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ALLERTHRINS AS PYRETHROID AXONIC EXCITOXIN INSECTICIDE ACTS AS AN ENZYME INHIBITOR OF GLUCURONYL TRANSFERASE WITH MICROSOMAL CYTOCHROME P450 ENZYMES AND DEPOLARIZATION OF ACTION POTENTIAL

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ABSTRACT

Pyrethrins are naturally-occurring compounds with insecticidal properties that are found in pyrethrum extract from certain chrysanthemum flowers. The pyrethrins are often used in household insecticides and products to control insects on pets or livestock. Pyrethroids are manufactured chemicals that are very similar in structure to the pyrethrins, but are often more toxic to insects as well as to mammals and last longer in the environment than the pyrethrins. More than 1,000 synthetic pyrethroids have been developed, but less than a dozen of them are currently used. Permethrin is the most frequently used pyrethroid insecticide.

KEYWORDS: Allethrins, Pyrethrins, Pyrethroids, Prallethrin, Tetramethrin, Cypermethrin, Deltamethrin, Piperonyl butoxide.

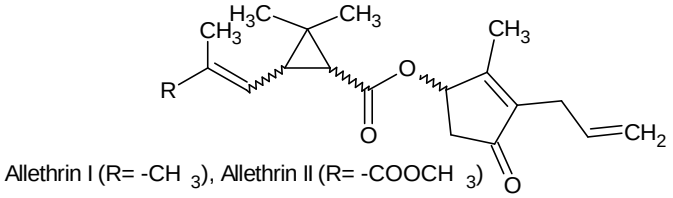
INTRODUCTION

The **allethrins** are a group of related synthetic compounds used in insecticides. They are synthetic pyrethroids, a synthetic form of a chemical found naturally in the chrysanthemum flower. They were first synthesized in the United States by Milton S. Schechter in 1949. Allethrin was the first pyrethroid. The compounds have low toxicity for humans and birds and are used in many household insecticides such as **Raid** as well as mosquito coils. Raid is the brand name of a line of insecticide products produced by S.C. Johnson & Son, first launched in 1956. Effective in: American cockroach, German cockroach, Brown banded cockroach, Oriental cockroach, Flea, Carpenter ant, Spider, Black carpet beetle, Stable fly,

Blue bottle fly, Millipede, Indian meal moth, Mosquito, Tick, Paper wasp, Yellow Jacket, Bald-faced Hornet, Sow bug, House fly, Earwig, Centipede.[1]

Figure-1: Insecticides

Prallethrin is a pyrethroid insecticide. Prallethrin 1.6% w/w liquid vaporizer is a repellent insecticide which is generally used for the control of mosquitoes in the household. Marketed as a mosquito repellent by Godrej as GoodKnight Silver Power and SC Johnson as All Out in India. It is also the primary insecticide in certain products for killing wasps and hornets, including their nests. It is the main ingredient in the consumer product Hot Shot Ant & Roach Plus Germ Killer spray. The World Health Organization published in 2004 that Prallethrin is of low mammalian toxicity, with no evidence of carcinogenicity and is very toxic to bees and fish but of low toxicity to birds. The initial active ingredient was the first synthetic pyrethroid, allethrin. Raid derivatives aimed at particular invertebrate species can contain other active agents such as the more toxic cyfluthrin, another synthetic pyrethroid. Currently Raid Ant & Roach Killer contains pyrethroids, piperonyl butoxide and permethrin; other products contain tetramethrin, cypermethrin and imiprothrin as active ingredients. Raid Flying Insect Killer, a spray, uses prallethrin and D-phenothrin.[2]



Allethrin I (R= -CH 3), Allethrin II (R= -COOCH 3)

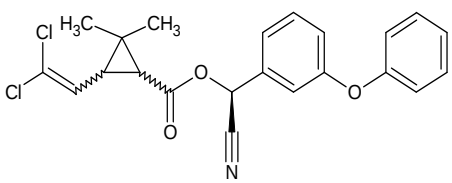
Figure-2: Allethrin I & Allethrin II

It is highly toxic to fish and aquatic invertebrates. At normal application rates, allethrin is slightly toxic to bees. Insects subject to exposure become paralyzed (nervous system effect) before dying. Allethrins are toxic to cats because they either do not produce, or produce less of certain isoforms of glucoronyl transferase, which serve in hepatic detoxifying metabolism pathways. They are also used as an ultra low volume spray for outdoor mosquito control.

Allethrin I and allethrin II differ by having a methyl group and a methyl ester, respectively, on one terminus. Each of these allethrins consists of the eight possible stereoisomers. A partly enantiopure variant of allethrin I, consisting of only two stereoisomers in an approximate ratio of 1:1, is called bioallethrin. The same mixture of isomers, but in an approximate ratio of 3:1, is known as esbiothrin.

A **pyrethroid** is an organic compound similar to the natural pyrethrins produced by the flowers of pyrethrums (*Chrysanthemum cinerariafolium* and *C.coccineum*). Pyrethroids now constitute the majority of commercial household insecticides. In the concentrations used in such products, they may also have insect repellent properties and are generally harmless to human beings in low doses but can harm sensitive individuals. They are usually broken apart by sunlight and the atmosphere in one or two days, and do not significantly affect groundwater quality.[3]

Mode of action: Pyrethroids are axonic excitoxins, the toxic effects of which are mediated through preventing the closure of the voltage gated sodium channels in the axonal membranes. The sodium channel is a membrane protein with a hydrophilic interior. This interior is a tiny hole which is shaped precisely to strip away the partially charged water molecules from a sodium ion and create a favorable way for sodium ions to pass through the membrane, enter the axon and propagate an action potential. When the toxin keeps the channels in their open state, the nerves cannot repolarize, leaving the axonal membrane permanently depolarized, thereby paralyzing the organism. Pyrethroids can be combined with the synergist piperonyl butoxide, a known inhibitor of key microsomal cytochrome P450 enzymes from metabolizing the pyrethroid, which increases its efficacy (lethality).[4]



(*S*)-cyano(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

Figure-3: Pyrethroid

The earliest pyrethoids are related to pyrethrin I and II by changing the alcohol group of the ester of chrysanthemic acid. This relatively modest change can lead to substantially altered activities. For example, the 5-benzyl-3-furanyl ester called resmethrin is only weakly toxic to mammals (LD_{50} (rat, oral)=2,000 mg/kg) but is 20–50 times more effective than natural pyrethrum and is also readily biodegraded. Other commercially important esters include tetramethrin, allethrin, phenothrin, barthrin, dimethrin and bioresmethrin. Another family of pyrethroids have altered acid fragment together with altered alcohol components. These require more elaborate organic synthesis. Members of this extensive class include the dichlorovinyl and dibromovinyl derivatives. Still others are tefluthrin, fenpropathrin, and bioethanomethrin.[4]

Piperonyl butoxide (PBO) is an organic compound used as a component of pesticide formulations. It is a waxy white solid. It is a synergist. That is, despite having no pesticidal activity of its own, it enhances the potency of certain pesticides such as carbamates, pyrethrins, pyrethroids, and rotenone. It is a semisynthetic derivative of safrole. PBO was developed in the late 1930s and early 1940s to enhance the performance of the naturally derived insecticide pyrethrum. Pyrethrum is and was an important insecticide against mosquitoes and other disease-carrying vectors, thereby providing public health benefits, e.g., preventing malaria. Although exhibiting little intrinsic insecticidal activity of its own, PBO increases the effectiveness of pyrethrins, thus is called a synergist. PBO was first patented in 1947 in the US by Herman Wachs. PBO was first registered in the United States in the 1950s. PBO is mainly used in combination with insecticides, such as natural pyrethrins or synthetic pyrethroids, in ratios (PBO: pyrethrins) ranging from 3:1 to 20:1. Appearing in over 1,500 United States EPA-registered products, PBO is one of the most commonly registered synergists as measured by the number of formulas in which it is present. It is approved for pre- and postharvest application to a wide variety of crops and commodities, including grain, fruits and vegetables. The application rates are low; the highest single rate is 0.5 lbs PBO/acre. It is also used extensively as an ingredient with insecticides to control insect pests in and around the home, in food-handling establishments such as restaurants and for human and veterinary applications against ectoparasites (head lice, ticks, fleas). A wide variety of water-based PBO-containing products such as crack and crevice sprays, total release foggers, and flying insect sprays are produced for and sold to consumers for home use. PBO has an important public health role as a synergist used in pyrethrins and pyrethroid formulations

used for mosquito control (e.g. space sprays, surface sprays and bed nets). Because of its limited, if any, an insecticidal property, PBO is never used alone.

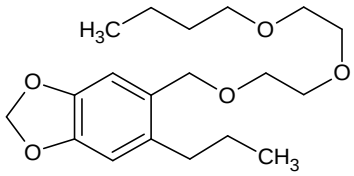


Figure-4: Piperonyl butoxide

PBO acts as an insecticide synergist by inhibiting the natural defense mechanisms of the insect, the most important of which is the mixed-function oxidase system, (MFOs) also known as the cytochrome P-450 system. The MFO system is the primary route of detoxification in insects, and causes the oxidative breakdown of insecticides such as pyrethrins and the synthetic pyrethroids - thus when PBO is added, higher insecticide levels remain in the insect to exercise their lethal effect. An important consequence of this property is that, by enhancing the activity of a given insecticide, less may be used to achieve the same result. PBO does not appear to have a significant effect on the MFO system in humans. PBO is found to be an efficacious, low-potency, neutral antagonist of G-protein-coupled CB1 receptors. Other synergists for pyrethroid insecticides include Sesamex and Sulfoxide (not to be confused with the functional group).

Types: Allethrin-the first pyrethroid synthesized, Bifenthrin-active ingredient of *Talstar*, *Capture*, *Ortho Home Defense Max*, and *Bifenthrine*, Cyfluthrin-an active ingredient in Baygon, dichlorovinyl derivative of pyrethrin, Cypermethrin- including the resolved isomer alpha-cypermethrin, dichlorovinyl derivative of pyrethrin, Cyphenothrin- active ingredient of K2000 Insect spray sold in Israel and the Palestinian territories, Deltamethrin-dibromovinyl derivative of pyrethrin, Esfenvalerate, Etofenprox, Fenpropathrin, Fenvalerate, Flucythrinate, Flumethrin, Imiprothrin, λ-Cyhalothrin, Metofluthrin, Permethrin-ichlorovinyl derivative of pyrethrin, Prallethrin-active ingredient in Baygon and All Out (India), Resmethrin-active ingredient of *Scourge*, Silafluofen, Sumathrin-active ingredient of Anvil, Γ-Fluvalinate, Tefluthrin, Tetramethrin, Tralomethrin, Transfluthrin-an active ingredient in Baygon.

Pyrethroids are toxic to beneficial insects such as bees and dragonflies and to fish and other aquatic organisms. At extremely small levels, such as 4 parts per trillion, pyrethroids are lethal to mayflies, gadflies and invertribrates that constitute the base of many aquatic and

terrestrial food webs. Pyrethroids are unaffected by conventional secondary treatment systems at municipal wastewater treatment facilities. They appear in the effluent, usually at levels lethal to invertebrates. Earlier studies suggested that most vertebrates have sufficient enzymes for rapid breakdown of pyrethroids, except for cats. Pyrethroids are highly toxic to cats because they do not have glucuronidase, which participates in hepatic detoxifying metabolism pathways. A recent study, however, suggests that developing mice exposed to deltamethrin (a pyrethroid pesticide) show neurological and behavioral changes resembling Attention Deficit/Hyperactivity Disorder (ADHD) in humans. In terms of LD_{50} for rats, Tefluthrin is the most toxic at 29 mg/kg. Anaphylaxis has been reported after pyrethrum exposure, but allergic reaction to pyrethroids has not been documented. Increased sensitivity occurs following repeated exposure to cyanide, which is found in pyrethroids like β-cyfluthrin.[5]

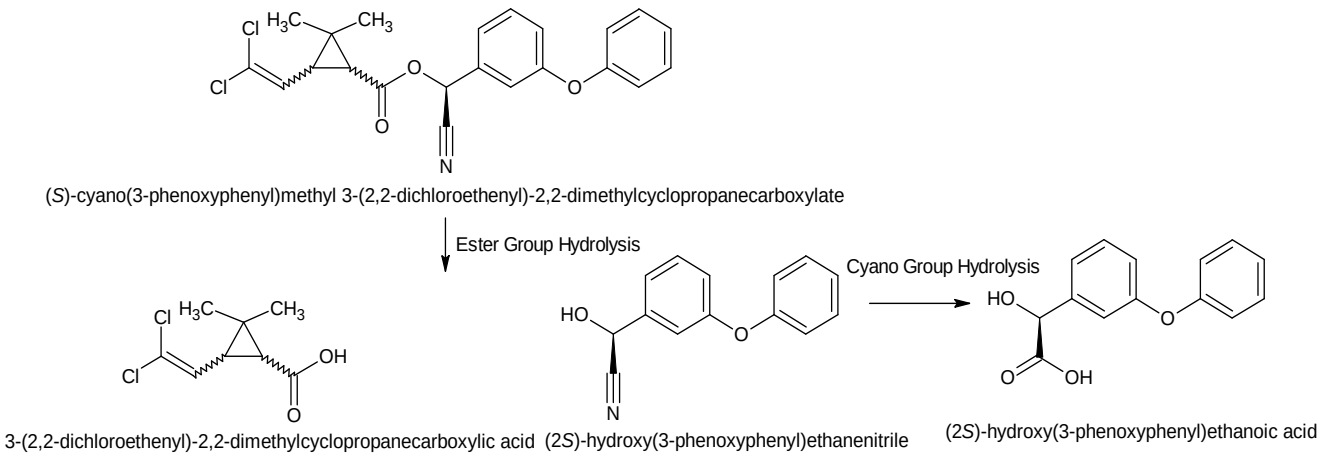
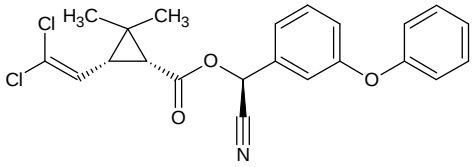


Figure-5: Pyrethroid hydrolysis

Ant chalk, also known as Chinese chalk or Miraculous Insecticide Chalk, is an insecticide in the form of normal looking chalk. It contains the pesticides cypermethrin and deltamethrin.

Cypermethrin is a synthetic pyrethroid used as an insecticide in large-scale commercial agricultural applications as well as in consumer products for domestic purposes. It behaves as a fast-acting neurotoxin in insects. It is easily degraded on soil and plants but can be effective for weeks when applied to indoor inert surfaces. Exposure to sunlight, water and oxygen will accelerate its decomposition. Cypermethrin is highly toxic to fish, bees and aquatic insects, according to the National Pesticides Telecommunications Network (NPTN). It is found in many household ant and cockroach killers, including Raid ant chalk.[6]



(*S*)-cyano(3-phenoxyphenyl)methyl (1*R*,3*R*)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

Figure-6: Cypermethrin

Cypermethrin is used in agriculture to control ectoparasites which infest cattle, sheep and poultry. In veterinary medicine, it is effective at controlling ticks on dogs. Cypermethrin is a moderately toxic through skin contact or ingestion. Excessive exposure can cause nausea, headache, muscle weakness, salivation, shortness of breath and seizures. In humans, cypermethrin is deactivated by enzymatic hydrolysis to several carboxylic acid metabolites, which are eliminated in the urine. Worker exposure to the chemical can be monitored by measurement of the urinary metabolites, while severe over dosage may be confirmed by quantitation of cypermethrin in blood or plasma. Cypermethrin is very toxic to cats which cannot tolerate the therapeutic doses for dogs. This is associated with glucuronidase deficiency in cats, the enzyme responsible for metabolizing cypermethrin. As a consequence, cypermethrin remains much longer in the cat's organism than in dogs or other mammals and can be fatal in large doses.

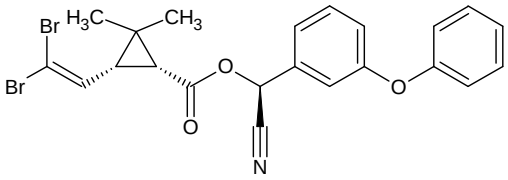
In male rats cypermethrin was shown to exhibit a toxic effect on the reproductive system. After 15 days of continual dosing, both androgen receptor levels and serum testosterone levels were significantly reduced. These data suggested that cypermethrin can induce impairments of the structure of seminiferous tubules and spermatogenesis in male rats at high doses. Long-term exposure to cypermethrin during adulthood is found to induce dopaminergic neurodegeneration in rats and postnatal exposure enhances the susceptibility of animals to dopaminergic neurodegeneration if rechallenged during adulthood.[7]

If exposed to cypermethrin during pregnancy, rats give birth to offspring with developmental delays. In male rats exposed to cypermethrin, the proportion of abnormal sperm increases. It causes genetic damage: chromosomal abnormalities increased in bone marrow and spleen cells when mice were exposed to cypermethrin. Cypermethrin is classified as a possible human carcinogen, because it causes an increase in the frequency of lung tumors in female mice. Cypermethrin has been linked to an increase in bone marrow micronuclei in both mice and humans. One study showed that cypermethrin inhibits gap junctional intercellular

communication, which plays an important role in cell growth and is inhibited by carcinogenic agents. Studies have shown that residue from cypermethrin can last for 84 days in the air, on walls, the floor and on furniture. Cypermethrin is a broad-spectrum insecticide, which means it kills beneficial insects as well as the targeted insects. Fish are particularly susceptible to cypermethrin, but when used according directions, application around residential sites pose little risk to aquatic life. Resistance to cypermethrin has developed quickly in insects exposed frequently and can render it ineffective.[8]

Deltamethrin is a pyrethroid ester insecticide. Deltamethrin products are among the most popular and widely used insecticides in the world and have become very popular with pest control operators and individuals in the United States. This material is a member of one of the safest classes of pesticides: synthetic pyrethroids. This pesticide is highly toxic to aquatic life, particularly fish and therefore must be used with extreme caution around water. Although generally considered safe to use around humans, it is still neurotoxic to humans. Deltamethrin is able to pass from a woman's skin through her blood and into her breast milk. Allergen and causing asthma in some people. There are many uses for deltamethrin, ranging from agricultural uses to home pest control. Deltamethrin has been instrumental in preventing the spread of diseases carried by tick-infested prairie dogs, rodents and other burrowing animals. It is helpful in eliminating and preventing a wide variety of household pests, especially spiders, fleas, ticks, carpenter ants, carpenter bees, cockroaches and bed bugs. Deltamethrin is also one of the primary ingredients in ant chalk.[9]

Deltamethrin is a pyrethroid composed of a single stereoisomer, of a possible 8 stereoisomers ($2^n=2^3=8$), selectively prepared by the esterification of (1*R*,3*R*)- or *cis*-2,2-dimethyl-3-(2,2-dibromovinyl)cyclopropanecarboxylic acid with (*α*,*S*)- or (+)-*α*-cyano-3-phenoxybenzyl alcohol or by selective recrystallization of the racemic esters obtained by esterification of the (1*R*,3*R*)- or *cis*-acid with the racemic or (*α*-*R*, *α*-*S*, or *α*-*R*/*S*)- or + or − alcohol. Deltamethrin plays key role in controlling malaria vectors and is used in the manufacture of long-lasting insecticidal mosquito nets. It is used as one of a battery of pyrethroid insecticides in control of malarial vectors, particularly *Anopheles gambiae* and whilst being the most employed pyrethroid insecticide, can be used in conjunction with, or as an alternative to, permethrin, cypermethrin and other organophosphate-based insecticides, such as malathion and fenthion. Resistance to deltamethrin (and its counterparts) is now extremely widespread and threatens the success of worldwide vector control programmes.[10]



(*S*)-cyano(3-phenoxyphenyl)methyl (1*R*,3*R*)-3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropanecarboxylate

Figure-7: Deltamethrin

Resistance has been characterized in several insects, including important vectors of malaria like the mosquito *Anopheles gambiae* as well as non-disease carrying pests like bed bugs.

Figure-8: Ant chalk and chrysanthemum flowers

Mosquitoes: Methods of resistance include thickening of the cuticle of the insect to limit permeation of the insecticide, metabolic resistance via over expression of metabolizing cytochrome P450 mono-oxygenases and glutathione-S-transferases and the knockdown resistance, sodium channel mutations which render the action of insecticides ineffectual, even when co-administered with piperonyl butoxide. Characterization of the different forms of resistance among mosquitoes has become a top priority in groups studying tropical medicine due to the high mortality of those who reside in endemic areas.[11]

Bed bugs: Two mutations, the valine to leucine mutation (V419L) and the leucine to isoleucine mutation (L925I) in voltage-gated sodium channel α-subunit gene, have been identified as responsible for knockdown resistance to deltamethrin in bed bugs. One study found that 88% of bed bug populations in the US had at least one of the two mutations, if not both, meaning that deltamethrin resistance among bed bugs is currently making this insecticide obsolete.[12]

In humans: Since deltamethrin is a neurotoxin, it temporarily attacks the nervous system of any animal with which it comes into contact. Skin contact can lead to tingling or reddening of the skin local to the application. If taken in through the eyes or mouth, a common symptom is facial paraesthesia, which can feel like many different abnormal sensations, including burning, partial numbness, pins and needles, skin crawling, etc. There are no reports indicating that chronic intoxication from pyrethroid insecticides causes motor neuron damage or motor neuron disease. Recently, in South Africa, residues of deltamethrin were found in breast milk, together with DDT, in an area that used DDT treatment for malaria control, as well as pyrethroids in small scale agriculture. There are no antidotes and treatment must be symptomatic, as approved by a physician. Over time, deltamethrin is metabolized, with a rapid loss of toxicity and passed from the body. A poison control center should be contacted in the event of an accidental poisoning.

In domestic animals: Cases of toxicity have been observed in cattle following use of agricultural deltamethrin preparation in external application for tick control.[13]

CONCLUSION

Allethrin is used almost exclusively in homes and gardens for control of flies and mosquitoes and in combination with other pesticides to control flying or crawling insects. The purified d-trans-isomer of allethrin is more toxic to insects and is used for control of crawling insects in homes and restaurants. Allethrin is a synthetic duplicate of a component of pyrethrum. Pyrethrum is a botanical insecticide extracted from chrysanthemum flowers. Allethrin, the first synthetic pyrethroid, was introduced in 1949 and is a mixture of several isomeric forms. The most common form is a 4:1 mixture of the *trans*- and *cis*-isomers. It is available in aerosol, coil, mat, dust and oil formulations. Aerosol and spray formulations of the purified d-trans- isomer of allethrin are also available. D-trans allethrin is usually combined with synergists such as piperonyl-butoxide for better action.

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