Of these, 158 were occupational and attributed to inappropriate handling, spraying with high concentrations or for long durations, spraying against the wind, clearing blocked sprays by mouth and hands, and lack of personal protection. The remaining 167 cases were accidental, described as mostly ingestion of 5–500 ml of 2.5% deltamethrin. Two of the occupational cases died of convulsions while all others recovered within 1–6 days with treatment [3, 54, 59].

2.4 Irritation and sensitization

Technical deltamethrin (98% purity) is non-irritant to rabbit skin. When applied in formulations containing 2.5% active ingredient, deltamethrin is slight to moderately irritating to rabbit skin [58, 60]. Technical deltamethrin and formulations

containing deltamethrin cause transient eye irritation in rabbits and rats. No potential for sensitisation was found using technical deltamethrin in guinea pigs [3-4].

In humans, deltamethrin formulations can cause redness, burning sensation and itching following skin contact [3, 54, 64, 60]. Cutaneous and mucous membrane irritation was reported in some workers involved in the manufacture of deltamethrin in Europe the 1970s, exposed dermally to technical deltamethrin and its formulations [3, 64, 70]. The effects reported included pruritis, a blotchy local burning sensation and blotchy erythema for about 2 days, followed by desquamation of the contaminated area, itching of the face, especially around the mouth, rhinorrhoea and lachrymation [3, 68, 70]. No long-term effects were observed in these workers and later manufacturing plants have provided better protection to prevent such effects [3, 64, 70]. Transient abnormal facial sensation, sneezing and rhinorrhoea have been reported among workers packing deltamethrin in workshops in China with no mechanical ventilation or air conditioning [3, 61]. Dizziness, fatigue, nausea and red miliary papules were also reported to a lesser extent, but no signs of acute poisoning such as headache and fasciculations. An airborne concentration of deltamethrin in the breathing zone of the workers was reported to be 5–12 $\mu g/m^3$.

Similar results were reported in a more detailed study of 50 spraymen by the Zhang *et al*., [68]. A few studies have reported adverse effects in humans from the use of deltamethrin on bednets. Skin irritation for 1 week after treatment of nets with a target dose of 25 mg/m^2 was reported by most of 352 householders in an open-ended questionnaire after 1 year of use in Assam [71-73]. Runny nose and sneezing has been reported in the first few days of use after treatment with target doses of 10–30 mg/m^2 [74-75]. It is widely agreed that skin sensations are an early manifestation of exposure, that they are due to local rather than systemic exposure, and that they are readily reversible on cessation of exposure.

2.5 Short-term exposure

Rats dosed orally by gavage for 13 weeks with doses of 0. 0.1, 1.0, 2.5 and 10 mg/kg bw/day deltamethrin in propylene glycol (PEG 200) showed slight hypersensitivity at the top dose and reduced body weight gain in males at 2.5 and 10 mg/kg bw/day. The no-observed-effect level (NOEL) based on body weight changes was 1 mg/kg bw/day. There were no effects on organ weight or microscopic pathology [3, 68]. In dogs given the same doses of deltamethrin in PEG 200 orally in gelatin capsules for 13 weeks, followed by a 20-week recovery period, liquid faeces were observed throughout the dosing period in all dosed groups and occasional dose-related vomiting was seen early in the dosing period at 1, 2.5 and 10 mg/kg bw/day. Signs of neurotoxicity (unsteadiness, tremors and jerking movements) were seen at 10 mg/kg bw/day, particularly in the first 4 weeks of dosing. Variations in the patellar reflex were observed at doses of 1 mg/kg bw/day and above and these persisted in some dogs during the recovery period after treatment with 1 mg/kg bw/day. In a 21-day dermal toxicity study in the rat, doses of 0, 100, 300 or 1000 mg deltamethrin/kg bw/day were applied in PEG 400 vehicle daily to shaved, intact skin [76]. No signs of systemic toxicity were seen. There were slight but statistically insignificant reductions in food consumption and body weight gain in male animals given 300 or 1000 mg/kg bw/day. Dermal irritation was observed in all treated groups and histopathological evidence of skin damage was seen in up to half of the animals in each treatment group. The occurrence of skin lesions was not dose related [76].

The lack of systemic toxicity indicates poor absorption dermally and a NOEL of 1000 mg/kg bw/day can be assumed for systemic toxicity from this study. In a short-term inhalation study, rats were exposed to aerosolised deltamethrin powder at mean concentrations of 3, 9.6 and 56.3 mg/m^3, for 6 h/day, 5 days/week, for 2 weeks, then for 4 days during a third week. About 87% was in the form of respirable particles [2-4, 64, 71]. Signs of toxicity (ataxia and arched back) were seen in the highest dose group. All groups showed signs of irritation from the powder and males in all groups showed an average of 5% reduction in body weight. Increased serum sodium ion levels were noted in the two highest dose groups. There were no deaths and no pathological findings in the highest dose group. Irritation and weight loss were slight at 3 mg/m^3, which can be considered a NOEL [2-4, 64, 71].

2.6 Long-term exposure

Deltamethrin fed in the diet for 2 years to CD-1 mice at concentrations of 0, 1, 5, 25 or 100 ppm (mg/kg of diet) and to rats at concentrations of 0, 2, 20 or 50 ppm was without any clear treatment-related effects in either species [2-4, 64, 71]. The highest doses in these studies were equivalent to around 15 mg/kg bw/day in mice and 2.5 mg/kg bw/day in rats. Studies in which deltamethrin in arachis oil was given by gavage at doses of 0, 1, 4 and 8 mg/kg b.wt/day to C57BL/6 mice or 0, 3 and 6 mg/kg bw/day to BDVI rats for 2 years have been evaluated by the International Agency for Research on Cancer [77]. In mice, there was reduced growth and survival at the top dose but no increase in tumour incidence. In rats, there was reduced growth at the top dose but no effect on survival. There was significant increase in thyroid adenomas of unspecified type in males receiving 3 mg/kg bw/day and in females receiving 6 mg/kg bw/day, compared to controls [3, 77]. IARC concluded that there was inadequate evidence for the carcinogenicity of deltamethrin in experimental animals and noting that there were no data available on cancer in humans, concluded that deltamethrin is not classifiable as to its carcinogenicity in humans [3, 77].

2.7 Mutagenicity

In vitro tests on gene mutations in bacteria and in cultured mammalian cells and a test for DNA damage in yeast cells were all negative. However, in three *in vivo* tests in mice by one group of authors [78-79] micronucleus formation, chromosomal aberrations in bone marrow and abnormal sperm morphology were seen. But in studies by other authors on micronucleus formation and chromosomal aberrations in bone marrow in mice no effects were seen. The overall evaluation of studies in vitro and *in vivo* was that deltamethrin is not a strong mutagenic or clastogenic compound [80-82].

2.8 Reproduction and developmental toxicity

In a multigeneration study in rats, in which there were three generations and two litters per generation, deltamethrin was given at doses of 0, 2, 20 or 50 ppm in the diet. The only effects were in the top dose group, equivalent to around 6 mg/kg bw/day. The effects seen were reduced body weight gain in top dose F_0 females, reduced food consumption in top dose F1 males and slightly reduced pup weight at weaning in the 50 ppm group [3, 81]. A NOEL of 20 ppm diet, equivalent to 2.4 mg/kg bw/day was determined in this study. Developmental toxicity studies were conducted in mice, rats and rabbits, given deltamethrin dissolved in oil, orally by gavage [3, 66-70]. In one study, Swiss CD-1 mice were given doses of 0, 0.1, 1 or 10 mg/kg bw/day deltamethrin in sesame oil on days 6–17 of pregnancy and sacrificed on day 18 of

pregnancy. Dose-related, but minimal reductions in fetal weight and delayed ossification were observed at all doses.

In another study by the same authors, in the same strain of mouse, using the same dose levels, same vehicle and the same period of dosing, retardation of fetal development was seen only at 1 and 10 mg/kg bw/day in animals sacrificed on day 18 of pregnancy [78, 93]. In this study, some females were allowed to litter out and no effect on pup weight was observed at any dose level at 1 and 21 days after birth.

2.9 Neurotoxicity and behavior

Clinical signs of neurotoxicity during acute dosing and short-term repeat dosing studies in rodents and dogs have already been described above. Such effects were not observed in long-term repeat dosing studies, when lower doses were administered. No effects on nerve or muscle histology were seen in any of the animal toxicity studies. In the studies described earlier, the lowest effect level for neurotoxicity was 0.1 mg/kg bw/day in the 90-day dog study, in which deltamethrin was administered in capsules. This method of administration would be expected to result in very rapid absorption once the capsule wall was broken down. Other short- and longer-term studies in rats and dogs demonstrated absence of neurotoxic signs at doses up to 1 mg/kg b.wt/day or higher. Special studies on neurotoxicity have revealed no potential for delayed neuropathy in hens. They did however confirm that neurotoxic and behavioural effects can occur at acute doses of 2 mg/kg b.w/day and above in rats and dogs [7, 78]. Two studies have been undertaken on the effects of neonatal treatment with two types of pyrethroid, bioallethrin (Type I) or deltamethrin (Type II), on brain neurochemistry and behaviour in mice [81-86].

An increasing number of reports have described various immune changes in individuals who have been inadvertently or occupationally exposed to chemical agents [81-84]. These range from unconfirmed reports with putative non-immunosuppressive compounds such as trichloroethylene and methyl isocyanate to more substantiated studies with polychlorinated biphenyls (PCBs), asbestos, and silica. In addition, the results from in vitro and *in vivo* experimental studies have suggested that many environmental chemicals can suppress the immune functions and alter host resistance to infectious agents or tumor cells [87-91]. The duration of immunosuppressive states might be transient or long-lasting depending on the severity and site of the specific xenobiotic effect [80-84]. It is often difficult to predict how a given chemical will interact with the immune system since there are numerous factors that influence toxicity. For instance, external factors such as housing and handling of the animals, stress, exercise, and intrinsic factors such as hormonal status or genetic disposition make each case unique [87-91]. Also, feedback or compensatory mechanisms associated with immunoregulation could further complicate these predictions. In many instances, it is these compensatory mechanisms that trigger immune mediated diseases and cellular dysfunction [87-91]. Although the obstacles are many, the adverse effects of pyrethroids on the immune system have become an increasingly diverse area of research. As mentioned above, immunosuppression is a common result of chemical exposure and can be assessed by a variety of methods. In immune cells, cytotoxicity usually occurs via two specific mechanisms or modes of cell death, either apoptosis or necrosis [91].

3. Pesticide- induced oxidative stress

The major source of organic free radicals and ROS is endogenous, particularly via the metabolism and bioactivation of xenobiotics or the reactivity of the actual parent compound. The consequence of increased free radical concentrations is either cellular injury or physiological dysfunction (Figure 3) [87-91]. Many compounds including pesticides have been found to result in free radical generation and have the potential to promote these types of injuries. For example, diquat and paraquat, bipyridyl herbicides, induce $O_2^{-\cdot}$ and H_2O_2 within cells [87-91]. Also, carbon tetrachloride undergoes dehalogenation to form a reactive trichloromethyl radical. This metabolite can interact with macromolecules by abstracting H atoms and generating more radical species. A number of halogenated hydrocarbons are capable of undergoing such dehalogenation reactions. For many pesticides, induction of oxidative stress is one the main mechanisms of their action [87-91]. The damage to membrane lipids, protein, and DNA is the endpoint biomarker of oxidative stress-inducing effects of pesticides [87-91]. Pesticides (DDT, BHC, piperonyl butoxide, and pyretheroids) have the ability induce any of the above events [87-91].

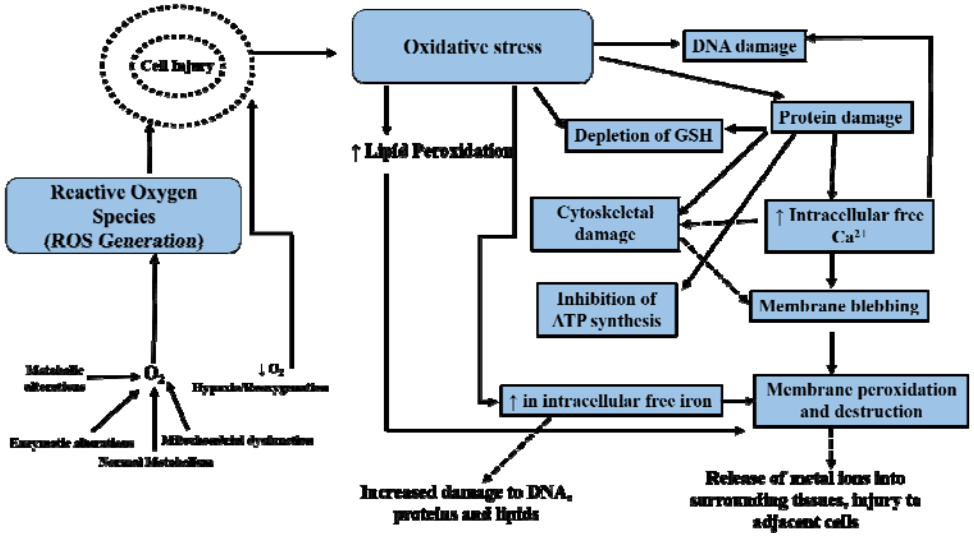


Fig 3: Mechanism of Oxidative cellular damage induced by pesticide

The above brief review of literature on the subject matter of the present study demonstrate that research area of toxicity of pesticides in particularly pyrethroids still offer a lot of opportunity to the scientists. There is a great deal of variability in the toxicity of even a single pesticide among terrestrial and aquatic species. When attempting to predict the toxicity of pesticides in estuarine ecosystems, effects of pesticide mixtures and interactions with nutrients should be considered. The toxicity of pesticides to humans and aquatic organisms, especially fishes, is an area of research requiring further study.

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