CHAPTER 3

Pyrethrins and Pyrethroid Insecticides

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3.1 Introduction

Pyrethrum is one of the oldest and most widely used botanical insecticides. Its insecticidal properties have been known for more than 150 years; although the earliest mention of the Chrysanthemum flowers from which it originates comes from early Chinese history, where it is believed that the flower passed into Europe along the silk roads.[1] The term "pyrethrum" refers to the dried and powdered flower heads of a white-flowered, daisy-like plant belonging to the *Chrysanthemum* genus. Pyrethrum's insecticidal properties were recognized in the middle of the 19th century, when an American named Jumticoff discovered that many Caucuses tribes used it for the control of body lice.[1] The earliest cultivation of pyrethrum, also called "Persian pyrethrum" or "Persian powders", was in the region of the Caucuses extending into Northern Persia.[2] The first Persian powders that were processed and commercialized in Europe in the 1820s were most likely prepared from a mixture of *C. roseum* and *C. corneum*. During and after 1876, these preparations were introduced into the USA, Japan, Africa and South America.[3,4] The superior insecticidal properties of *C. cinerariaefolium* were first discovered around 1845 and these species subsequently supplanted previously cultivated species. *Chrysanthemum cinerariaefolium* is currently cultivated in the USA, Japan, Kenya, Brazil, the Democratic Republic of the Congo, Uganda and India.[2,3]

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In 1917, the U.S. military made the first pyrethrum extracts by percolating the ground flower heads with kerosene, which were then incorporated into space sprays for use against house flies and mosquitoes.[1] Since pyrethrins are derived from plants, however, the supply has always been highly variable. A shortage during World War II hastened the search for synthetic insecticides like dichlorodiphenyltrichloroethane (DDT), which could be consistently produced and which was subsequently used by the Allies to manage insect vectors of human pathogens. The introduction of synthetic insecticides like organochlorines, organophosphates and carbamates represented a revolution in insect control because of their high insecticidal toxicity and consistent supply, however, they have been, or are being, phased out of use due to biomagnification, high non-target toxicity, or both.

The commercial limitations of pyrethrum extracts, which are collectively known as pyrethrins and are a mixture of six lipophilic esters, have long been recognized because of their high rate of photodegradation and a short "knockdown" (rapid paralysis) effect. After the discovery of the constituents of pyrethrins, researchers searched for derivatives of pyrethrins that had a higher resistance to photodegradation. This search directly led to the synthesis of pyrethroids. The advantages of pyrethrins and pyrethroids are that they are highly lipophilic, have a short half-life in the environment, have low toxicity to terrestrial vertebrates and do not biomagnify like older chemical classes, such as organochlorines (see Tables 3.1 and 3.2). In her book *Silent Spring*, Rachel Carson recognized that insecticides like pyrethrins offered alternatives to many of the insecticides that were used during the 1940s to 1970s.

Pyrethroids, the synthetic derivatives of pyrethrins, have changed structurally over the past several decades. However, the basic components of pyrethrins, a chrysanthemic acid linked to an aromatic alcohol through an ester linkage, have been conserved (see Figures 3.1 and 3.2). The widespread use of pyrethroids began in the 1970s after the development of photostable pyrethroids like permethrin and fenvalerate. Pyrethroid use has increased substantially throughout the world over the past few decades as organophosphate, carbamate and organochlorine insecticides are being phased out.[5–7] Pyrethrins and pyrethroids are estimated at 23% of the insecticide world market, with more than 3500 registered formulations, and are widely used in agriculture, residential areas, public health and food preparation.[8,9] Permethrin and cypermethrin are the most widely used pyrethroids in the USA, with about

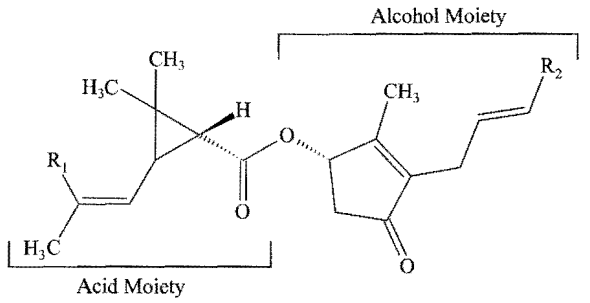
Table 3.1 Bioconcentration factors (BCF) for type I and II pyrethroids and DDT for rainbow trout (*Oncorhynchus mykiss*) from Muir *et al.*[221]

Compound	*BCF*
Cypermethrin	832
Permethrin	1940
Deltamethrin	502
Fenvalerate	403
DDT	72500

Table 3.2 LC_{50} values of pyrethrins, type I (allethrins, permethrin and resmethrin), II (cypermethrin and deltamethrin) and pseudopyrethroid (etofenprox) for mallard duck (*Anas platyrhynchos*), rat (*Rattus norvegicus*) and rainbow trout (*Oncorhynchus mykiss*).

Compound	*Mallard Duck*[a]	*Rat*[a]	*Rainbow Trout*[b]	*Source*
Pyrethrins	>5620	700	5.1	USEPA[118]
Allethrins	>2000	720	9.7	WHO[222]
Permethrin	>10000	8900	6.43	USEPA[10]; Kumaraguru and Beamish[223]
Resmethrin	>5000	4639	0.28	USEPA[68]
Cypermethrin	>2634	247	0.39	USEPA[10]
Deltamethrin	>4640	128	1.97	WHO[224]
Etofenprox	>2000	>5000	13	USEPA[25]

[a]Acute oral LC_{50} ($mg\,kg^{-1}$).
[b]96-h LC_{50} ($\mu g\,l^{-1}$).



Esters of chrysanthemic acid			Esters of pyrethric acid		
	R_1	R_2		R_1	R_2
Pyrethrin I	CH_3	$CHCH_2$	Pyrethrin II	$CH_3OC(O)$	$CHCH_2$
Cinerin I	CH_3	CH_3	Cinerin II	$CH_3OC(O)$	CH_3
Jasmolin I	CH_3	CH_2CH_3	Jasmolin II	$CH_3OC(O)$	CH_2CH_3

Figure 3.1 The chemical structure of the six constituents of pyrethrum extracts which are collectively known as pyrethrins.

910 tonnes of permethrin and 455 tonnes of cypermethrin applied annually.[10,11] Pyrethroids are also used extensively in urban areas, accounting for about 70% of the total usage in California.[6]

3.2 Structure and Chemistry

3.2.1 Pyrethrins

Pyrethrins are prepared from dried *Chrysanthemum cinerariaefolium* and/or *C. cineum* flower heads and are composed of six insecticidally active esters. Pyrethrin extracts are highly viscous liquids with high boiling points, sensitivity to oxidation, and are difficult to store for long periods.[12] Annual world

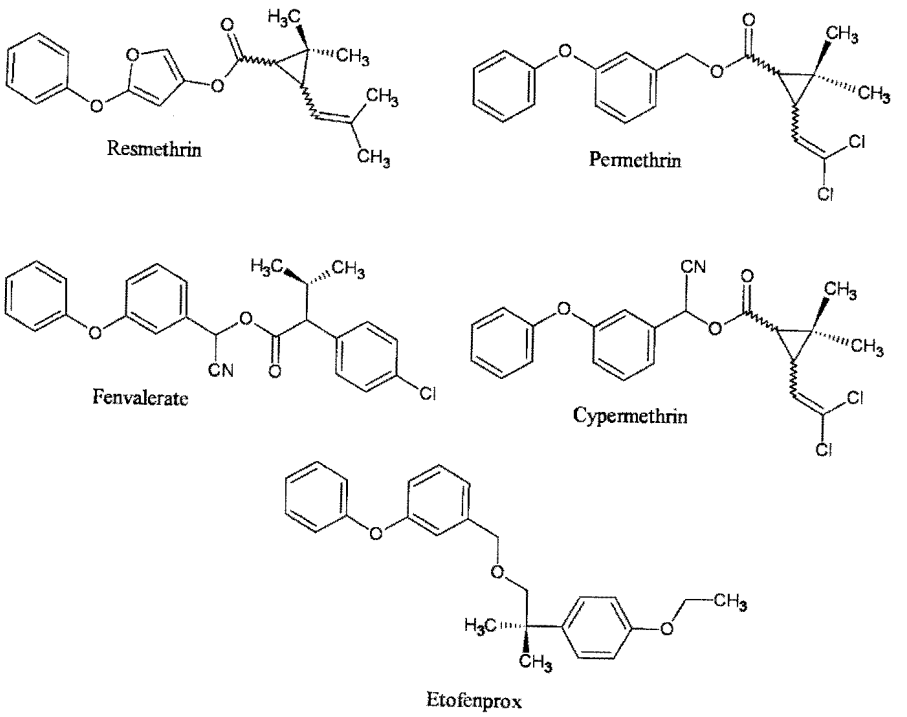


Figure 3.2 The chemical structure of type I (resmethrin and permethrin), type II (fenvalerate and cypermethrin) and pseudopyrethroids.

production of dried flowers has rarely exceeded 20 000 tonnes and, with an average pyrethrins content of 1.5%, the potential yield is 30 kg of 50% extract per tonne. With losses at various processing stages, however, the actual yield is only about 25 kg, giving a potential annual world production of 500 tonnes. Since availability is highly variable, demand often far exceeds supply.[1]

In 1924, Staudinger and Ruzicka[13] elucidated that the active constituents, pyrethrin I and II, are esters of 2,2-dimethyl-3-(2-methyl-l-propenyl)-l-cyclopropanecarboxylic acid (chrysanthemic) and of 3-(2-methoxycarbonyl-l-propenyl)-2,2-dimethyl-l-cyclopropanecarboxylic acid (pyrethric acid), respectively. The six constituents of pyrethrins are pyrethrin I and II, cinerin I and II, and jasmolin I and II. They are collectively known as pyrethrins, which are the esters of two carboxylic acids, chrysanthemic and pyrethric acid (see Figure 3.1). Naming of the six esters of pyrethrins is derived from the alcohol component distinguished by name and number, which are designated by the Roman numeral I and II that represent the esters of the chrysanthemic and pyrethric acid, respectively (see Figure 3.1). There is considerable variation in the proportions of the different constituents of pyrethrins, with the average extract containing 73% pyrethrin I and II, 19% cinerin I and II, and 8% jasmolin I and II.[14] Pyrethrin I and II differ in their insecticidal properties, with pyrethrin I showing greater lethality and pyrethrin II showing greater knockdown.[15]

3.2.2 Pyrethroids

The highly variable availability of pyrethrins encouraged the development and use of synthetic alternatives, which has led to the development of pyrethroids. When the stereochemistry of pyrethrins was elucidated, it formed the model from which pyrethroids were derived; the majority of pyrethroids were derived by modifying the chrysanthemic acid moiety of pyrethrin I and esterifying the alcohols. Synthetic pyrethroids have been developed in order to improve the specificity and activity of pyrethrins, while maintaining the high knockdown and low terrestrial vertebrate toxicity. There is a small group of structural features that pyrethroids require if they are to possess high insecticidal activity, irrespective of the rest of the molecule or the nature of the target species. The pyrethroid active esters are 3-substituted cyclopropanecarboxylic acids which all have a 1*R*-configuration, a gem-dimethyl substitution at the C-2 of the cyclopropane ring, and only those phenylacetates that contain the corresponding substitute in the 2-position. About 1000 different pyrethroid structures have been synthesized; some are very different from the original structures of the pyrethrin I and II, including structures lacking the dimethylcyclopropane ring and the ester linkages (see Figures 3.1 and 3.2). The level of activity is determined by penetration, metabolism and target site sensitivity, which is in turn determined by the structure of the molecule.

It has been known since the 1840s that pyrethrins are highly photolabile, with a half-life of less than five hours in direct sunlight, greatly limiting their commercial use.[16] The first pyrethroids were synthesized by the replacement of specific structural elements found in pyrethrin I with isosteric moieties to improve metabolic and photochemical stability. Although the synthesis of analogs of pyrethrins began as soon as the active constituents were identified, it was not until 1949 that the first commercially successful pyrethroid, allethrin, was introduced.[17]

The next significant development was through the modification of the alcohol component of pyrethrin I, which was esterified, and this led to the synthesis of resmethrin in 1967.[18] Resmethrin represented the first compound that had an insecticidal activity that was equal to, or greater than, that of pyrethrins, but which exhibited a lower mammalian toxicity. The synthesis of resmethrin and other chrysanthemate esters raised the issue of the stereochemistry of the acid moiety as a determinant of biological activity and metabolism (see Figure 3.2). Pyrethroids have three asymmetric carbon atoms and can have as many as eight possible stereoisomers. The presence of two chiral centers in the cyclopropane ring of chrysanthemic acids produces two pairs of diastereomers, which are designated *cis* and *trans* based on the orientation of the C-1 and C-3 substitutions in relation to the plane of the cyclopropane ring,[19] but only those with the *R* configuration at the cyclopropane C-1 are insecticidally active.[20]

Despite its positive attributes, resmethrin is not photochemically stable and lacks the degree of persistence needed for agricultural commercialization. In 1973, permethrin was synthesized[21] and was the first compound that exhibited sufficient photostability for agricultural use. Permethrin revolutionized pyrethroids as a class, subsequently leading to their widespread use in pest

management applications. Permethrin was synthesized by replacing the methyl groups with chlorine atoms in the acid side-chain, which block photochemical degradation on the adjacent double bond (see Figure 3.2).[21] Permethrin is ten to 100 times more stable in light than resmethrin, yet it is as active against insects as resmethrin while maintaining low mammalian and avian toxicity (see Table 3.2). Like most pyrethroids, the 1*R-trans* isomer of permethrin is rapidly metabolized in organisms, with the 1*R-cis* isomer being more stable and toxic.[22] After the discovery of permethrin, researchers searched for compounds with a higher insecticidal activity than that of pyrethroids and this led to the discovery of the cyano substitute at the benzylic carbon of the 3-phenoxybenzyl group (see Figure 3.2).

Pyrethroids are categorized according to their structure and toxicology, including those lacking the α-cyano group on the phenoxybenzyl moiety (type I) and those with a α-cyano group on the phenoxybenzyl moiety (type II; see Figure 3.2). The next phase of pyrethroid development involved the search for a greater structural variety that could reduce the cost of synthesis and expand the biological activity for new uses.[19] The discovery that less expensive α-substituted phenylacetic acids could be used as substitutes for cyclopropanecarboxylic acids when esterified with the appropriate pyrethroid alcohols, led to the development of pyrethroids like fenvalerate (see Figure 3.2). Pyrethrins and pyrethroids are extremely toxic to many aquatic organisms (see section 3.7), which has led to research looking for pyrethroids that reduce aquatic toxicity while maintaining the favorable properties of the photostable pyrethroids.

The discovery of fenvalerate, which is a α-substituted phenylacetic acid form of the cyclopropanecarboxylic acids, led to the development of the non-ester pyrethroids which are also known as pseudopyrethroids. The common features of permethrin and fenvalerate were used to develop the pseudopyrethroid etofenprox (see Figure 3.2). Pseuodopyrethroids were mainly derived during the 1980s and were found to be substantially different from pyrethrin I and type I and II pyrethroids, so they were not placed into the classical pyrethroid insecticide classification.[23,24] Pseudopyrethoids, such as etofenprox, have approximately 2% of the toxicity to fish of conventional pyrethroids, but they maintain high potency to insects with a characteristic low mammalian toxicity (see Table 3.2).

Pseudopyrethoids have not been widely used in the USA, but etofenprox was recently registered for the control of adult mosquitoes, with crop labeling being currently evaluated.[25] In addition to reducing the toxicity of pyrethroids to aquatic organisms, "green" processes are currently being developed for the preparation of pyrethroids, such as chemoenzymatic synthesis, and the reduction of the 1,2-addition of haloalkanes to polymer-bound olefins has been carried out in solid-phase synthesis to add the dihaloethenylcyclopropane carboxylate moieties.[26]

Due to the similar modes of action of pyrethroids and DDT analogs, researchers have developed "hybrid" pyrethroids that contain the features of both pyrethroids and DDT. The only compound that has been developed for commercial applications is cycloprothrin.[27] Cycloprothrin, a type II pyrethroid, is not as toxic to target organisms as other type II pyrethroids like deltamethrin, but is less toxic to fish.

3.2.3 Physical Properties

Pyrethrins and pyrethroids are highly nonpolar chemicals that have low water solubility and volatility, high octanol–water partition coefficients, and a high affinity to bind to soil and sediment particles (see Table 3.3). Pyrethrins and pyrethroids are rapidly degraded *via* photochemical reactions which result from isomerization of the substituents on the cyclopropane ring, oxidation of the acid and alcohol moieties, dehalogenation of dihalovinyl derivatives, and decarboxylation occurring in type II pyrethroids.[28,29] The non-ester pyrethroids are not subject to hydrolysis, but are broken down *via* oxidation reactions. There is evidence that hydrogen peroxide photochemically produces a hydration reaction with ether cleavage proceeding *via* reaction with a hydroxyl radical.[29] Pyrethroid photodegradation follows first-order kinetics with the main reactions being ester cleavage, photooxidation, photoisomerization and decyanation.[30,31]

In soil under both standard atmospheric and flooded conditions, the photolysis half-life in water ranges from 34.7 to 165 days (see Table 3.4). On soil,

Table 3.3 Physical properties of pyrethroids.

Compound	*Molecular Weight*	*Log P*	*Water Solubility* ($\mu g\,l^{-1}$)	*Vapor Pressure (mm Hg)*	K_{ow} ($\times 10^6$)	K_{oc} ($\times 10^5$)	K_h ($atm.m^3\,mol^{-1}$)
Permethrin	391.3[b]	6.1[a]	0.084[a]	2.2×10^{-8}[b]	1.3[a]	2.8[a]	1.4×10^{-2}[b]
Bifenthrin	422.9[a]	6.4[a]	0.00014[a]	1.8×10^{-7}[a]	3[a]	2.4[a]	7.2×10^{-3}[a]
Cypermethrin	416.3[c]	6.5[a]	0.004[a]	3.1×10^{-9}	3.5[a]	1.4[c]	3.4×10^{-7}[a]
λ-Cyhalothrin	449.9[a]	7[a]	0.005[a]	1.6×10^{-9}[a]	10[a]	3.3[a]	1.9×10^{-7}[a]
Deltamethrin	505.2[a]	4.5[a]	0.0002[a]	9.3×10^{-11}[a]	3.4[a]	7[a]	3.1×10^{-7}[a]
Etofenprox	376.4[d]	6.9[e]	0.023[e]	2.5×10^{-8}[d]	7.9[d]	9.9[e]	3.5×10^{-2}[e]

Log P = Partition coefficient. K_{ow} = Octanol : Water partition coefficient. K_{oc} = Organic carbon adsorption coefficient. K_h = Henry's law constant.
[a]Laskowski.[33]
[b]USEPA.[10]
[c]USEPA.[11]
[d]USEPA.[25]
[e]Vasquez *et al.*[141]

Table 3.4 Half-lives of pyrethroids in water, light and soil from Laskowski.[33]

	Hydrolysis half-life			*Photolysis half-life*		*Soil Degradation half-life*	
Compound	*pH 5*	*pH 7*	*pH 9*	*Water*	*Soil*	*Aerobic soil*	*Anaerobic soil*
Permethrin	S	S	242	110	104	39.5	197
Bifenthrin	S	S	S	408	96.6	96.3	425
Cypermethrin	619	274	1.9	30.1	165	27.6	55
λ-Cyhalothrin	S	S	8.66	24.5	53.7	42.6	33.6
Deltamethrin	S	S	2.15	55.5	34.7	24.2	28.9

S = Stable.

the photolysis half-life is generally fewer than 55 days, with faster degradation occurring on dry soil. Aerobic degradation occurs rapidly, with the major degradation pathways resulting from ester cleavage, oxidation and hydroxylation.[32,33] The loss of permethrin from water by adsorption on sediment leaves less than 2% in the aqueous phase after seven days[32] with 95% of pyrethroids being adsorbed by sediments within one minute.[34] In natural water–sediment mixtures, ester cleavage is the major degradation process for both type I and II pyrethroids.[32] Pyrethroids are degraded slowly in acidic and neutral pH, but degradation is more rapid in alkaline water.[33] In addition to abiotic reactions, bacteria are capable of degrading pyrethroids and can be specific to both the compound and the stereochemistry.[35,36]

3.3 Mode of Action

Pyrethrins, pyrethroids, DDT and DDT analogs belong to a group of chemicals that are neurotoxic and share a similar mode of action that is distinctive from other classes of insecticides. There are several ways that pyrethrins and pyrethroids can enter the body of an organism to exert their effects. The first mode is non-stereospecific with rapid penetration through the epidermis, followed by uptake by the blood or hemolymph carrier proteins and subsequent distribution throughout the body. Pyrethroid diffusion along the epidermis cells is the main route of distribution to the central nervous system (CNS) after penetration.[37] Pyrethroids also can enter the CNS directly *via* contact with sensory organs of the peripheral nervous system. The sensory structures of both invertebrates and vertebrates are sensitive to pyrethroids.[38] Pyrethroids can also enter the body through the airway in the vapor phase, but such penetration represents only a small contribution due to the low vapor pressure of pyrethroids (see Table 3.3). Pyrethroids can also be ingested, and penetration into the blood–hemolymph through the alimentary canal can play an important role in toxicity.

Pyrethroids have been classified toxicologically into two subclasses based on the induction of either whole body tremors (T syndrome) or a coarse whole body tremor progressing to sinuous writhing (choreoathetosis) with salivation (CS syndrome) following near-lethal dose levels in both rats (*Rattus norvegicus*) and mice (*Mus musculus*), and closely follows the chemical structure of the two types of pyrethroids.[39,40] Type I pyrethroids are characterized by the T-syndrome which consists of aggressive sparring, sensitivity to external stimuli, fine tremors progressing to whole body tremors and prostration. Type I pyrethroids also elevate core body temperature, which is attributed to the excessive muscular activity associated with tremors. Type II pyrethroids are characterized by the CS syndrome which is comprised initially of pawing and burrowing behavior followed by profuse salivation, choreoathetosis, increased startle response, and terminal chronic seizures. Type II pyrethroids decrease core body temperature, which is attributed to excessive salivation and wetting of the ventral body surface. Although salivation typically co-occurs with

choreoathetosis, a TS syndrome (tremor with salivation) has also been observed in a few pyrethroids. Multiple lines of evidence show that pyrethroids, as a class, do not act in a similar fashion on the voltage-gated sodium channels, and the classifications of toxicology are not absolute for either invertebrates or vertebrates.[41,42] For example, the type I pyrethroid, bioallethrin, exhibits toxicological symptoms of both type I and II intoxication.

As expected, increasing the dose levels of pyrethrins and pyrethroids results in a proportional increase in motor activity, which is the classic dose–response effect with respect to neurotoxic substances. Pyrethrins and pyrethroids act very quickly to produce symptoms of lost coordination and paralysis which are known as "the knockdown effect", and which are often accompanied by spasms and tremors that induce intense repetitive activation in sense organs and in myelinated nerve fibers. The spasms can be violent and can cause the loss of extremities, such as legs and wings in insects.

The most compelling evidence of a similar mode of action for pyrethrins, pyrethroids, and DDT comes from resistance studies examining knockdown resistance (*kdr*) demonstrating cross resistance. Physiological and biochemical studies of pyrethrins, pyrethroids and DDT show that in both vertebrates and invertebrates the primary mode of action is the binding of the voltage-gated sodium channel.[38,42–44] Mammals, unlike insects, however, have multiple isoforms of the sodium channel that vary by tissue type, as well as biophysical and pharmacological properties.[45]

To understand the primary mode of action, the mechanism by which voltage-gated sodium channels work needs to be reviewed. When the voltage-gated sodium channel is stimulated, it causes a depolarization of the membrane, which changes the nerve cell's permeability to Na^+ and K^+. The excited membrane becomes permeable to Na^+, with a small number of ions acted on when electrical and concentration gradients rush into the membrane causing the depolarization of the membrane. The sodium ions carry a current inward, which is referred to as the "action potential". The inward movement of sodium ions causes the membrane potential to overshoot the membrane potential with the inside becoming positive relative to the outside of the membrane surface. During a spike, the membrane is absolutely refractory, and a stimulus of even greater magnitude cannot cause the gates to open wider or more Na^+ to flow inward. In addition, a neuron is partially refractory for a further few milliseconds and only a strong stimulus will cause a new response.[46] The upper limit of impulses per second is about 100, with each depolarization event lasting only about two to three milliseconds.[46] Pyrethrins and type I pyrethroids modify the sodium channels such that there is a slight prolongation of the open time (*i.e.* sodium tail currents of approximately 20 milliseconds), which results in multiple long action potentials. Type II pyrethroids significantly prolong channel open time (*i.e.* sodium tail currents of 200 milliseconds to minutes), resulting in an increased resting membrane potential and often inducing a depolarization-dependent block of action potentials.

Type I pyrethroids cause multiple spike discharges, while type II pyrethroids cause a stimulus-dependent depolarization of the membrane potential which

reduces the amplitude of the action potential, and a loss of electrical excitability in both vertebrates and invertebrates.[38,47] The toxic action is exerted by preventing the deactivation or closing of the gate after activation and membrane depolarization. This results in destabilizing the negative after potential of the nerve due to the leakage of Na^+ ions through the nerve membrane. This causes hyperactivity by delaying the closing sodium channels which allows a persistent inward current to flow after the action potential, causing repetitive discharges that can occur either spontaneously or after a single stimulus. The sodium channel residue that is critical for regulating the action of pyrethroids is the negatively-charged aspartic acid residue at position 802 located in the extracellular end of the transmembrane segment 1 of domain II, which is critical for both the action of pyrethroids and the voltage dependence of channel activation.[48]

The differences between type I and II pyrethroids are expressed in the motor nerve terminals, where type I cause presynaptic repetitive discharges, and type II cause a tonic release of transmitter indicative of membrane depolarization.[38,49] Type II pyrethroids are a more potent toxicant than type I in depolarizing the nerves.[49] Type II pyrethroids are associated with faster activation–deactivation kinetics on the $Na_{v1.8}$ sodium channels than type I pyrethroids in vertebrates.[42] The higher toxicity of type II pyrethroids is mostly attributed to the hyperexcitatory effect on the axons which results from their stronger membrane depolarizing action. Type I pyrethroids modify the sodium channels in the closed state, while type II pyrethroids modify the open but not inactivated sodium channels.[50] However, this relationship does not always hold true; *cis*-permethrin and fenvalerate interact with both closed and open sodium channels, but they bind with greater affinity to the open state.[51–53] Type I repetitive discharges have been shown to be suppressed by cypermethrin, indicating that the two pyrethroid types can interact antagonistically.[53]

Pyrethroids affect the voltage-sensitive calcium channels, γ-aminobutyric acid (GABA) receptors and GABA-activated channels, and voltage-sensitive chloride channel.[43,54] Recent findings suggest that pyrethroids can modulate the activity of voltage-gated calcium (Ca^{2+}) channels.[55] However, these studies report conflicting results on the inhibitory effects of pyrethroids on voltage-gated calcium channels. Neal *et al.*[56] demonstrated that allethrin significantly altered the voltage dependency of activation and inactivation of L-type voltage-gated calcium channels, which suggests that differential modulation of voltage-gated calcium channels subtypes could elucidate some of the conflicting observations of other studies. Type II pyrethroids are more potent enhancers of Ca^{2+} influx and glutamate release under depolarizing conditions than type I pyrethroids.[41,51]

The GABA receptor–chloride ionophore complex is also a target of type II pyrethroids. GABA is an inhibitory transmitter in the synapse of the CNS of both vertebrates and invertebrates. Pretreatment with diazepam (a benzodiazepine anticonvulsant known to act on the GABA receptors) has been shown to selectively delay the onset of toxic symptoms of type II, but not type I, pyrethroids in cockroaches and mice.[38] Radioligand binding studies have

shown that deltamethrin, but not its non-toxic α-*R*-cyano epimer, inhibited [^{3}H]dihydropicrotoxin binding to the chloride ionophore in the rat brain GABA receptor complex.[38] Pyrethrins and pyrethroids also inhibit the Cl^- channel function at the GABA receptor–ionophore complex.[57]

An additional target proposed for type II pyrethroids is the membrane chloride ion channel.[58] Generally type II pyrethroids decrease the open channel probability of chloride channels, but the type I pyrethroids do not seem to have an effect on the chlorine channel.[42,54,59] Upon further investigation, Burr and Ray[59] found that the type I pyrethroid bioallethrin, and type II pyrethroids β-cyfluthrin, cypermethrin, deltamethrin and fenpropathrin, significantly decreased the probability that the ligand-gated chloride channel would be an open channel. However, they found that the type I pyrethroids, bifenthrin, bioresmethrin, *cis*-permethrin and *cis*-resmethrin, and the type II pyrethroids, cyfluthrin, lambda-cyhalothrin, esfenvalerate and tefluthrin, did not. Interestingly, the type I pyrethroid, bioallethrin, significantly alters the probability of opening the ligand-gated chloride channel, but has generally a weaker response than type II pyrethroids.[42] One hypothesis was that bioallethrin may be a mixed-type pyrethroid.[43,59] The blockade of the voltage-sensitive chloride channels is associated with salivation, which is a hallmark of type II pyrethroid intoxication and could contribute to the enhanced excitability of the CNS.[43]

Pyrethroids inhibit the Ca-ATPase, Ca-Mg ATPase neurotransmitters and the peripheral benzodiazepine receptors,[60] but their action on these sites is minor compared with the voltage-gated sodium channels. The effects on these sites could, however, enhance the uncontrolled convulsions and tremors.[43]

3.3.1 Enantioselective Toxicity

Formulations of pyrethroids are mixtures of the 1*R-cis*- and 1*R-trans*-isomers. Only the cyclopropanecarboxylic acid esters that have the *R* absolute configuration at the cyclopropane C-1 and α-cyano-3-phenoxybenzyl esters with the *S* absolute configuration at the C-α are toxic.[38] Of the four stereoisomers of permethrin and resmethrin, the highest acute toxicity is observed in the 1*R-cis*- and 1*R-trans*-isomers, which contribute 94 to 97% of the toxic dose, while the 1*S-trans*- and 1*S-cis*-isomers contribute insignificantly to the toxicity.[19,61,62] Studies of the non-toxic isomers of pyrethroids found that they were less than 1% as toxic as the corresponding toxic isomer.[63] Chronic toxicity tests in *Daphnia magna* with respect to survival and fecundity for 1*R-cis*-bifenthrin have been shown to have 80-fold greater toxicity than 1*S-cis*- bifenthrin after 14 days.[64] The difference in toxicity can be attributed to the absorbed dose of 1*R-cis*-isomer which was approximately 40-fold higher than that of 1*S-cis*- isomer. Pyrethroids exhibit significant enantioselectivity in oxidative stress, with the *trans*-permethrin exhibiting 1.6 times greater cytotoxicity than *cis*-permethrin at concentrations of 20 mg l^{-1} in rat adrenal pheochromocytoma cells.[65] It should be noted that effects on neurotoxicity at both the cellular and visible level occur at doses 2000 times greater than exposures seen in the environment.

3.3.2 Effects of Sex, Age and Size on Toxicity

Studies of the toxicity of insecticides have shown a significant difference in sensitivity between sexes, with invertebrate males generally more sensitive than females, but the opposite is true for mammals. This may be due to size differences, lipid content, and enzyme activity, but differences between sexes may not always be observed.[10,11,66–68] Age and size are the most important factors influencing the susceptibility of organisms to insecticides, because these factors are related to increases in body fat content and enzymatic activity.[67,69] Adult males and gravid females of German cockroaches (*Blattella germanica*) were generally found to be more sensitive than non-gravid females to pyrethroids.[70] However, whilst the body mass of gravid and non-gravid females did not differ, that of the males was smaller. In contrast to invertebrates, female rats are more sensitive to pyrethroids than males; this difference in sensitivity is most likely due to hormone differences. A larger body mass does not necessarily mean that a higher dose is required to kill insects. This was demonstrated by Antwi and Peterson,[71] who showed that house crickets (*Acheta domesticus*) were more sensitive to pyrethroids than adult convergent lady beetles (*Hippodamia convergens*) and larval fall armyworms (*Spodoptera frugiperda*).

Younger invertebrates and vertebrates are generally more sensitive than older immature organisms, with susceptibility decreasing with each successive stage.[72,73] The sensitivity of the younger developmental stages is most likely due to age-related differences in pharmacokinetics and pharmacodynamics. These differences may be a result of the lower enzymatic activity, particularly of the esterases and cytochrome P450 monooxygenases (CYP), of younger organisms and in insects where the cuticle has not hardened, allowing more of the insecticide to be absorbed. In vertebrates, however, the evidence is unclear as to whether the differences in sensitivity of the voltage-gated sodium channel isoforms are due to the isoform of the sodium channel since they differ between fetal and post-natal rats. Therefore, regulatory agencies do not assume an increased toxicity of pyrethroids to juveniles based on pharmacokinetic dynamics.[74]

3.3.3 Temperature

DDT and pyrethroids share of a number of similar properties in their mode of action. The temperature and mode of action of pyrethroids have been connected since Vinson and Kearns[75] found that DDT had a higher toxicity at lower temperatures because of an intrinsic susceptibility of some physiological systems, rather than penetration or metabolism which was subsequently confirmed for pyrethrins.[76] A strict negative temperature correlation is not always observed because type II pyrethroids are in some cases positively correlated with temperature (see Table 3.5).[77,78] The same temperature dependent toxicities have been observed in warm-blooded animals.[37] The decreased toxicity at higher temperatures is mostly the result of desorption of the pyrethroid from the target site. In contrast to insects, mites show a positive temperature effect to both type I and II pyrethroids.[79]

Table 3.5 The lethal concentration that kills 50% of a population (LC_{50}) for 3-phenoxybenzyl pyrethroids and DDT against third instar larvae of tobacco budworm (*Heliothis virescens*) and Asian citrus psyllid (*Diaphorina citri*) at 37.8, 26.7 and 15.6 °C from Sparks *et al.*[77] and Boina *et al.*[78]

Compound	*Temp °C*	*LD_{50} ($\mu g\, g^{-1}$)*	*LD_{50} Ratio 37.8–15.6 °C*
Permethrin	37.8	1.94	–9
	26.7	1.44	
	15.6	0.22	
Sumithrin	37.8	4.64	–24.2
	26.7	2.51	
	15.6	0.19	
Cypermethrin	37.8	0.51	–1.81
	26.7	0.24	
	15.6	0.28	
Deltamethrin	37.8	0.016	1.55
	26.7	0.044	
	15.6	0.088	
Fenvalerate	37.8	0.22	2.29
	26.7	0.39	
	15.6	0.51	
Bifenthrin	17	1.94	–9
	27	1.44	
	37	0.22	
DDT	37.8	62.36	–15.35
	26.7	31.49	
	15.6	4.06	

3.4 Metabolism

In mammals and birds, pyrethroids augment the electrical activity in the brain, spinal column and peripheral neurons which underlie the induced paresthesia, convulsions, and tremors.[38] The low toxicity of pyrethroids is attributed to their rapid metabolism in the blood and liver, with more than 90% of pyrethroids being excreted as metabolites in urine within 24 hours after exposure.[80–82] Indeed, although extensively used, there are relatively few reports of human, domestic animal or wild animal pyrethroid poisonings.[83,84]

Cytochrome P450s are extremely important in the metabolism of xenobiotics and endogenous compounds. Cytochrome P450s can metabolize a large number of substrates because they exist in numerous different isoforms and they have several functional roles, including growth, development and metabolism of xenobiotics. The two types of primary metabolic enzymes involved in the detoxification of pyrethroids are microsomal monooxygenases and esterases. The detoxification of pyrethrins and pyrethroid insecticides is primarily through oxidative metabolism by CYP, which yields metabolites with hydroxyl groups substituted in both the acidic and basic moieties.[85] The presence of a

cis-substituted acid moiety and a secondary alcohol moiety indicates that hydrolytic metabolism would be limited, and subsequent studies in mammals have found hydrolysis to be minimal.[86] The metabolic pathway of *cis*- and *trans*-permethrin is displayed in Figure 3.3 and shows the different CYP involved in the metabolism of pyrethroids. The initial biotransformation of pyrethroids is through attack by either esterases at the central ester bond, or by CYP-dependent monooxygenases at one or more of the acid or alcohol moieties, and this generally achieves detoxification of the compound (see Figure 3.3).

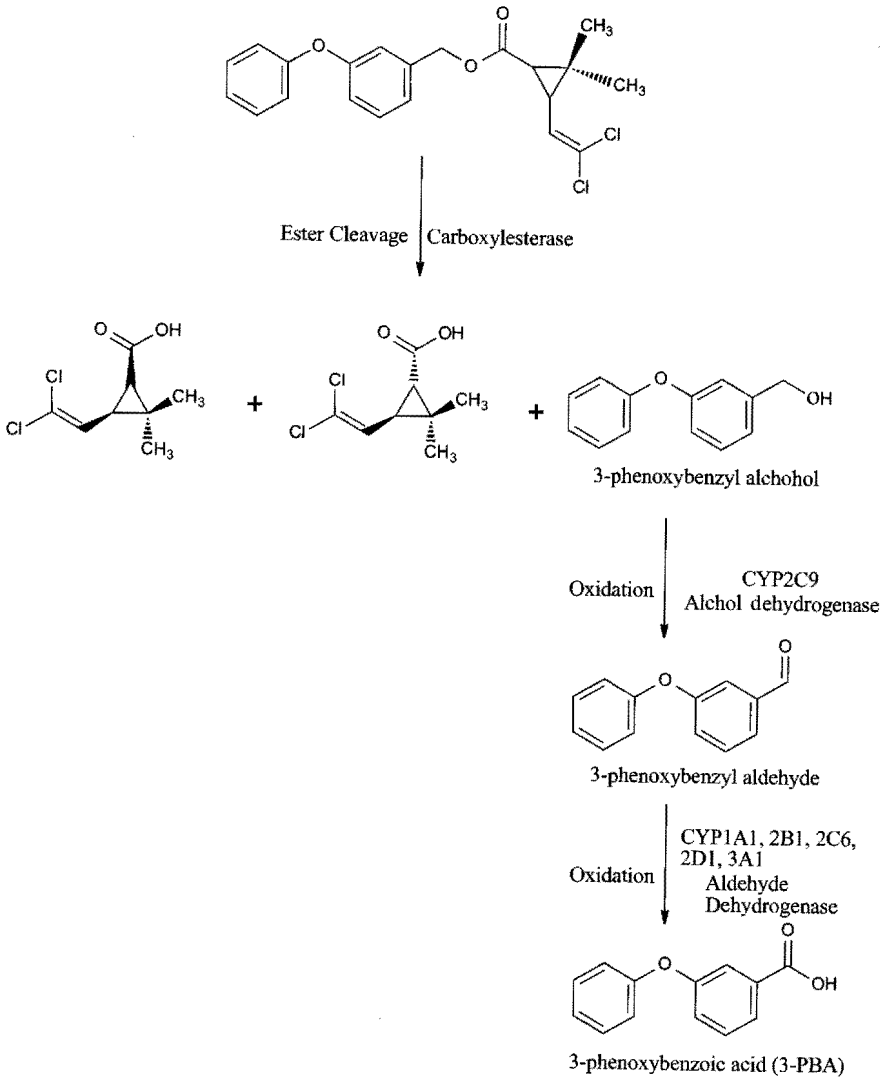


Figure 3.3 Metabolism of permethrin in mammals. Abbreviation CYP: cytochrome P450.

CYPs are not, however, involved in the hydrolysis or in the oxidation of the *trans*-isomers of pyrethroids to phenoxybenzyl alcohol and phenoxybenzoic acid, the main forms of pyrethroids that are excreted (see Figure 3.3).[87] The human alcohol and aldehyde dehydrogenases are the enzymes involved in the oxidation of phenoxybenzyl alcohol to phenoxybenzoic acid (see Figure 3.3).[87]

For type I pyrethroids, following ester cleavage, the primary alcohol moieties undergo further oxidation *via* the aldehyde to carboxylic acids. However, type II alcohols lose the cyanide non-enzymatically to form the aldehyde.[43] The principal sites of oxidation for pyrethrins I in rats are the terminal double bond and the *trans* methyl group of the isobutenyl substituent of the acid moiety, which undergoes sequential oxidation to a carboxylic acid.[88] In mammals, as in insects, the *cis*-isomers are generally more toxic than the corresponding *trans*-isomers. This phenomenon may be because the liver fractions are poor at metabolizing *cis*-isomers, while the *trans*-isomers are readily metabolized by esterases.[87] The *cis*-isomers are also less readily absorbed by the stomach hence limiting their toxicity.[37] For reference, technical-grade mixtures of permethrin contain 30% of *cis*-isomer, while formulations contain about 35%.

Pyrethroids are metabolized predominantly by esterases. The first stage involves cleavage of the ester bond, generating 3-phenoxybenzaldehyde, 3-phenoxybenzoic acid, and (2,2-dichlorovinyl)-3,3-dimethylcyclopropanecarboxylic acid as major metabolites (see Figure 3.3).[89] The major metabolites detected in the urine of mammals (see Figure 3.3) are 3-phenoxybenzoic acid (3PBA; the product of the oxidation of the hydrolytic product of many of pyrethroids), 4-fluoro-3-phenoxybenzoic acid (4F3PBA; a metabolite of the fluorine-substituted pyrethroid insecticides), and *cis*- and *trans*-(2,2-dichlorovinyl)-3,3-dimethylcyclopropane-1-carboxylic acid (*cis*- and *trans*-DCCA; metabolites of chlorinated pyrethroids, such as permethrin, cypermethrin and cyfluthrin).[80,82,90]

There are also specific metabolites for certain pyrethroids. For example, *cis*-(2,2-dibromovinyl)-3,3-dimethylcyclopropane-1-carboxylic acid (DBCA) is the main metabolite of deltamethrin.[90] The ratio of *trans : cis* DCCA can be used to determine the exposure pathway *via* dermal and oral routes.[91] Other, more minor, metabolites include those resulting from hydroxylation at the acidic gem dimethyl group and at the phenoxy group of the alcohol and from oxidation, which results in carboxylic acids and phenols.[92] Once these oxidations occur, the resulting carboxylic acids and phenols may be conjugated by a variety of enzymes, and are subsequently excreted as either free metabolites or conjugated with sugars or amino acids which are rapidly excreted.

3.5 Synergists

Yamamoto[93] defined synergism as where the interaction of two or more toxins is such that their combined effect is greater than simply the sum of their individual toxicities. For pesticide formulations, synergists are typically nontoxic compounds at the dosage applied, but which enhance the toxicity of the active pesticide ingredient. The main route of detoxification of insecticides is through

CYP-mediated detoxification. The CYP enzymes bind molecular oxygen and receive electrons from NADPH to introduce an oxygen molecule into the toxicant, thus catalyzing the oxidation of toxicants. *N*-Octyl bicycloheptene dicarboximide (MGK-264) and piperonyl butoxide (PBO) are the most commonly used synergists and are incorporated into insecticide formulations to inhibit the CYP.[94,95] The enhancement of toxicity for pyrethroids is not as great as it is for pyrethrins.[96] Synergists are mixed at a concentration of two to 50 times that of the insecticide, and enhance the toxicity one to 100 times.

Piperonyl butoxide and MGK-264 have been shown to increase the toxicity of pyrethroids to aquatic organisms, but there is no indication that PBO acts as a synergist in mammals.[52,94,97–99] In addition to inhibiting mixed function oxidases, PBO has also been shown to enhance the penetration rates of pyrethroids through the cuticle of insects.[100]

3.6 Resistance

The fact that pyrethrins, pyrethroids and DDT share a common mode of action, and therefore a common binding domain on the sodium channel, has important implications for the continued use of pyrethrins and pyrethroids in pest management. Resistance to insecticides may cost more than $1.4 billion per year in the USA alone.[101] Selection for resistance to either class of insecticides will lead to resistance to both, which has been extensively documented in mosquitoes.[102] Pyrethroids are currently the most widely used insecticides for the indoor and outdoor control of mosquitoes and are the only chemical recommended for the treatment of mosquito nets (the main tool for preventing malaria in Africa). However, mosquito-borne diseases are emerging and re-emerging in parts of the world and it is thought to mainly be due to widespread mosquito resistance to pyrethroids and the drug resistant strains of vector-borne pathogens.

Insect resistance is dependent on the volume and frequency of applications of insecticides and the inherent characteristics of the insect species. Resistance to pyrethroids comes in two forms: (1) non-metabolic resistance through the decreased sensitivity or reduction in the number of voltage-gated sodium channels, and (2) metabolic resistance *via* detoxifying enzymes, oxidases and decreased cuticle penetration. There are four mechanisms by which resistance is expressed: (1) decreased sensitivity of the sodium channels due to altered structure, (2) decreased sensitivity to pyrethroids through a change in the kinetics of the channel, (3) reduced number of channels available for pyrethroids to bind, and (4) altered lipid membrane around the nerve.[103]

The main form of non-metabolic resistance is the *kdr* and *super-kdr* mutations.[104] Farnham[105] first demonstrated that *kdr* resistance is caused by a recessive gene, and characterized it as resistance to the knockdown effect (*i.e.*, it lowers the sensitivity of the sodium channel). German cockroaches that demonstrate knockdown resistance take about twice as long as susceptible ones to express toxic symptomology.[106] Resistant strains subsequently recover two

to four hours after the knockdown and appear normal within 24 hours. The *kdr* gene has been mapped to the autosome 3 that confers an enhanced level of resistance that is designated *super-kdr*.[105,107] *Kdr* resistance is genetically linked to the *para*-homologous sodium channel gene, but correlation between presence of the *para* mutation and knockdown resistance has been infrequently observed and depends on the strain of the insect being studied.[108,109] An important attribute of *kdr* resistance is that synergists do not appreciably alter the toxicity.[110] Decreased cuticle penetration of pyrethroids has been demonstrated in a number of insect species and is generally found in addition to other resistance mechanisms like increased enzyme activity.[111,112]

The detoxification of insecticides through the action of CYP is one of the more important resistance mechanisms. Metabolic resistance can be reduced through the use of a synergist, but non-metabolic resistance cannot.[113] The CYP binds molecular oxygen and receive electrons from NADPH to introduce an oxygen molecule into the substrate. Resistance *via* CYP is associated with overtranscription of a single CYP gene, *Cyp6g1*, in *Drosophila melanogaster*.[114] Cytochrome P450 resistance slows female emergence time and produces smaller body size and lowers energy reserves (glycogen and lipids), which when combined affect the fitness of resistance compared to non-resistant female mosquitoes.[115] Resistance can also be associated with decreased cuticle penetration.[116] Resistance has also been associated with increases in carboxylester hydrolases and glutathione transferases, but these pathways most likely do not confer a large resistance because they play a small role in the detoxification of pyrethrins and pyrethroids.[117]

3.7 Risk Assessment

3.7.1 Human Health Risk Assessment

Human health risk assessments have been performed for pyrethrins and pyrethroids by the United States Environmental Protection Agency (USEPA), other government regulatory agencies around the world and university researchers. The USEPA has found that dietary exposure to pyrethrins and pyrethroids is below reference doses;[10,11,68,118] these results are supported by the current weight of evidence based on urinary metabolites (see section 3.8). Permethrin has been observed in animal models to be a carcinogen and the USEPA estimated the worst-case lifetime average daily exposure based on a tier 1 conservative model to be $0.117\,\mu g\,kg^{-1}\,day^{-1}$. This exposure does not result, however, in an increase in incidents of cancer to the general US population.[10]

One commonly overlooked use of pyrethrins and pyrethroids is with ultra-low volume (ULV) application techniques, which are applied from trucks, helicopters or airplanes and are used for the control of public health pests such as adult mosquitoes and midges. Ultra-low volume applications are commonly used in and around residential areas, so exposure to bystanders within the spray area may occur. This type of application utilizes small droplets of 5 to 25 μm

which produce aerosol clouds that are designed to stay aloft to impinge on flying pests and can thus travel considerable distances. Carr *et al.*[119] conducted a dietary risk assessment for aerial ULV applications of resmethrin above agricultural fields as a result of a public health emergency, and found that exposures would result in negligible human dietary risk.

Peterson *et al.*[120] performed a tier-1 deterministic human health risk assessment for acute and subchronic exposures to pyrethroids used in mosquito management after truck-mounted ULV applications. They found that the acute and subchronic risks to humans would result in negligible risk. Schleier III *et al.*[121] followed up with a probabilistic risk assessment and found that Peterson *et al.*[120] overestimated risk, as expected, by about ten-fold. Subsequent risk assessments of acute and subchronic exposures to pyrethroids used during ULV applications in and around military bases revealed that the risks would not exceed their respective reference dose.[122,123] However, Macedo *et al.*[123] found that aggregate exposure to permethrin from ULV applications and impregnated battle dress uniforms exceeded the standard threshold of an excess of one-in-a-million cancer risk above background levels. Schleier III *et al.*[122] completed a probabilistic risk assessment for exposure to indoor residual sprays using cypermethrin and lambda-cyhalothrin which exceeded their respective reference doses. Although these studies found risks that exceeded their respective toxic endpoint, more realistic exposures would reduce the risk estimates, which is common when using higher tiered risk assessments.[121,124]

3.7.2 Ecological Risk Assessment

Pyrethroids are extremely toxic to many aquatic organisms, and thus could pose a substantial ecological risk (see section 3.10). In this section, we have employed a species sensitivity distribution from the USEPA's Ecotox Database[125] for permethrin using 41 aquatic species based on 96 hour LC_{50}s (see Figure 3.4). Species sensitivity distributions are used to calculate the concentrations at which a specified proportion of species will be affected, referred to as the hazardous concentration (HC) for p% of the species (HCp). The resulting HC5 is $0.047\,\mu g\,l^{-1}$, which amounts to approximately 33% of the maximum concentrations seen in the environment (see section 3.9). The minimum concentration observed in the environment is $0.0054\,\mu g\,l^{-1}$, which would result in 0.35% of the species reaching their respective LC_{50} value. At the maximum concentrations seen in the environment ($3\,\mu g\,l^{-1}$), which are rarely observed, 65% of the species would be affected (see Figure 3.4). These results are supported by aquatic risk assessments performed for pyrethroids. The toxicity of pseudopyrethroids, like etofenprox, is lower with respect to aquatic organisms than other pyrethroids currently used; thus they represent a lower risk to the aquatic environment.[126]

A probabilistic aquatic risk assessment conducted by Maund *et al.*[124] for cotton-growing areas focused on pyrethroid exposure in static water bodies as a worst-case scenario. They found that exposures were several orders of

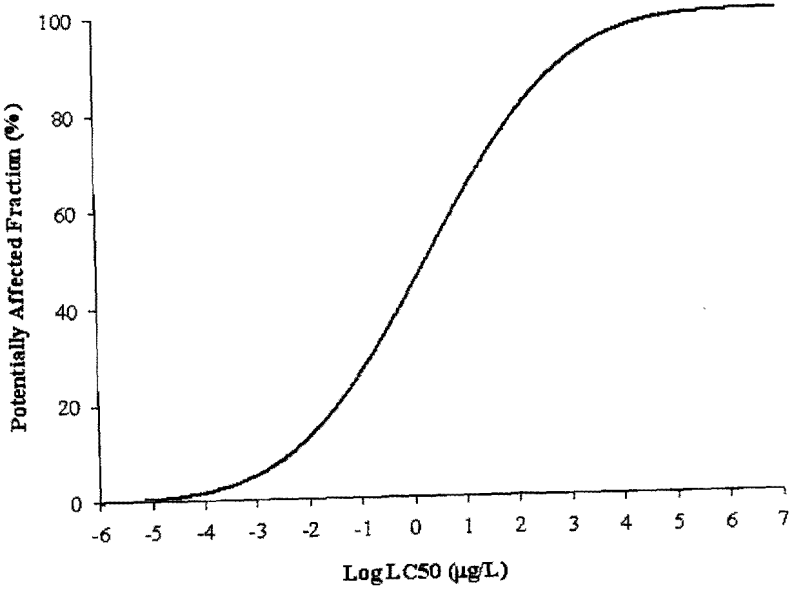


Figure 3.4 Acute species sensitivity distribution constructed from the lethal concentrations that kill 50% of a population (LC_{50}) for permethrin, demonstrating the proportion of species affected for aquatic organisms.

magnitude lower than those that would cause effects based on laboratory and field studies. Davis *et al.*[127] conducted a deterministic ecological risk assessment for truck-mounted ULV applications of pyrethroids, and found that the risks to mammals, birds, aquatic vertebrates, and aquatic and terrestrial invertebrates were negligible. These results were subsequently supported using actual environmental concentrations after aerial and truck-mounted ULV applications.[128–131] Studies by Schleier III and Peterson[131] using caged house crickets as a surrogate for medium- to large-sized terrestrial invertebrates showed that ULV applications of permethrin did not result in increased mortality. These results can most likely be applied to smaller insects as well, because house crickets have been found to be more sensitive to pyrethroids than adult convergent lady beetles and larval fall armyworms.[71]

3.8 Biomonitoring and Epidemiology

Current human biomonitoring and epidemiological studies show that pyrethroid exposures to the general population are low and adverse effects are highly unlikely. The main route of exposure for the general public to pyrethrins and pyrethroids is through dietary intake.[7] Urinary metabolite data from both the USA and Germany show that exposure to pyrethroids in the general population is similar, with the highest exposure coming from the most commonly used pyrethroids, permethrin and cypermethrin,[7,90,132–134] with

infrequent exposure to pyrethroids like cyfluthrin and deltamethrin.[90] The average daily intake of permethrin in the USA due to diet has been estimated at about $3.2\,\mu g\,day^{-1}$, which is approximately 0.1% of the acceptable daily intake.[135] Children have been found to have higher levels, which may be attributed to their higher ingestion rates of household dust.[132] Even when residential areas have been treated directly with truck-mounted ULV applications of pyrethroids, urinary metabolites have shown no statistical difference when compared with results from untreated areas.[136] The use of biomarkers to monitor pyrethroid exposure may be problematic because the estimation of daily absorbed doses of pyrethroids from volume-weighted or creatinine-adjusted concentrations can lead to substantial under- or over-estimation when compared with doses reconstructed directly from amounts excreted in urine during a period of time.[137]

Occupational application of pyrethroids resulting in the highest concentrations of metabolites in urine samples are from indoor pest-control operators. However, occupational exposures to pyrethroids do not seem to lead to adverse effects.[138] Weichenthal *et al.*[74] reviewed the epidemiological evidence relating to occupational exposures and cancer incidence in agricultural workers applying permethrin, and found an increased odds ratio, but the associations were small and imprecise because of small sample sizes and clear exposure–response relationships were not observed. This is most likely because pyrethroids are slowly absorbed across the skin which prevents high levels of exposure. Karpati *et al.*[139] found no increase in asthma cases after truck-mounted ULV applications in residential neighborhoods in New York, New York, USA. Epidemiologically, the USEPA found that the weight of evidence shows no clear or consistent pattern of effects to indicate an association between pyrethrins or pyrethroid exposure and asthma and allergies.[140]

3.9 Environmental Fate

Commercially available pyrethroids are effective in the field at rates of $0.2\,kg\,ha^{-1}$ or less, with the most active compounds, such as cypermethrin, being effective at rates of $0.015\,kg\,ha^{-1}$. The main routes that pyrethroids enter aquatic systems are *via* bound soil surface movement (run-off) or through drift. When considering the potential for run-off, it is important to remember that pyrethrins, pyrethroids and pseudopyrethroids rapidly degrade in most soil types, under both aerobic and anaerobic conditions, and are strongly absorbed to soil (see Table 3.3).[33,141] The strong adsorption of pyrethroids to soil suggests that when such aquatic contamination does occur, it will most likely be in the form of erosion of soil particles through high wind or large rain events. If pyrethroids drift into water bodies, they are rapidly absorbed by the sediments and organic content in the water column, so they will only be present in the water phase for a short time. The most frequently detected pyrethroids in irrigation, storm water run-off and sediments are bifenthrin, lambda-cyhalothrin, cypermethrin and permethrin, with bifenthrin measured at the highest

concentrations because it is commonly used for residential pest control.[142–145] Concentrations of pyrethroids in the environment range from 0.0054 to 0.015 $\mu g l^{-1}$ in the dissolved phase and 0.0018 to 0.870 $\mu g l^{-1}$ in suspended sediment in urban or agricultural areas.[146]

Run-off losses of pesticides from treated fields have been extensively studied, with losses ranging from less than 1% to 10% of the applied product entering waterways.[147] Run-off studies after single and multiple applications of pyrethroids found $\leq 1\%$ of the applied chemical is present throughout the year.[148,149] Residue analysis of water and sediment samples following the final application of a cumulative seasonal exposure, simulated with 12 drift applications and six run-off events of lambda-cyhalothrin and cypermethrin, showed that pyrethroid residues were rapidly lost from the water column with residues of lambda-cyhalothrin and cypermethrin of less than 0.002 $\mu g\ l^{-1}$.[150] Residues in sediment reached a maximum level of approximately 25 $\mu g\ kg^{-1}$, subsequently declining to $<9\ \mu g\ kg^{-1}$ within four months.[150]

The greatest amount of pesticide run-off occurs when severe rain events occur soon after application. The size of the draining catchment has been shown to be negatively correlated with the concentration of insecticide present after agricultural pesticide application.[147] Concentrations of pyrethroids after run-off events ranged from 0.01 to 6.2 $\mu g l^{-1}$ in the aqueous phase, and non-point sediment loads were 1 to 300 $mg\ kg^{-1}$.[147] Insecticide concentrations of less than 10 $\mu g l^{-1}$ were only observed in catchment sizes of less than 100 km^2, with the majority of detections occurring in catchments less than 10 km^2.[147]

Pesticide spray drift is defined as the physical movement of a pesticide through air at the time of application or soon thereafter to any site other than that intended for the application.[151,152] Models and field studies show that as the distance from the spray sources increases the concentration deposited decreases, resulting in a concentration gradient in the water.[128,153–157] Generally, aerial applications result in higher levels of spray drift compared with ground applications, which can be partly attributed to the equipment used on ground sprayers that reduces drift.

Measurements of pyrethroid concentrations in farm ponds following spray drift from aerial applications found 0.2 to 7% of the product deposited in the water, which was dependent on the distance from the spray source.[158] Vineyards treated with cypermethrin *via* mistblowers resulted in surface deposits from spray drift ranging from 0.04 to 0.45 $mg\ m^{-2}$ and concentrations in subsurface water ranging from 0.4 to 1.7 $\mu g l^{-1}$ soon after spraying, decreasing to $<0.1\ \mu g l^{-1}$ within a few hours.[159] Shires and Bennett[160] observed peak concentration after aerial applications to winter wheat of 0.03 $\mu g l^{-1}$ of cypermethrin in subsurface water samples. The concentrations declined rapidly after spraying and generally resulted in little to no adverse effects on invertebrates and caged fish, but there was a slight increase of invertebrate drift.[159,160]

Jensen *et al.*[161] found no detectable concentrations of pyrethrins and permethrin in water samples from wetlands before and after truck-mounted ULV. Weston *et al.*[162] found no detectable concentrations of pyrethrins ten and 34 hours after application in suburban streams after airplane ULV applications

over Sacramento, California, USA. Schleier III *et al.*[129] found no detectable concentrations of pyrethrins one hour after airplane ULV applications in irrigation ditches and static ponds. Concentrations of resmethrin is Suffolk County, New York, USA were detected in 11% of water samples taken with concentrations ranging from non-detectable to 0.293 $\mu g l^{-1}$, and no concentrations were detected after two days.[163] Zulkosky *et al.*[164] measured concentrations of resmethrin ranging from non-detectable to 0.98 $\mu g l^{-1}$ and non-detectable concentrations of sumithrin one hour after truck-mounted ULV application. Schleier III and Peterson[128] measured concentrations of permethrin after truck-mounted ULV applications ranging from 0.0009 to 0.005 $\mu g\ cm^{-2}$, depending on the distance from the spray source. The lower concentrations of pyrethrins and pyrethroids measured after ULV applications are most likely due to the lower use rate, which is $<5\%$ of agricultural applications.

3.10 Ecotoxicology

Pyrethrins and pyrethroids are broad spectrum insecticides, and as such they may also impact on beneficial insects, such as parasitoids, predators and bees.[37] They are also highly toxic to aquatic organisms which are generally more susceptible to pyrethroids than terrestrial organisms (see Table 3.2).[165,166] Birds rapidly eliminate pyrethroids *via* ester hydrolysis and oxidation, and generally eliminate the insecticides two to three times faster than mammals.[166] The lower toxicity and higher elimination rate is most likely a function of the higher metabolic rates of birds.

Pyrethroids are highly toxic to fish and aquatic invertebrates, excluding mollusks, and are slightly less toxic to amphibians. Symptoms of intoxication in fish include hyperactivity, loss of balance and the development of darkened areas on the body. Generally the toxicity of pyrethroids to fish increases with an increasing octanol–water partition coefficient.[167] The sensitivity of fish is mainly due to their poor ability to metabolize pyrethroids, with the only major metabolite recovered from a variety of pyrethroids in rainbow trout (*Oncorhynchus mykiss*) being the 4′-hydroxy metabolite which is produced through oxidation.[168–170] Fenvalerate and permethrin exposure to trout shows little to no esterase activity or ester hydrolysis, which is the main detoxification route for mammals and birds.[171–173] In trout exposed to cypermethrin, low levels of ester hydrolysis were observed, but at levels which were nevertheless lower than those in other vertebrates.[169]

The higher acute toxicity of pyrethroids to fish can be accounted for by the uptake and reduced metabolism with higher brain sensitivities compared with that of other vertebrates.[174] Pyrethrins and pyrethroids are most toxic to trout species, but the differences between fish species are less than a half an order of magnitude.[175] Trout are two to three times more sensitive to pyrethroids than bluegill sunfish (*Lepomis macrochirus*) and fathead minnows (*Pimephales promelas*), and three to six times more sensitive than southern leopard frogs (*Rana sphenocephala*) and boreal toads (*Bufo boreas boreas*).[176] Pyrethroid toxicity to

amphibians has not been extensively studied and there is limited knowledge of the mechanism by which they are less sensitive than other aquatic organisms. This is important given that amphibians are generally the most sensitive organisms to environmental pollutants, with many of the declines in numbers attributed to their high sensitivity to environmental toxins.[177]

Gills are the most likely route of exposure for fish to anthropogenic agents because of their large surface area, countercurrent flow and thin epithelial layer.[178] However, fish exposure to pyrethroids through gills only results in 20% to 30% of the total absorbed dose.[172] It is unclear as to what the main route of uptake is for fish. The *trans*-permethrin is 110 times more toxic to rainbow trout than to mice by both intravenous and intraperitoneal administration.[179] The half-life of pyrethroids in mammals and birds is six to 12 hours, but in trout the half-life is greater than 24 hours.[171] Lethal brain residues in rainbow trout of permethrin, cypermethrin and fenvalerate were 6% to 33% of the lethal brain residues in mice and quail, indicating that the mode of action and metabolism of pyrethroids are important factors in the increased toxicity to fish.[169,179–181] The difference is due to microsomal oxidation, with the metabolism of *trans*-permethrin being 35 times greater in mice compared with that in rainbow trout, which is most likely the cause of the increased sensitivity of fish.[179,180] Pyrethroids may also affect the respiratory surfaces and renal ion regulation which can contribute to the increased toxicity in fish.[182,183]

A large number of toxicity tests have been carried out on a wide range of terrestrial and aquatic organisms under laboratory conditions, in the presence and absence of sediment and dissolved organic matter. Type II pyrethroids have a greater toxicity than pyrethrins and type I pyrethroids to both aquatic and terrestrial invertebrates.[165,184] The difference in toxicity has been attributed to the decreased degradation of the cyano-substituted pyrethroids by both hydrolases and oxidases.

Pyrethroids undergo minimal biomagnification in vertebrates and invertebrates because of their rapid metabolism and excretion.[185] For example the octanol–water partition coefficient (K_{ow}) for permethrin is about six, while for the major metabolites it is approximately three. These characteristics are often associated with a propensity to biomagnify, much like DDT. However when pyrethroids are compared with the bioconcentration factor of DDT which is known to biomagnify in organisms they are only less than 3% of DDT (see Table 3.1). There have been limited studies on the bioconcentration factor of pyrethrins because they are rapidly metabolized, but it has been estimated to be 11 000 based on the K_{ow}.[16]

Although pyrethroids display very high acute toxicities to aquatic organisms when in the aqueous phase, the presence of suspended sediment substantially reduces the freely dissolved concentration of pyrethroids, and therefore their bioavailability. Pyrethrins and pyrethroids have little mobility in soils and are associated with sediments in natural water; consequently, they will only be in the water phase for a relatively short time, limiting their exposure to many organisms.[186,187] In addition, the half-lives of many pyrethroids in aquatic systems that are not bound to sediment are one to five days, which suggests that

small streams are more likely to show effects on non-target organisms because of the lower dilution of the insecticides. Therefore, chronic exposures to organisms that do not have a benthic lifestyle will most likely not result in observed effects because pyrethroids dissipate rapidly (dissipation half-life in the water column is generally less than one day). The rapid dissipation of pyrethroids makes it difficult to reconcile field exposures with those used in laboratory studies that maintain constant concentrations from ten to 100 days. The pH of the water used does not influence the toxicity of pyrethrins or pyrethroids, but hard or saline water can increase the toxicity to aquatic organisms.[171,175] In addition, the values obtained for aquatic organisms in the laboratory can be difficult to reproduce because pyrethroids strongly bind to solvents or surfaces such as glass, which can cause an overestimation of the toxicity values.[188]

Concerns have been expressed that pesticide mixtures, especially pyrethroids with their widespread use, may have greater than additive toxicity in the environment. Brander *et al.*[189] found that type I and II pyrethroids can be antagonistic to one another, lowering the toxicity of the mixture to *D. magna*. This is most likely due to the competitive binding at the voltage-gated sodium channels, but there have been few studies to examine the physiological and biochemical mechanisms involved.[53] In addition to other pyrethroids present in the environment, other pesticides such as fungicides have been shown to interact synergistically with pyrethroids.[190,191] However the concentrations that have been observed to increase the toxicity are greater than those seen in the environment, and given the physicochemical properties of pyrethroids, these exposures are unlikely to result in a substantial increase in toxicity.

In addition to the concern of increased toxicity due to the addition of pyrethroids to aquatic systems, research has shown that the pyrethroid synergist PBO can increase the toxicity of pyrethroids already present in the environment.[97–99,162] However the concentration needed to significantly affect populations of organisms is unknown and is strongly dependent on the amounts and types of pyrethroids already present. Concentrations of PBO in both irrigation ditches and static ponds rapidly decreased to $0.012\,\mu g\,l^{-1}$ within 36 h after applications of synergized formulations, greatly reducing the exposure of organisms to both the pyrethroid and PBO.[129]

3.10.1 Formulation Toxicity

There is contradictory evidence about the differences in toxicity between pyrethroids with emulsifiers (*i.e.*, formulated products) and technical-grade pyrethroids. Emulsifiers are designed to keep the pyrethroid in solution, but they can also inhibit the uptake of the active ingredient into organisms. Coats and O'Donnell-Jeffery[192] found that emulsifiable concentrate formulations of permethrin, fenvalerate and cypermethrin were two to nine times more toxic to rainbow trout than technical-grade materials. However, there was no significant difference in uptake in rainbow trout found between emulsified

formulations and technical-grade fenvalerate. Mosquito larvae are 67 times more susceptible to technical-grade fenvalerate than the formulated product.[171,193] Beggel *et al.*[194] observed larger sublethal effects of formulations than technical-grade bifenthrin on fathead minnows. Technical-grade fenvalerate was more toxic to fathead minnows than the emulsifiable concentrate formulation at 96 h, but by 168 h the two formulations were of similar toxicity.[170] Schleier III and Peterson[131] found that the toxicity of technical-grade permethrin was about 10-fold greater than an emulsifiable concentrate to house crickets. The influence of the formulation on the toxicity is more important after spray drift because it lands directly in the water body. Oil-based formulations could retain more of the insecticide because of their high hydrophobicity, which could result in the insecticide being bioavailable longer, while emulsified concentrates could disperse faster in the water.

3.11 Ecological Field Studies

Experiments with cypermethrin showed that its concentration in *D. magna* and *Chironomus tentans* decreased as the dissolved organic carbon content of the water increased.[195] Acute pyrethroid toxicity decreased 60% to 92% depending on the concentration of suspended sediments.[187] Yang *et al.*[186] found that pyrethroids adsorbed on particles or dissolved organic matter were completely unavailable for uptake by *D. galeata mendotae* after a 24-hour exposure period.

Pyrethroids have even been observed to have beneficial effects on aquatic organisms. A concentration of 0.005 $\mu g\,l^{-1}$ of fenvalerate resulted in an increase in longevity of *D. galeata mendotae* adults.[196] The intrinsic rate of increase was not affected by fenvalerate until the concentration reached 0.05 $\mu g\,l^{-1}$, however concentrations of 0.01 $\mu g\,l^{-1}$ caused the net reproductive rate and the generation time to decrease.[196] After 21 days of continuous and pulsed exposures to fenvalerate over a concentration range of 0.1 to 1 $\mu g\,l^{-1}$, recovery of *D. magna* to reproduction was similar to controls.[197] Reynaldi *et al.*[198] found that acute exposures of 0.3 $\mu g\,l^{-1}$ of fenvalerate resulted in reduced feeding activity and smaller body size in *D. magna*, and exposure to concentrations of 0.6 $\mu g\,l^{-1}$ or greater resulted in delayed maturation.

Changes in aquatic communities have mostly been found at concentrations of 5 to 10 $\mu g\,l^{-1}$ of pyrethroid in water with recovery occurring within weeks, which is 0.2 to 10 times the concentrations found in the environment.[199–201] Hill[158] reviewed approximately 70 freshwater field studies in natural or farm ponds, streams and rivers, rice paddies, and microcosms and mesocosms and found that there were little to no acute effects on fish and aquatic invertebrates. However, environmental concentrations could affect some of the most sensitive species. Kedwards *et al.*[202] applied cypermethrin aerially adjacent to a farm pond and observed that Diptera were most affected by increasing concentrations, but the populations quickly recovered after the application. The sediment-dwelling invertebrates Gammaridae and Asellidae were adversely affected by direct applications of cypermethrin and lambda-cyhalothrin in

experimental ponds, but increases in populations of Planorbidae, Chironomidae and Lymnaeidae were also observed.[203] Van Wijngaarden *et al.*[204] reviewed 18 microcosm and mesocosm studies using eight different pyrethroids with single and multiple exposures. They found that Amphipoda and Hydacarina were the most sensitive to pyrethroid exposure, and recovery to populations occurred within two months after the final application. Roessink *et al.*[14] compared lambda-cyhalothrin applied three times at one-week intervals at concentrations of 10, 25, 50, 100 and 250 $ng\,l^{-1}$ in mesotrophic (macrophyte dominated) and eutrophic (phytoplankton dominated) ditch microcosms (approximately 0.5 m^3). At concentrations of 25 $ng\,l^{-1}$ and greater, population and community responses were measured with indirect effects on rotifers and microcrustaceans more pronounced in the plankton-dominated systems. At concentrations of 100 and 250 $ng\,l^{-1}$, which is 100-fold higher than concentrations observed in the environment, the rate of recovery of the macroinvertebrate community was lower in the macrophyte-dominated systems, most likely due to the prolonged decline of the amphipods.

Dabrowski *et al.*[205] found that mayfly nymphs are more likely to be affected by spray-drift exposure than by run-off exposure because of the reduced bioavailability of sediment-bound pyrethroids. Schulz and Liess[206] observed chronic toxicity to *Limnephilus lunatus* after pulsed exposures to fenvalerate. Soil with low organic matter content has a greater toxicity than soil with high organic matter content.[207] However, soil aging was not found to exert any effect on lambda-cypermethrin toxicity in the springtail *Folsomia candida*.[207]

Researchers have provided evidence that the 1999 lobster (*Homarus americanus*) die-off in Long Island Sound was not caused by the use of ULV resmethrin and sumithrin (also known as delta-phenothrin) insecticides in response to the introduction of West Nile virus.[208–210] Jensen *et al.*[161] showed that the use of truck-mounted ULV above wetlands had no significant impact on aquatic macroinvertebrates and *Gambusia affinis*, but did have a significant impact on flying insects. However, flying insect abundance recovered 48 hours after application. Milam *et al.*[211] found less than 10% mortality for *Pimephales promelas* and *Daphnia pulex* after truck-mounted and airplane ULV applications of permethrin. Davis and Peterson[212] found little impact on aquatic and terrestrial invertebrates after single and multiple applications of either permethrin or sumithrin by truck-mounted ULV. After airplane ULV applications of pyrethrins, Boyce *et al.*[213] found no impact on large-bodied insects within the spray zone, but they did observe an impact on smaller-bodied insects.

3.12 Conclusions

Pyrethroids have become widely used because they are highly effective against many pests, have low mammalian and avian toxicity, and lack environmental persistence. The discovery of the first photostable pyrethroid, permethrin, revolutionized pyrethroids as a class and subsequently led to their increased use in pest management. Pyrethroids represent an incredibly diverse set of

compounds that are currently used for all major pest control applications. However, they are broad-spectrum insecticides that are highly toxic to non-target terrestrial insects and many aquatic organisms.

Currently, the mode of action of pyrethroids is well understood and is characterized by either fine tremors (T-syndrome/Type I pyrethroids) or choreoathetosis and salivation (CS-syndrome/Type II pyrethroids), although not all steps between cellular changes in excitability and behavior are well understood. The secondary modes of action for pyrethroids are not well understood and more research is needed in this area.

The environmental fate and physical properties of pyrethrins and pyrethroids are well understood. Pyrethroids are persistent in soils and sediment with half-lives greater than 30 days, but their half-lives are substantially lower than legacy pesticides such as DDT. Pyrethroids are rapidly biodegraded and, contrary to their high K_{ow} values, they do not biomagnify through higher trophic levels of the food chain. Due to their long half-lives in sediment, certain sediment-dwelling invertebrates may be affected by pyrethroids, especially in urban areas where the insecticides are heavily used. A surprising finding is that pyrethroid exposure of fish through their gills results in only 30% or less of the total absorbed dose, which is contrary to many other anthropogenic agents. Although the environmental effects of fenvalerate and esfenvalerate on aquatic organisms have been studied extensively, more research is required on the effects of pseudopyrethroids on aquatic organisms.

Commercial research and development efforts in the discovery of novel pyrethroids have largely ceased since the late 1990s; however, work is still being done to introduce single- or enriched-isomer mixtures of compounds like cypermethrin and cyhalothrin. With the voluntary cancellation of fenvalerate and esfenvalerate[214] and the end of major development of pyrethroids by many manufacturers (with the exception of companies like Sumitomo which recently developed metofluthrin for commercial use in Japan),[215] pyrethroid development seems to be well past its peak. The key to the continued commercialization of pyrethroids in Europe and the USA may lie with pseudopyrethroids like etofenprox that have yet to be widely used, but display lower acute toxicity to aquatic organisms.

About 80 species of arthropods are resistant to pyrethroids around the world.[216] Across the USA, there has been an increase in *kdr* resistance in bed bugs (*Cimex lectularius*), which is thought to have led to their reappearance in many cities.[217] Pyrethroids suffer from an inherent disadvantage because at the outset *kdr* resistance also confers resistance to DDT analogs, and prior resistance to DDT has already selected for this mechanism of resistance. This is of great concern with respect to pyrethroid resistance among *Anopheles gambiae* in West Africa, which could render the use of pyrethroid-impregnated bed nets ineffective in the prevention of malaria.[218] This trend could be exacerbated because of the renewed use of DDT as an indoor residual spray. The increasing cost for the discovery of insecticides with novel modes of action, in conjunction with other insecticides like organophosphates losing registration, could render pyrethrins and pyrethroids less effective.

Pyrethrins, pyrethroids and their synergists that were registered after 1984 are currently undergoing registration reviews in the USA to evaluate the effectiveness of recent regulatory decisions and to consider new data.[219] The registration review is focused on developmental neurotoxicity, because recent studies have shown decreases in rat pup weight, pup weight gain, and/or brain weight.[74] In addition, the USEPA has recently updated spray drift regulations for pyrethroids, increasing the buffer between sprayed areas and aquatic environments.[220]

Even though pyrethroids are not pest-specific insecticides and have been used for the past 40 years, they continue to be commonly used. This is because they target a wide variety of pests, have low application rates, have low mammalian toxicity and have a favorable environmental fate profile. Provided that they are used appropriately, pest resistance to them is managed effectively and regulations for them are based on scientific evidence, the pyrethrins and pyrethroids will continue to be used well into the foreseeable future.

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