

# Pyrethrum Flowers and Pyrethroid Insecticides

by John E. Casida\*

The natural pyrethrins from the daisy-like flower, *Tanacetum* or *Chrysanthemum cinerariifolium*, are nonpersistent insecticides of low toxicity to mammals. Synthetic analogs or pyrethroids, evolved from the natural compounds by successive isosteric modifications, are more potent and stable and are the newest important class of crop protection chemicals. They retain many of the favorable properties of the pyrethrins.

Most insect pests of crops, livestock, and man have been easily controlled for the past 35 years by relatively inexpensive organochlorine and organophosphorus compounds and methylcarbamates. Control of pest insects is progressively more difficult and costly because of increasing restrictions on some of the major insecticides of these types. They are considered to have unfavorable persistence, environmental impact and/or toxic effects on higher animals including man. There is an urgent need for alternative chemical or biological control methods for pest control. Pyrethroids developed within the past seven years are helping to meet this need. These insecticides are structural modifications of one of the oldest insect control agents, the remarkably effective but unstable pyrethrins from pyrethrum flowers. The newer pyrethroids have greatly improved potency and stability. It is appropriate as the use of pyrethroids expands to examine their origin, properties and safety aspects as compared with the pyrethrins and their prospects for filling current and projected gaps in insect control capabilities.

Pest insect control until the 1940's was moderately successful with the use of primarily compounds from natural sources either directly or after simple extractions or other treatments. These "first generation" insecticides were inorganic arsenic- or fluorine-containing toxicants or botanicals such as nicotine, rotenone, and pyrethrins. Except for the

pyrethrins, they were displaced in the 1940's and 1950's by synthetic organic or "second generation" insecticides which provided nearly complete control at reduced cost due to high potency or persistence or both these properties. There are four principal classes of second generation insecticides, i.e., organophosphorus compounds, methylcarbamates, chlorinated hydrocarbons, and pyrethroids; all act as nerve poisons. The first two classes inhibit acetylcholinesterase and thereby disrupt synaptic transmission. The others probably act at nerve membranes principally by altering sodium conductance mechanisms. Several of the chlorinated hydrocarbons (e.g., DDT, aldrin, and dieldrin) have been restricted or banned because of unacceptable persistence, effects on wildlife, and evidence of possible carcinogenic activity. Some of the important organophosphorus and methylcarbamate insecticides are very hazardous to manufacture, formulate and apply due to their high acute toxicity when ingested, inhaled or absorbed through the skin. Most of the pyrethroids appear at present to have generally favorable persistence and toxicological characteristics.

The first and second generation insecticides act on systems important for survival in both pest and other organisms including mammals. They therefore lack the selectivity which is theoretically possible with hormones or antihormones, agents that disrupt cuticle or chitin formation, or other types of insect growth regulators. These "third generation" insecticides have not yet been perfected for extensive use, and there are definite limitations in the types of pest

\*Pesticide Chemistry and Toxicology Laboratory, Department of Entomological Sciences, University of California, Berkeley, California 94720.

infestations where such slow-acting compounds are likely to prove acceptable. Chemical control of insects depends almost completely at present on first and second generation insecticides including pyrethrins and pyrethroids. The common names of important compounds are given in Table 1.

Table 1. Common names of natural esters and synthetic analogs and origin or possible origin of names.

Name	Origin
Natural materials	
Pyrethrins	<i>Pyrethrum cinerariifolium</i> (old genus name)
Pyrethrins I	Derived from chrysanthemum monocarboxylic or chrysanthemic acid
Pyrethrins II	Derived from methyl ester of chrysanthemum dicarboxylic acid, i.e., pyrethric acid
Rethrins	<i>Pyrethrins</i> and related cyclopentenolone derivatives
Cinerins	<i>Tanacetum cinerariifolium</i>
Jasmolins	Similar structure to <i>jasmone</i> from <i>Jasminium grandiflorum</i>
Pyrethrin analogs with specific chemical groups	
Allethrin	Allyl analog
Phenothrin	Phenoxy analog
Tetramethrin	Tetrahydrophthalimidomethyl analog
Pyrethrin analogs by Michael Elliott et al.	
Resmethrin	Discovered at Rothåmsted Experimental Station
Permethrin	Enhanced persistence
Cypermethrin	Cyano analog of permethrin
Decamethrin	Deca (10)-fold more potent
Other origins	
Kadethrin	Knockdown analog of pyrethrin
Fenvalerate	A phenylisovalerate pyrethroid

## Pyrethrum Flowers

In the early 1800's pyrethrum flowers were used by Caucasian tribes and in Persia to control body lice. The flowers were first produced commercially in Armenia in 1828. Production started in Dalmatia (Yugoslavia) about 1840 and was centered there until the first World War, in Japan until shortly before the second World War, and in East Africa since then. More than half of the world's current production comes from Kenya, with important amounts from Tanzania, Rwanda, and Ecuador. Insect powder was first imported into the United States in about 1860, and several unsuccessful attempts were made over the next 90 years to produce the flowers commercially in this country. Since about 60 years ago the flowers were extracted with kerosene or similar solvents to give liquid sprays more effective than the powders.

The pyrethrum plant of commerce is the daisy, *Tanacetum cinerariifolium* (Trev.) Schultz Bip.

[*Pyrethrum cinerariifolium* Trev. and *Chrysanthemum cinerariifolium* (Trev.) Vis.], a herbaceous perennial of the family Compositae. The producing areas are near the equator, from 1800 to 4000 m in altitude, and with rainfall of 50 to 200 cm spread throughout at least seven months of the year. Under these growing conditions, flowering continues for seven to 11 months each year. In Kenya alone, more than 85,000 families are engaged in growing pyrethrum. Worldwide, perhaps 200,000 farmers are involved in pyrethrum culture. Pyrethrum production is currently estimated at about 15,000 tons of dried flowers per year, about half the amount currently needed for the world market. The dried flowers contain 1-2% pyrethrins by weight, averaging about 1.3%; so, the production of pyrethrins is about 150 to 200 tons per year. Present annual production averages about 560 kg dried flowers per hectare, although plant selection and improved propagation and cultivation techniques make it possible to produce 900 kg of 1.8% or higher dried flowers annually in some growing areas.

The pyrethrins are localized in the secretory ducts of the achenes, where they are protected from photodecomposition and isolated so they are not toxic to insects feeding on or visiting pyrethrum flowers. The flowers are hand picked when four or five rows of disc florets are open, and each flower contains about 3-4 mg pyrethrins. After drying in the sun or mechanically, the flowers are ground and extracted with hexane. Evaporating the hexane yields a dark, viscous oleoresin concentrate containing about 30% pyrethrins. The concentrate is either diluted with plant or mineral oil to 25% pyrethrins (oleoresin extract) or purified by methanol extraction and charcoal treatment to produce a dewaxed and decolorized refined extract. This purification removes components which earlier gave allergic responses evidenced as dermatitis in humans sensitive to ragweed pollen.

Pyrethrum extract is important to control of pest insects in the household, in barns, and in stored products, and for direct application to man and livestock. Before the second World War, powdered pyrethrum flowers or pyrethrum extract were employed for control of agricultural and horticultural insect pests, a use largely superseded in the 1940's by the more effective and simpler chlorinated hydrocarbon and organophosphorus insecticides. Compared with these synthetic organic insecticides, the persistence of the pyrethrins, even with various additives to retard photooxidation, is not adequate for crop protection or silviculture. The present uses for pyrethrum are well established and dependable methods of insect control, but for very specific purposes not likely to change in the foreseeable future.

The selection of resistant strains, a problem with most other insecticides, has had little impact on the use pattern of the pyrethrins.

The pyrethrins knock down houseflies, mosquitoes, and other flying insects rapidly and, at appropriate doses, the insects die a few minutes or hours later. Instructions for space sprays or aerosol applications through the 1940's cautioned users to be neat and tidy, and to sweep the flies outside the house after knockdown; under these circumstances the user was oblivious to the recovery of the flies. The hyperexcited state preceding or associated with knockdown is also useful in other ways. It repels and disorients biting flies and mosquitoes which therefore bite less frequently. It flushes cockroaches from their hiding places to contact lethal doses of the insecticide. Three developments helped establish and maintain these uses for pyrethrum. The first was an alternative method for delivering pyrethrins to control mosquitoes by incorporating ground pyrethrum flowers with other ingredients into mosquito coils, which, burned throughout the night, generated a smoke that repelled, expelled, knocked down, or killed mosquitoes in human habitats. The second in 1941 was the aerosol can or "bomb" which, although now used to disperse many types of household and industrial agents, was originally perfected to deliver pyrethrum extract. It produces droplets below 30  $\mu\text{m}$  in diameter, essential for maximum effectiveness and economical use of the pyrethrins. The final development was an additive or synergist, piperonyl butoxide, which was discovered in 1949. Although essentially noninsecticidal, it increases the potency of pyrethrum by more than fourfold when added at two to ten parts of synergist per part of pyrethrins. The pyrethrins-synergist combination is much more economical than the insecticide alone, since the synergist costs less than 5% per unit weight of the pyrethrins. The synergist also increases the likelihood that insects knocked down will subsequently die rather than recover. In addition to piperonyl butoxide, another type of synergist, MGK 264, has also been important for many years.

Pyrethrum is generally considered to be the safest insecticide and was once labeled as "nontoxic to humans and pets." This labeling is no longer allowed, so it is difficult for the user to differentiate the relative safety of various household insecticide products. After use for more than a century, there are very few cases of human illness associated with exposure to pyrethrum, and most of these are early reports of dermatitis or allergic reactions due to impurities no longer present in the purified extract. Pyrethrins were once used at three consecutive daily doses of 10-20 mg per adult or 5 to 10 mg per child to control intestinal worms without reported ill effects.

However, it is known that accidental oral or dermal exposure to high doses of pyrethrins can cause a temporary numbness of the tongue and lips. Pyrethrum extract has low acute toxicity to mammals and birds despite a very high toxicity to insects, other invertebrates and fish (lethal concentrations of a few parts per billion in water). Tests with laboratory mammals indicate that pyrethrum, even at high doses or combined with piperonyl butoxide, does not produce carcinogenic, mutagenic or teratogenic effects. Any pathological changes observed at high doses are in the liver.

The pyrethrins are very unstable in light and air, limiting the areas where they are effective but also providing a safety factor against the accumulation of hazardous residues. Uses of pyrethrum and its synergists are regulated by restrictions under the Environmental Protection Agency and by tolerances for levels in food and feed under the Food and Drug Administration. The tolerance values for post harvest applications to various plant products are commonly 1-3 ppm for pyrethrins and 8-20 ppm for piperonyl butoxide. In several cases, these compounds are exempted from the requirement for tolerances because their safety relative to the levels likely to be present under normal conditions is acknowledged.

## Chemistry of the Pyrethrins

Pyrethrum extract contains six closely related insecticidal esters, collectively referred to as the pyrethrins, which differ only in the terminal substituents in the side chains of the acid and alcohol components. The acid is a substituted cyclopropane-carboxylic acid and the alcohol a substituted cyclopentenolone. Three alcohols are involved, pyrethrolone, cinerolone and jasmolone for the pyrethrins, cinerins, and jasmolins, respectively (Table 2). The two acids are chrysanthemic acid for the I series and pyrethric acid for the II series. The main structural features of these compounds were elucidated between 1910 and 1916 but not reported until 1924 by Hermann Staudinger and Leopold Ruzicka, two Swiss chemists each later awarded a Nobel Prize for pioneering discoveries in several fields of chemistry. Important contributions on characterization and synthesis in the period 1919 to 1966 were also made by Masanao Matsui and Ryo Yamamoto in Japan, William Barthel, Frances LaForge, Milton Schechter and coworkers in The United States, and Leslie Crombie, Michael Elliott, Peter Godin and Stanley Harper and their associates in England. The six individual esters are not available commercially and are more economically produced as botanicals than by chemical manufacture.

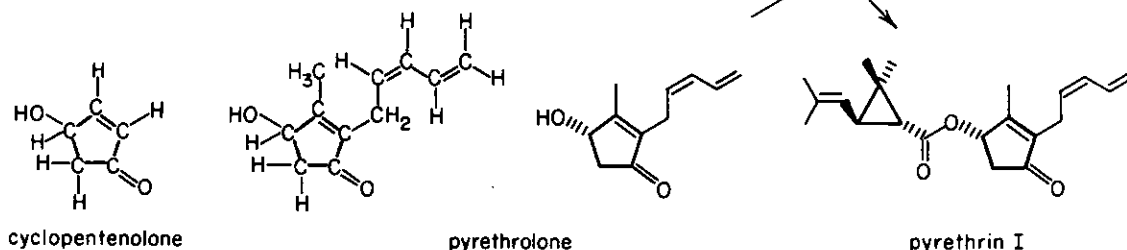
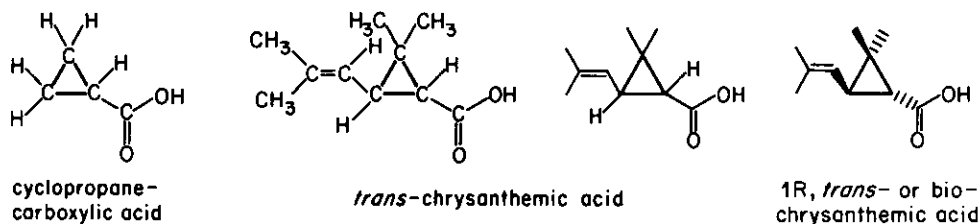


Table 2.

	R	%	Name
<u>chrysanthemates</u>			
	CH=CH <sub>2</sub>	35	pyrethrin I
	CH <sub>3</sub>	10	cinerin I
	CH <sub>2</sub> CH <sub>3</sub>	5	jasmolin I
<u>pyrethrates</u>			
	CH=CH <sub>2</sub>	32	pyrethrin II
	CH <sub>3</sub>	14	cinerin II
	CH <sub>2</sub> CH <sub>3</sub>	4	jasmolin II

They could probably be obtained, if needed, by total synthesis, by reconstitution from the acids and alcohols derived from pyrethrum flowers, or by isolating the natural materials using various combinations of column adsorption and partition chromatography, gas-liquid chromatography and high pressure liquid chromatography.

The pathways used by pyrethrum flowers in biosynthesis of the acid moieties of the pyrethrins from mevalonic acid are well established and of the alcohol moieties are partially understood. The pyrethrates originate biosynthetically from chrysanthemic acid or chrysanthemates by oxidation of the *trans*-methyl group of the isobutenyl substituent, followed by biomethylation [Eq. (1)]. Oxidation of an isobutenyl methyl substituent is involved in biosynthesis of pyrethrates in pyrethrum flowers and metabolism of chrysanthemates in mammals and insects. The R' substituent may be hydrogen as in

chrysanthemic acid or an alcohol moiety as in the pyrethrins. The oxidases and dehydrogenases require pyridine nucleotide cofactors as indicated. Biomethylation utilizes *S*-adenosylmethionine as the methyl donor. Pyrethrate-hydrolyzing esterases require no cofactors.

The biological activities of the pyrethrum constituents depend on the structures and stereochemical characteristics of both the acid and alcohol components. Pyrethrins I and II are considerably more potent than the cinerins and jasmolins. The chrysanthemates (I) are generally more potent for kill and the pyrethrates (II) for knockdown. Thus, pyrethrum contains a combination of an excellent knockdown agent (pyrethrin II) and a potent insecticidal component (pyrethrin I). The pyrethrins have three chiral centers and therefore eight different optically active forms are possible (Fig. 1). There is also geometrical isomerism (E or Z) in the side chain of

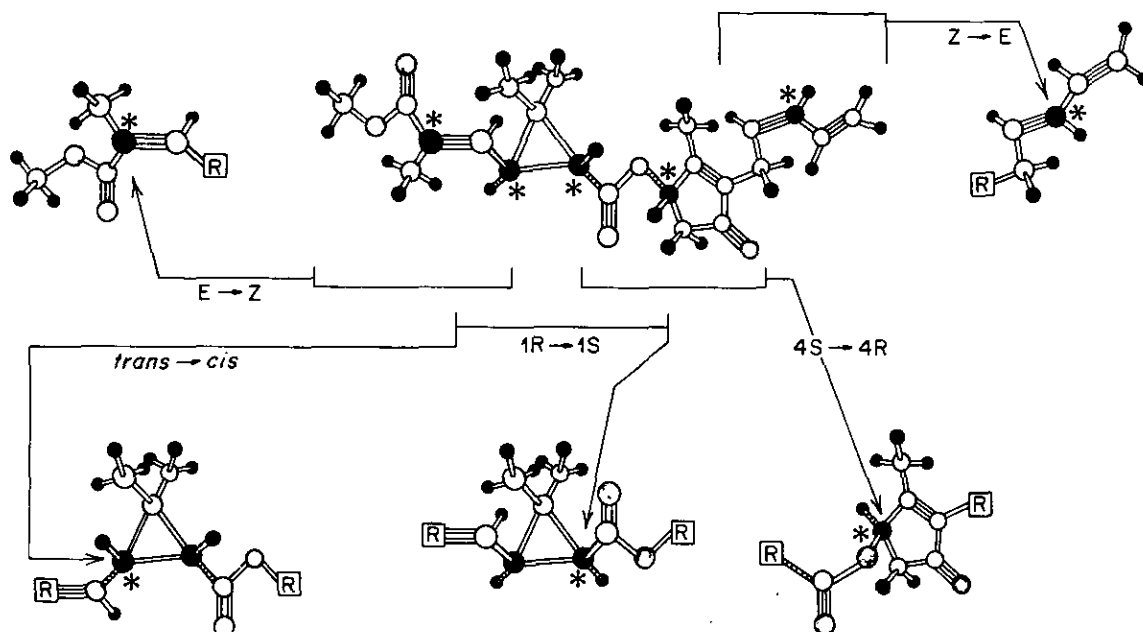
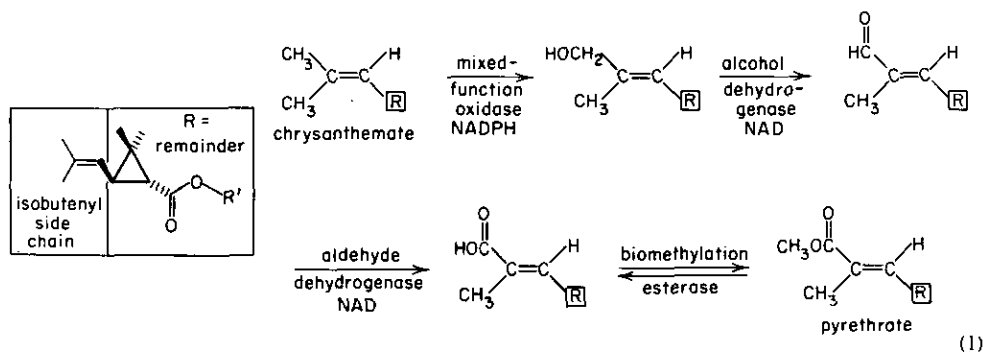


FIGURE 1. Pyrethroid stereochemistry is illustrated with pyrethrin II. Asterisks designate chiral or asymmetric centers.  $\boxed{R}$  indicates the remainder of the molecule beyond the bracketed portion. Partial structures give optical isomers in the bottom row and geometrical isomers at the sides of the upper row. Arrows indicate names for the transformations and the chiral center or double bond where inversion takes place. Two isomers are possible, the natural one in the pyrethrin II structure and the alternative one in the partial structure, in each of the five cases. This makes  $2^5$  or 32 possible isomers. Pyrethrin I lacks the methoxycarbonyl group at the upper left so it has only  $2^4$  or 16 possible isomers.

the alcohol (chrysanthemates) or of the acid and alcohol (pyrethrates) increasing the number of possible stereoisomers to 16 for the chrysanthemates and 32 for the pyrethrates. Although these isomers have not all been prepared and tested, the available evidence strongly suggests that the naturally occurring configuration is likely to be the most potent one.

## History of Pyrethroids

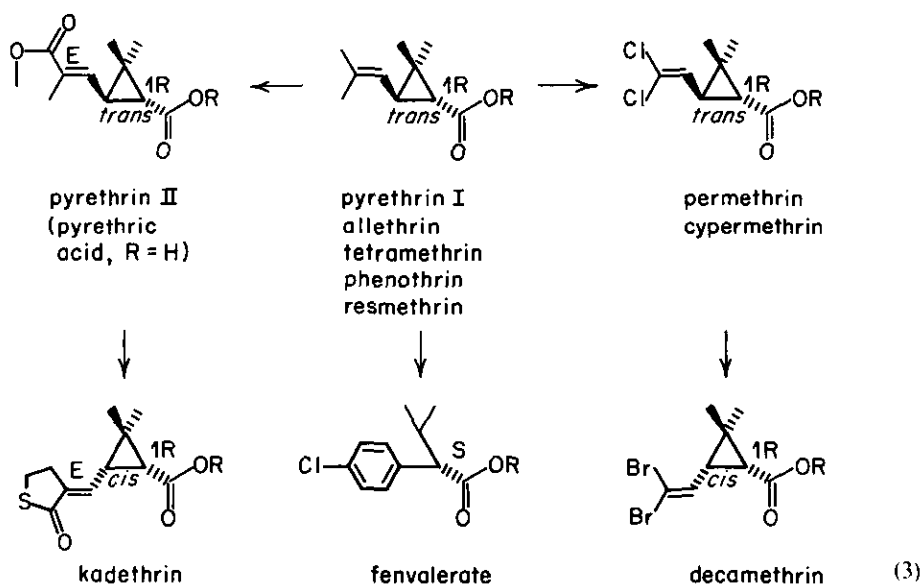
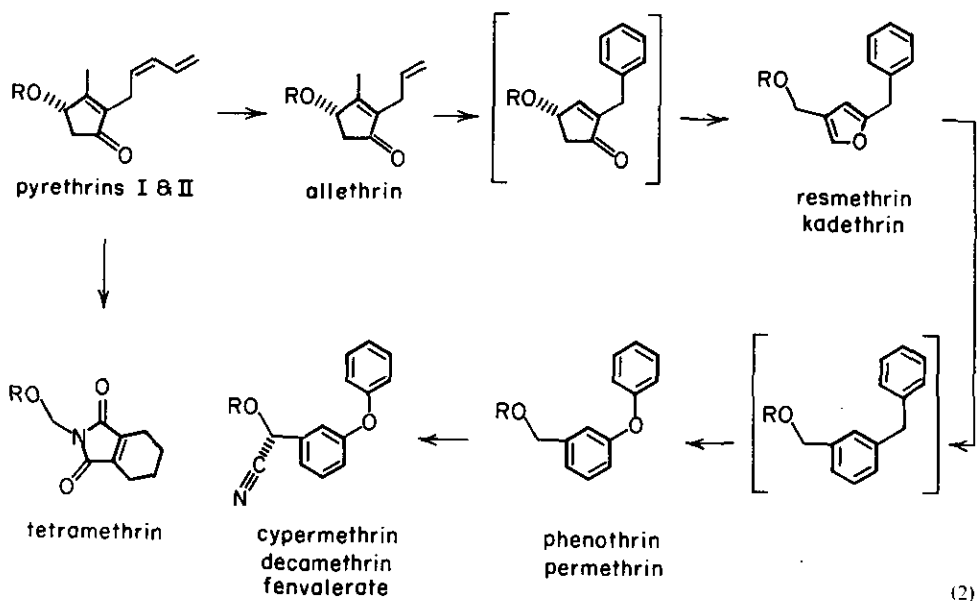
Synthesis of naturally occurring compounds and their bioactive analogs is a normal part of natural products chemistry research. These investigations are important in structural elucidation, often using

simplified compounds as models. If model chemicals for the pyrethrum constituents are insecticidal, they are pyrethroid insecticides. The principles by which second generation insecticides were later discovered were already recognized over 60 years ago, since Staudinger and Ruzicka prepared about 100 candidate pyrethroids between 1910 and 1916, although none was particularly insecticidal. After correcting some details of the pyrethrins structures assigned by Staudinger and Ruzicka, LaForge, Barthel, and Schechter derived a simpler synthetic analog, in which an allyl group replaced the pentadienyl side chain of the alcohol moiety. This compound, allethrin, the first commercial pyrethroid, culminated

wartime research in both the United States and England seeking pyrethrum substitutes to minimize dependence on the natural material produced in areas where shipping channels and therefore available supplies might be disrupted.

Few new pyrethroids were discovered following commercialization of allethrin until developments about 15 years ago in the laboratories of the Sumitomo Chemical Company (Osaka and Takarazuka, Japan) and of Michael Elliott, Norman Janes and their co-workers at Rothamsted Experimental Station (Harpenden, England). The acid moiety was standardized as the now commercially-

available chrysanthemic acid and new alcohol moieties were examined. Pyrethroids developed at this time served essentially as pyrethrum substitutes without expanding the general scope of use. Variations of the acid moiety were then made, using the best alcohol moieties available. At present, dozens of laboratories in many countries are examining thousands of potential pyrethroids each year. There are four primary optimization goals at present: high effectiveness as knockdown agents for flies and mosquitoes (i.e., pyrethrum substitutes); maximum potency as broad spectrum insecticides; adequate stability for plant protection; reasonable cost rela-



tive to the use levels for adequate pest control.

It is sometimes difficult to decide whether or not a synthetic insecticide is a pyrethroid. Generally, new compounds may be considered pyrethroids if their biological properties depend on stereochemical features similar to those of the pyrethrins. The most active compounds are carboxylic acid esters with the carbons adjacent to the carboxyl group bearing appropriate substituents positioned, if they are at chiral centers, in a configuration corresponding to pyrethrin I. Structural optimization is normally achieved by sequential isosteric replacements of critical substituent groups, as illustrated in Eq. (2) for the alcohol moiety and Eq. (3) for the acid moiety. Selecting appropriate replacement groups is not as easy or obvious as it might appear. Each novel moiety was discovered in tests of many hundreds or thousands of esters, most of which proved to be essentially non-insecticidal. Some of the acid and alcohol moieties are closely related to those of the natural esters, while others seem far removed, e.g., chlorophenyl-containing acid moieties and cyano-containing alcohol moieties. One test for a pyrethroid acid moiety is to determine if it is most potent with the normal pyrethroid alcohol moieties; the same argument applies for pairing candidate alcohol with acid moieties. The acid moieties of some pyrethroids bear a close structural resemblance to a portion of

molecules of the DDT type, raising the question of whether pyrethroids and DDT might act in part at similar or the same neuroreceptors. Although there are many similarities of action between pyrethroids and DDT, the relevant neuroreceptors are not adequately defined so specific neurophysiological tests cannot be used to differentiate unequivocally pyrethroids from nonpyrethroids.

## Pyrethroids as Pyrethrum Substitutes

Five pyrethroids are used in much the same manner as pyrethrum extract (Fig. 2). They are highly insecticidal but not persistent enough for agricultural use. Three are primarily knockdown agents and the other two are very potent for kill. Household sprays are usually a mixture to mimic the action of pyrethrum. They contain a knockdown agent, a more insecticidal component, and a synergist, normally piperonyl butoxide. With the exception of kadethrin, these compounds are chrysanthemates.

The knockdown property requires rapid penetration conferred by the polarity of either the acid or alcohol component. Instability results from susceptibility to photooxidation at allyl, isobutenyl, furan and thiolactone substituents. For example, the

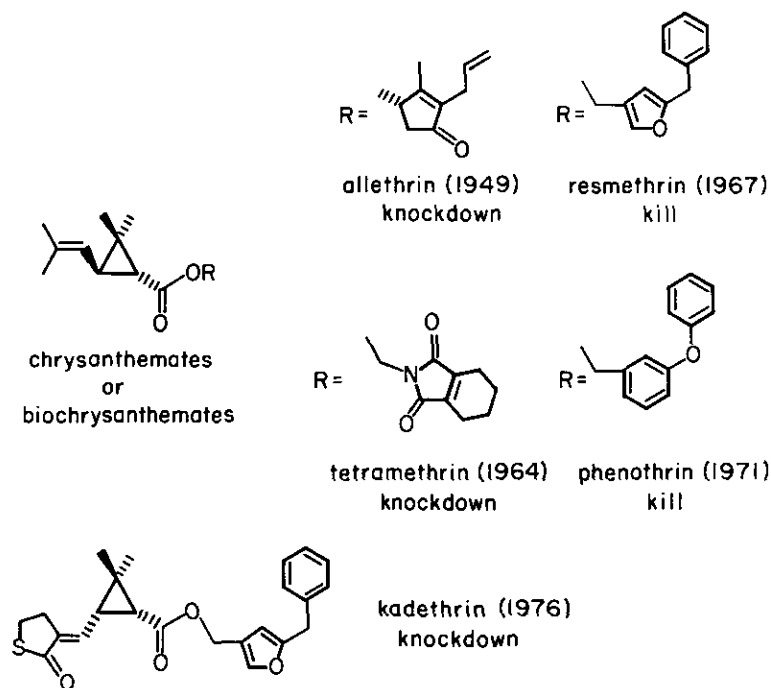


FIGURE 2. Pyrethrum substitutes used or proposed for use to knock down household insects or to kill household, garden, and stored products pests.

isobutenyl group of chrysanthemates undergoes epoxidation and methyl oxidation and the furan ring degrades via an unstable peroxide intermediate. The years for discovery or first reports in the literature are given. Commercialization usually followed a few years later. Allethrin is employed as the isomer shown (*S*-bioallethrin) or as a mixture of two (4*RS* or bioallethrin) or eight isomers. Tetramethrin, resmethrin and phenothrin are available as mixtures of four isomers (1*RS*, *cis*, *trans*) and potentially as various mixtures of two isomers (1*RS*, *trans*; 1*RS*, *cis*; 1*R*, *cis*, *trans* or forte mixtures). Kadethrin is used as the individual isomer shown.

*S*-Bioallethrin, the most potent isomer of allethrin, has the same optical configuration as pyrethrin I. It is generally less active than the pyrethrins but more stable due to the less easily-oxidized alcohol moiety side chain. The other two knockdown pyrethroids, in contrast to the pyrethrins and allethrin, contain elements in addition to carbon, hydrogen and oxygen, i.e., nitrogen in tetramethrin of Sumitomo Chemical Company and sulfur in Kadethrin of Roussel-Uclaf (Paris). Kadethrin is the most potent knockdown agent, even more active than pyrethrin II, but is very labile due to the photoinstability of both the furan ring and the thiolactone moiety.

Resmethrin has insecticidal potency equal or superior to the pyrethrins on a wide variety of pests. The cyclopentenolone nucleus of the pyrethrins is replaced by the sterically equivalent furylmethyl unit and the pentadienyl side chain by a benzyl group.

Phenothrin is derived from resmethrin by replacing the furan ring by a phenyl group and the methylene bridge by oxygen, resulting in a more stable but usually less active compound. Both insecticides lack significant knockdown properties and the 1*R*, *trans* isomers (i.e., bioresmethrin and biophenothrin) are more potent with some species and the 1*R*, *cis* isomers with others. Synergists are of little or no value with resmethrin and phenothrin at normal ratios of synergist to insecticide. Resmethrin was discovered in Rothamsted and offered for commercialization by the National Research Development Corporation (NRDC) based in London. Phenothrin was discovered independently in England and Japan.

## Pyrethroids for Crop Protection

Four pyrethroids are currently used for crop protection: permethrin, cypermethrin, decamethrin, and fenvalerate, compounds obtained by replacing photolabile centers in earlier esters with alternative and more stable structural units (Fig. 3). These pyrethroids are derived from phenoxybenzyl alcohol first synthesized for other purposes in 1935 or from  $\alpha$ -cyanophenoxybenzyl alcohol known since 1973. The acid moiety of permethrin was first investigated by Jiří Farkaš in Prague in 1958. He prepared the allethrin analog with enhanced insecticidal activity compared to the chrysanthemate. It took 15 years for this dichlorovinyl acid to appear once again in the literature, when Elliott showed its importance as a

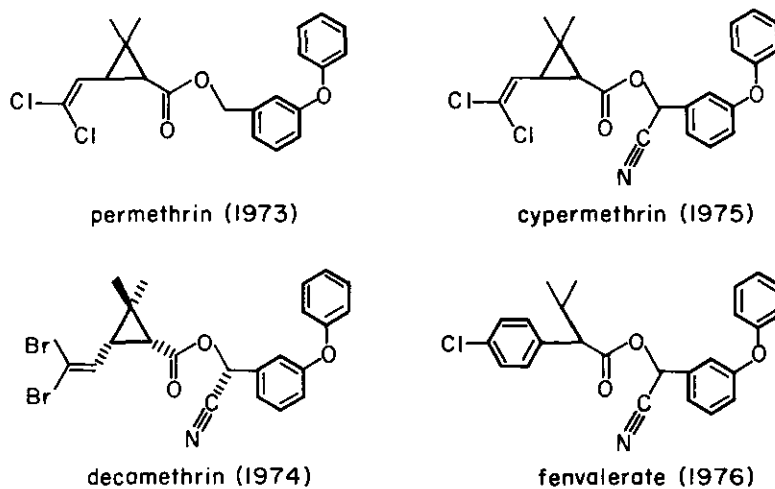


FIGURE 3. Pyrethroids used for crop protection or public health pest control. The years for discovery or first reports in the literature are given. Commercialization usually followed a few years later. The compounds are shown as the isomer composition normally employed for crop protection. The most potent of the eight isomers of cypermethrin is equivalent in insecticidal activity to decamethrin, in which bromine replaces chlorine.



pyrethroid acid having derived it by isosteric modifications. Permethrin, containing this photostable component, was the first pyrethroid with properties appropriate for crop protection. The  $\alpha$ -cyano derivatives, cypermethrin and decamethrin, also first prepared at Rothamsted, are extremely active insecticides. The cyano substituent in the S-configuration increases the potency by about 3- to 6-fold. The R-configuration is essentially inactive. Decamethrin and the equivalent 1R, *cis*,  $\alpha$ S isomer of cypermethrin are the most potent pyrethroids at present. The research of Sumitomo Chemical Company culminating in fenvalerate involved a series of discoveries, i.e. the useful properties of phenoxybenzyl alcohol, of its  $\alpha$ -cyano analog, and of the indicated non-cyclopropanecarboxylic acid as an excellent substitute for chrysanthemic acid analogs. Fenvalerate is generally in the range of 0.3 to 2 times the potency of permethrin, depending on the pest species.

## Pyrethroid Metabolism and Environmental Degradation

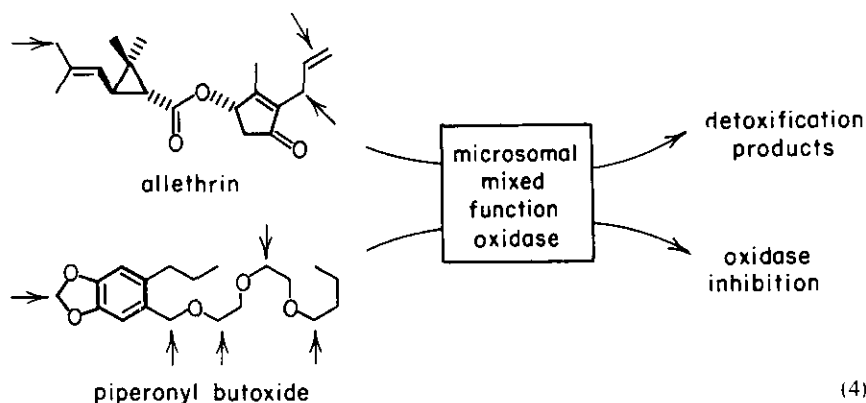
Two ways have been used to enhance the stability and therefore the potency of pyrethroids such as pyrethrin I. The first involves adding a synergist or antioxidant to retard metabolic or photochemical oxidative reactions. The second and much more effective procedure replaces substituents susceptible to photochemical or metabolic degradation with alternative groupings that confer greater overall stability to the molecule. Much of the safety of the pyrethrins is attributed to their instability. Thus, the stabilizing process could potentially generate compounds persisting in mammals and acting as environmental contaminants. The pyrethroid should be protected from abiotic (mainly photochemical) degradation and insect metabolism but susceptible to metabolism in mammals and environmental sys-

tems. The author and his colleagues at Berkeley have emphasized research on metabolism and environmental degradation, as have Miyamoto, Ohkawa, and co-workers of Sumitomo.

Metabolic detoxification is a major factor limiting the insecticidal activity of the pyrethrins and other chrysanthemates. Houseflies metabolize pyrethrin I, S-bioallethrin, and biotetramethrin by oxidation of a methyl group in the isobutenyl substituent to the corresponding carboxylic acid, a pathway paralleling the first steps in the biosynthetic conversion of chrysanthemic acid or its esters to pyrethric acid or pyrethrates in pyrethrum flowers [Eq. (1)]. Houseflies also oxidize allethrin in the alcohol component, probably at the double bond and the methylene group of the allyl moiety. These reactions are effected by the housefly microsomal mixed-function oxidase system when fortified with reduced nicotinamide-adenine dinucleotide phosphate (NADPH), the critical cofactor.

Synergist action involves inhibition of pyrethroid detoxification resulting in greater persistence in insects and higher potency. The microsomal mixed-function oxidase system metabolizes both the pyrethroid and the synergist, *e.g.*, allethrin and piperonyl butoxide. Sites of oxidation are indicated by arrows in Eq. (4). Piperonyl butoxide, both *in vivo* and *in vitro*, inhibits housefly metabolism of allethrin and other chrysanthemates, the synergist in the process undergoing metabolism at methylene substituents adjacent to oxygen atoms. The synergist is usually a better metabolic inhibitor in insects than in mammals.

Metabolic considerations played an important role in designing pyrethroid acid and alcohol moieties for enhanced insecticidal activity. Oxidation at an isobutenyl methyl group was circumvented by the dihalovinyl replacement or by shifting to the fenvalerate acid moiety. Pyrethroids are also detoxified by hydrolytic processes. Insect esterases generally

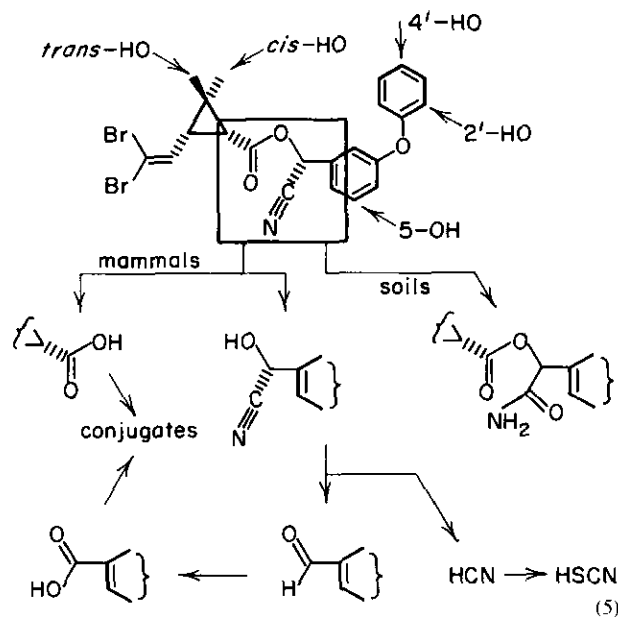


(4)

hydrolyze *trans*-chrysanthemates faster than *cis*-chrysanthemates, providing a partial explanation for the greater toxicity of the *cis*-isomer in some cases. Suitable esterase inhibitors synergize the insecticidal activity of several pyrethroids but such combinations are not commonly used. The  $\alpha$ -cyano substituent also retards esterase hydrolysis and possibly oxidative detoxification as well. Thus, the structural features used in optimizing the insecticidal activity of decamethrin are those designed to resist metabolism, i.e. a dihalovinyl group, the *cis*-isomer about the cyclopropane ring, and the cyano substituent. Even these modifications have not completely overcome the limiting effect of decamethrin detoxification in houseflies, since it can be synergized at least tenfold by a very high level of piperonyl butoxide or related synergist.

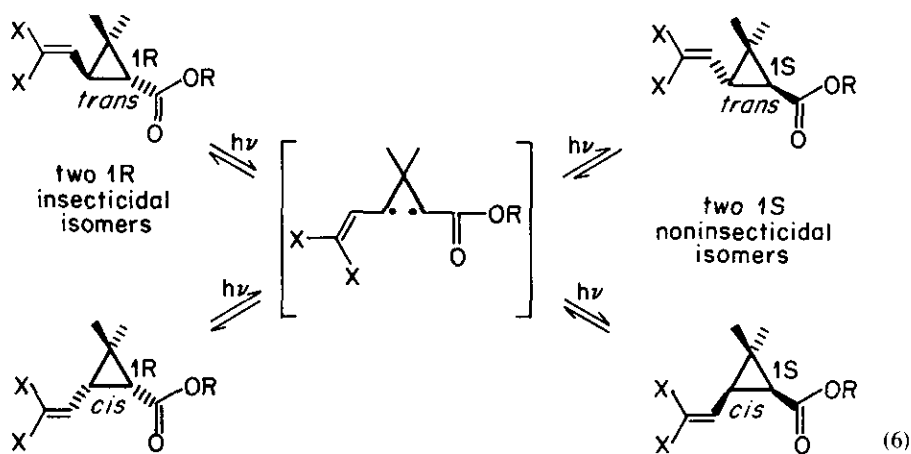
Mammals also metabolize pyrethroids by oxidation and ester cleavage. The same detoxification reactions account for the low toxicity of pyrethrin I and allethrin to mammals and the need to use a synergist for increasing their toxicity to insects. Fortunately, piperonyl butoxide as normally used gives little if any increase in toxicity of these rethrins to mammals. However, high synergist levels to block mammalian detoxification by oxidases (piperonyl butoxide) or esterases (organophosphorus compounds) generally increase pyrethroid toxicity. Caution must be exercised in using synergists because of such potential hazards. Structural modifications to stabilize the pyrethrins to insect metabolism could produce very hazardous compounds if they stabilized them in a parallel fashion to mammalian metabolism. Fortunately this is not the case for pyrethroids studied so far, e.g. decamethrin. Although the dibromovinyl group is not oxidized in mammals, there are still five sites of oxidation at methyl and aryl groups, the 4'-position being major, and ester hydrolysis is also important [Eq. (5)].

Decamethrin metabolism in rats and mice involves hydroxylation at either methyl group or any one of three aromatic positions. Ester cleavage by esterase action or possibly oxidative processes yields the acid and alcohol fragments. The *cis*-hydroxymethyl derivative is detected only after ester cleavage. The cyanohydrin breaks down to hydrogen cyanide and the aldehyde which is then oxidized to the acid. The two carboxylic acids are excreted with or without conjugation with glucuronic acid or amino acids such as glycine and taurine. The hydroxymethyl and phenolic derivatives are conjugated in part as sulfate esters. The liberated cyanide is quickly detoxified by conversion to thiocyanate which is excreted or temporarily bound in the stomach and hair prior to excretion. In soil a portion of the cyano moiety of related compounds is hydrated to the amide.



Metabolism studies of this type made on pyrethrins I and II and all the synthetic analogs discussed above clearly show that structural modifications can be made for enhanced insecticidal activity and photostability while maintaining rapid biodegradation in mammals. There are structure-dependent differences in the persistence of pyrethroid residues in mammals and birds; for example, although the residues are low, the more metabolically-stable *cis*-permethrin persists longer than *trans*-permethrin in fat, milk and eggs.

Environmental movement and fate were of little concern with the unstable pyrethrins and early chrysanthemates but are of considerable importance with the more stable pyrethroids used for crop protection. As with DDT, the newer halogen-containing pyrethroids are highly liposoluble, almost insoluble in water and persist on surfaces due to low vapor pressure (the pyrethrins and permethrin are viscous liquids and decamethrin a crystalline solid). Air movements are not likely to disperse these pyrethroids except during application or shortly thereafter. They are quite persistent on plants due to a combination of retention in leaf cuticular waxes (so that they are not washed off by rain), low volatility, and resistance to photochemical degradation. Studies at Berkeley show that photodecomposition of the pyrethroids shown in Figure 3 involves isomerization at the cyclopropane ring [Eq. (6)], ester cleavage, decarboxylation, diphenyl ether cleavage, oxidation to benzoic acid derivatives, and dehalogenation. These occur slowly enough that if only abiotic factors were involved these pyrethroids would be some of the most persistent organic insecticides.



The photoisomerization shown in Eq. (6) involves a breaking and re-forming of the cyclopropane ring via a diradical intermediate. The final equilibrium balance favors the *trans* isomers (upper structures) about 2:1 over the *cis* isomers (lower structures). Only the 1R isomers at the left are insecticidal. X refers to methyl, halogen or other substituents. This is one of many processes involved in pyrethroid photodecomposition, usually yielding less active products.

It is fortunate that environmental cleansing involves biotic as well as abiotic processes since the degradation rate of agricultural pyrethroids is greatly increased once they enter biological systems. Plants metabolize these pyrethroids, on partitioning out of cuticular waxes, by ester cleavage (*trans* isomer more rapid than *cis*), methyl and aryl oxidation and conjugation reactions as in mammals (except that glucoside rather than glucuronide conjugates are formed in plants). Although there is no evidence for plant metabolites that are hazardous, the residue analyses often consider several metabolites and photoproducts in addition to the parent compounds. Pyrethroids are not expected to undergo a high level of biological magnification on passing through food chains. They are nearly immobile in soils due to their low water solubility, rapid adsorption and minimal vapor diffusion. Although contamination of aquatic systems is a serious potential problem from direct application or erosion of treated soil, it is not likely to occur by diffusion or leaching. Thus, under field conditions the pyrethroids are rapidly absorbed into stream banks, pond sediments and organic matter to decrease their concentration in water. Soils high in microbial activity extensively metabolize pyrethroids within a few weeks by ester and diphenyl ether cleavage, hydration of the cyano moiety and other reactions ultimately leading to carbon dioxide. Pyrethroids do not seem to affect soil microorganisms adversely.

## Pyrethroid Toxicology

Pyrethroids are generally broad-spectrum insecticides. They control a large variety of insects, although the effective dose may vary greatly between the most and least sensitive species. In stored products protection a synergist is commonly added. In food and fiber production the pyrethroid is often used in the same fields as one or more other insecticides, miticides or ovicides. To protect susceptible honeybees, pyrethroids must be applied at times and in amounts to minimize pollinator and hive damage. Predator and parasite kills may lead to resurgences of pests no longer controlled by their natural enemies. Pyrethroids are not effective in controlling soil insects possibly due to soil binding and metabolism of the compounds. Crustaceans and beneficial aquatic insects are potential non-target victims of pyrethroid uses to control mosquito larvae and other dipterous larvae of medical importance.

Resistance has previously curtailed the use of almost every type of insecticide and poses a serious threat to the future of pyrethroids. Cross resistance does not appear to be a problem between pyrethroids and organophosphates or methylcarbamates. However, previous selection of houseflies with DDT for a recessive factor conferring knockdown resistance (*kdr*) carries with it a cross-resistance to pyrethroids. Houseflies on Danish farms developed pyrethroid resistance when pyrethrins and pyrethroids replaced chlorinated hydrocarbon and organophosphorus insecticides. One pyrethroid-resistant field strain was subsequently selected in the laboratory with bioresmethrin to a resistance factor of 1400-fold. Despite no previous exposure, this strain was more than 60,000-fold resistant to decamethrin. Thus, the most potent of all insecticides on a normal strain has almost no effect on this resistant strain. This is the most dramatic example available of pyrethroid resistance. Some of the housefly resistance mecha-

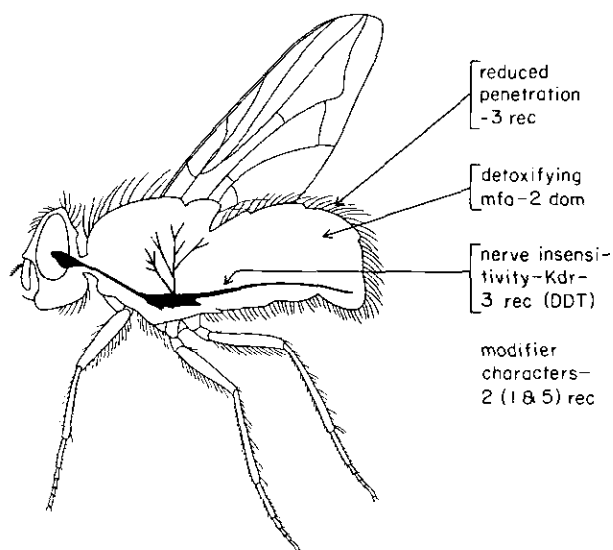


FIGURE 4. Housefly resistance mechanisms of three distinct types are recognized from studies involving crosses of resistant unmarked fly strains with susceptible flies carrying markers on appropriate chromosomes. Bioassays and the visible markers are used to associate resistance factors with individual chromosomes. Recessive factors on chromosome 3 confer reduced penetration to many insecticides and knockdown resistance (kdr) to pyrethroids and DDT. The detoxifying mixed-function oxidases or incompletely dominant mfo of chromosome 2 are also associated with resistance to many other types of insecticides. Pyrethroid resistance is greatly enhanced by recessive modifier characters conferred by chromosome 2 and to a lesser degree by 1 and 5.

nisms are considered in Figure 4. Low levels of field resistance are also known in local areas with mosquitoes, Australian cattle ticks, some lepidopterous pests on cotton, and a few other pest species. It may be possible to forestall pyrethroid resistance by restricting their use to minimal doses and numbers of applications and by more fully utilizing integrated pest management systems. Routine application of pyrethroids at high doses, as done in the past with other insecticides, practically guarantees that resistance will reach levels where economic use of pyrethroids is no longer possible.

Fish are sensitive to pyrethroids at part per billion levels, so great care must be taken in treating agricultural crops and forests to avoid contaminating lakes and streams and commercial fish-producing areas. The high sensitivity of fish is possibly related to the ability of their gills to concentrate pyrethroids which then disrupt nerve-controlled respiratory mechanisms. Birds seem to be unusually tolerant and have survived high oral doses of several synthetic pyrethroids. Although the mechanism of avian insusceptibility is not known, chickens rapidly metabolize and excrete orally-administered permethrin.

Mammals appear to be relatively tolerant to pyrethroids, so in this respect these synthetic insecticides are welcome alternatives to some of the other second generation insect control agents. Selectivity is often expressed as a ratio for the amount of insecticide per gram of body weight to kill 50% of a group of orally treated rats divided by the comparable value for various topically-treated insects. This selectivity ratio averages about 4000 for many pyrethroids but is less than 100 for various chlorinated hydrocarbon, organophosphorus and methylcarbamate insecticides. A few compounds (pyrethrin II and kade-thrin) administered intravenously are toxic to rats at levels equivalent to their potency on susceptible insects. The relatively low toxicity to mammals following oral, dermal or inhalation exposure therefore results largely from factors preventing entry into the nervous system, such as metabolic detoxification. Excessive exposure to certain pyrethroids may result in skin irritation in sensitive individuals.

Lifetime feeding studies with mammals are at least as important as acute toxicity observations in evaluating the safety of pyrethroids. Some of these studies have been completed and others are still in progress on each pyrethroid proposed or in use for crop protection. Tolerance values or the maximum allowable residues in food and feed will be based on the dietary levels found to have no effect, the amount of residues normally present when the compounds are used in accordance with good agricultural practice, and a safety factor to correct for possible differences in sensitivity of humans and the laboratory mammals.

Pyrethroids are nerve poisons, but their mode of action at the molecular level remains obscure. They cause repetitive discharges in arthropod nerve due to interference with axonal sodium and potassium channels. The repetitive firing is attributed primarily to prolongation of the turning off of the increase in sodium conductance and secondarily to the suppression of the increase in potassium current. It is not clear which symptoms in insects or other animals are due to effects on the central or the peripheral nervous system or both. Pyrethroids are more toxic to insects at low than high temperatures, as is also the case with DDT. Many types of isolated nerve preparations from insects and other arthropods are highly sensitive to pyrethroids, but none of the investigated systems so far is an adequate model of the effects on organisms. In pyrethroid poisoning of various insect species, fish and mammals, there is probably no need to invoke a fundamentally different primary mode of action. Poisoning of rats and mice is related to but not necessarily dependent on the levels of some pyrethroids in the brain.

Structure-activity studies, particularly with sy-

nergist-treated insects, help to define the configuration of the physiologically-important nerve receptor. The flexible pyrethroid molecule with its high stereospecificity must adopt a conformation in which all structural features essential for potency are appropriately oriented with respect to each other and to a complementary chiral receptor. The most sensitive and relevant receptor must be isolated and defined pharmacologically as a prelude to understanding pyrethroid mode of action at the molecular level.

## Summary

Pyrethroids are the most potent lipophilic insecticides. They are also the most expensive per unit weight. The cost is increased by producing the single, most potent optical isomer using advanced techniques of synthesis and resolution. Less active isomers and byproducts can often be converted to a useful isomer or intermediate in a recycling process. The pyrethroids may potentially provide an excellent cost/benefit ratio in agricultural pest insect control, in part because they persist sufficiently to require relatively few applications. This economic situation would change drastically if resistance phenomena required increases in pyrethroid doses of two- to ten-times. The potency of pyrethroids also means a smaller environmental burden of the parent compound and its photoproducts and metabolites, with their possible undesired effects. Thus with decamethrin, a single compound of high chemical and isomeric purity, application at 10 g/hectare for pest control gives an initial deposit of 1 mg/m<sup>2</sup>. Most other types of pesticides, because of lower potency, require deposits of 50 to 200 times as high. Insecticides as active as some pyrethroids are known among the chlorinated hydrocarbons, organophosphates, and methylcarbamates, but with the latter compounds this remarkably high insecticidal activity is usually accompanied by unacceptable mammalian toxicity.

Pyrethroids do not provide new or unique approaches to insect control. They are strictly alternatives to or replacements for current compounds. Synthetic analogs have been used for 30 years as pyrethrum substitutes without diminishing the demand for the natural product. However, the pyrethrum industry in various countries must become better organized and more efficient in production and distribution continually to compete with the ever-increasing number of synthetic alternatives, although these take time to develop such a proven safety record. The more stable pyrethroids are being increasingly used to replace DDT and other chlorinated hydrocarbons. Both classes include long residual contact insecticides effective on many of the

same pest complexes. The current pyrethroids are not phytotoxic, so their use results in higher yields than are obtained with other equally-effective but phytotoxic insecticides. Pyrethroids are not suitable replacements for organophosphates and methylcarbamates as plant systemics because of low water solubility or as soil insecticides due to soil binding, metabolism, and low vapor pressure. The future of pyrethroids as contact insecticides and stomach poisons will depend on what further restrictions are placed on the present insecticides, the comparative seasonal cost for pest control with pyrethroids and with other compounds, and the final risk assessments based on the toxicological findings.

Advances in the past seven years establish pyrethroid insecticides as one of the major classes of pesticide chemicals. They also indicate that theoretically additional structural modifications can increase their potency more than 10-fold further and/or reduce the seasonal pest control cost by a similar factor. Alternative pyrethroids are available for introduction if there are toxicological problems with the current compounds. Structure optimization is now focusing on new properties in addition to potency, low mammalian toxicity, competitive price and suitable persistence. These goals are: diminished toxicity to fish or to honeybees, predators and parasites; broader spectrum of activity including mites and aphids to reduce the need for pesticide mixtures; effective on strains resistant or cross resistant to current pyrethroids; potent as ovicides for insect and mite eggs; effective as nematocides and anthelmintics. How many new pyrethroids can be justified and might it be practical to develop? At current or anticipated costs probably no more than four to eight additional pyrethroids could be developed for agricultural use over the next ten years on a worldwide basis. It is therefore important to use the current pyrethroids at doses and in a manner to minimize the selection of resistant strains and thereby conserve this valuable resource for control of pest insects in the years and hopefully decades ahead.

The author is indebted to the Rockefeller Foundation for appointment as a Scholar-in-Residence at the Bellagio Study and Conference Center at Lake Como, Italy where this article was prepared. It is similar to a lecture presented on receiving the 1978 Kenneth A. Spencer Award of the American Chemical Society. Helpful comments were provided by Michael Elliott and co-workers at Rothamsted Experimental Station, Tom Bogaard of McLaughlin Gormley King Co., Derek Gammon of the Pesticide Chemistry and Toxicology Laboratory, and Ruth Patrick of the Academy of Natural Sciences in Philadelphia. Portions of this review are based on studies supported by NIEHS Program Project 5 P01 ES00049 and EPA Grant R805999.

#### REFERENCES

1. Casida, J. E., Ed. *Pyrethrum. The Natural Insecticide*. Academic Press, New York, 1973.
2. Elliott, M., Ed. *Synthetic Pyrethroids*. ACS Symposium Series, No. 42, American Chemical Society, Washington, D.C., 1977.
3. Elliott, M., and Janes, N. F. Synthetic pyrethroids — a new class of insecticides. *Chem. Soc. Revs. (London)* 7: 473 (1978).
4. Elliott, M., Janes, N. F., and Potter, C. The future of pyrethroids in insect control. *Ann. Rev. Entomol.* 23: 443 (1978).
5. International Trade Center. *Pyrethrum: A Natural Insecticide With Growth Potential*. UNCTAD/GATT, Geneva, Switzerland, 1976.
6. Nelson, R. H., Ed. *Pyrethrum Flowers*, 3rd ed., 1945-1972. McLaughlin Gormley King Co., Minneapolis, 1975.