Toxicology and Environmental Fate of Synthetic Pyrethroids

By Doria Mueller-Beilschmidt

Synthetic pyrethroids are a diverse class of more than 1000 powerful, broad-spectrum insecticides used to control insect pests in agriculture, households, and stored products. Although they are based on the chemical structure and biological activity of pyrethrum, an extract from plants in the genus *Chrysanthemum*, the development of synthetic pyrethroids has involved extensive chemical modifications to make compounds that are more toxic and less rapidly degraded by light.

"The Chemistry, Development, and Economics of Synthetic Pyrethroids" (JPR 10(2):41-44) summarizes their chemical structures, history of development, and usage in the United States and internationally; this article describes the pyrethroids' toxicity to humans and other animals as well as their residues in food and their persistence in soils and water.

What Determines the Toxicity of a Synthetic Pyrethroid?

Pyrethroid toxicity is highly dependent on stereochemistry, the three dimensional configuration of the molecule. Each isomer (molecules consisting of the same atoms, but with different stereochemistry) has its own toxicity. Some pyrethroids have as many as eight different isomers and there are several different types. For example, many pyrethroids have pairs of isomers with different geometries, referred to as the *cis* and the *trans* isomers. Figure 1 illustrates the *cis* and *trans* isomers of permethrin. The *cis* isomer is generally more toxic than the *trans* isomer.

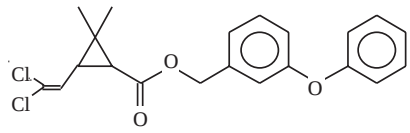
Acute toxicity of a mixture of two isomers depends on the ratio of the amounts of the two isomers in the formulation. For example, the female rat acute oral LD_{50}* of permethrin increases from 224 milligrams of the pyrethroid per kilogram of body weight (mg/kg) to 6000 mg/kg as the proportion of the *trans* isomer increases from 20 percent to 80 percent (see Figure 2).

Most commercial formulations have a fixed isomeric ratio. Formulations made of a single isomer (deltamethrin, for example) are likely to be much more toxic than those with four to eight isomers.[2]

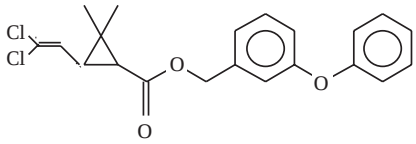
Route of exposure is critical in assessing the acute toxic potential of a pyrethroid. Based on laboratory tests with experimental animals, introduction of the compound into the brain is most toxic, followed by introduction into the blood vessels, introduction into the gut (intraperitoneal administration), oral exposure, inhalation, and dermal (skin) exposure.[2] Introduction into the brain or blood vessels is more toxic than other routes of exposure as a result of the metabolic processes in mammals which rapidly detoxify the poisons and the slow rate of absorption by

* LD_{50} is the amount of a chemical that will kill 50 percent of a population of test animals.

Figure 1

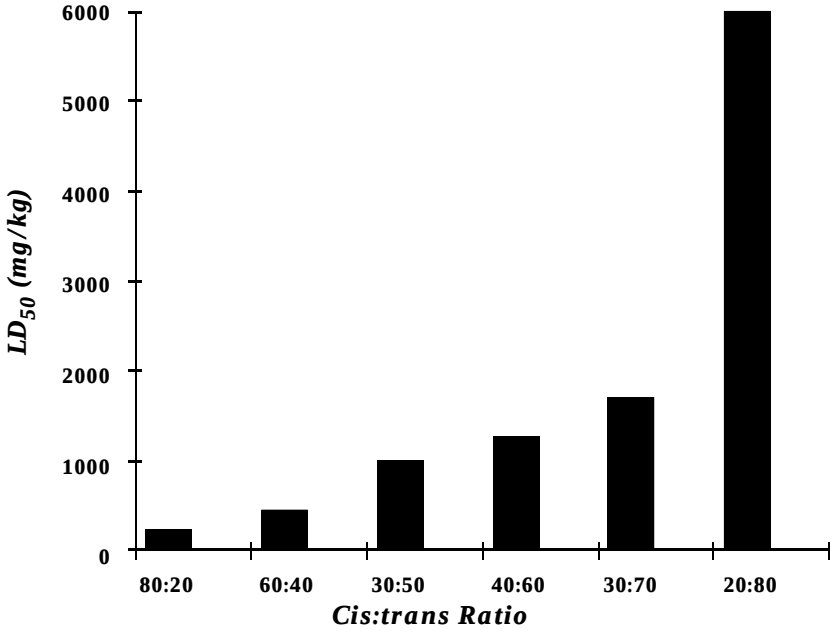


cis-permethrin



trans-permithrin

Figure 2
Acute Toxicity of Mixtures of Two Isomers of Permethrin



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the gut, skin, and lung tissue.[3]

Metabolites can also have an effect on the toxicity of a pyrethroid. The mouse intraperitoneal LD_{50} of trans-resmethrin is greater than 1500 mg/kg of body weight; it is over ten times less acutely toxic than three of its metabolites with LD_{50}s that range from 46 to 98 mg/kg.[4] The common pyrethroid metabolite 3-phenoxybenzoic acid may be significantly more toxic than the parent pyrethroid.[5] Deltamethrin, which is a primary metabolite of tralomethrin (Scout), has a higher acute toxicity than its parent compound.

Various other factors influence the toxicity of pyrethroids. Preexisting health conditions, such as respiratory or skin problems, can exacerbate the toxic effect of some pyrethroids in humans.[6-8] Also, more highly halogenated pyrethroids (those containing chlorine, bromine, or flourine), such as flucythrinate and tefluthrin, tend to be more toxic to mammals than those that are less halogenated, such as permethrin and cyfluthrin. The acute toxicities of some pyrethroids differ for male and female rats and mice.[2] Diet can also have an effect on the toxicity of pyrethroids.[9] DDT and pyrethroids are some of the few insecticides with toxicities that increase at lower temperatures.[3,10]

"Inert" Ingredients and Synergists

Since the technical (chemically pure) grade of a pyrethroid is usually formulated (mixed with carriers, solvents, etc.) for use in commercial pest control, the toxicity of these other ingredients must be taken into consideration when assessing the toxicity of a formulated product. For example, fenvalerate is much less toxic to mice than the formulated product, Pydrin.[11] A ten-fold difference in toxicity between formulations with the same active ingredient, but with different carriers, can be seen in some cases. Pyrethroid products formulated as emulsifiable concentrates (oil based formulations) usually have higher acute oral LD_{50}s (are less toxic) in rats than wettable powder (aqueous) formulations.[3]

"Inert" (secret) ingredients and contaminants can also affect the toxicity of a pyrethroid formulation, especially since the formulated product often contains more "inert" ingredients than active ingredients. Several "inerts" in pyrethroid formulations used in the U.S. are known or suspected carcinogens (such as silica, trimethylbenzenes, and ethyl benzene), or are chemicals which depress the central nervous system (such as xylenes). There are also hazardous contaminants, such as ethylene oxide, benzene, and arsenic, in several pyrethroid formulations.[12-15]

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Simultaneous contact with substances that inhibit detoxification processes, called synergists, can increase the acute toxic effects of a pyrethroid. High levels of some synergists (organophosphorus and carbamate compounds) can block esterases, enzymes that degrade pyrethroids by cleaving the molecule at the double bond between a carbon and an oxygen atom. Other synergists (piperonyl butoxide and sulfoxide) block the mixed function oxidases, enzymes which oxidize and detoxify a wide variety of compounds.[10,16] Simultaneous exposure to pyrethroids and organophosphates has also been shown to increase the inhibition by the organophosphates of cholinesterase, an enzyme in the nervous system.[17]

Acute Toxicity to Mammals

Acute oral toxicity to mammals varies widely among the pyrethroids. In general, they are less acutely toxic than the organophosphate, carbamate, and organochlorine pesticides. Exceptions include the pyrethroids showing the highest acute oral toxicities: esfenvalerate (Asana), deltamethrin, bifenthrin, tefluthrin, flucythrinate, cyhalothrin (Karate), and fenpropathrin. All of these pesticides belong to the third generation of pyrethroids (JPR 10(2):43), those containing a cyano group (a carbon atom and a nitrogen atom bonded together).

Acute and subacute studies have shown that the main effects of pyrethroids are neurotoxicity at high doses and liver hypertrophy (enlargement of the liver).[3,19] If death does not occur, these changes have been shown to be reversible. In fact, the capacity for recovery from the toxic effects seems to be a unique characteristic of pyrethroid poisoning in mammals.[3]

Many of the pyrethroids can be mildly to severely irritating to the skin and eyes.[3,20-22] Some pyrethroids also cause a sensitization of facial skin which has been observed to be reversible.[3] The dermal (skin) toxicity of some pyrethroid formulations is greater than that of the technical grade.[23] Adverse skin effects were not measured in tests on nonhuman animals.[3,24]

Chronic and Subchronic Toxicity

The most notable non-cancerous subchronic and chronic effects of pyrethroid insecticides on mammals are signs of acute toxicity, which are usually temporary and diminish considerably if the chronic exposure continues.

Other chronic effects are reduction in the growth rate of test animals, liver enlargement, and an in-

crease in the activity of some enzymes in the liver; these changes are not fully reversible.[5] Chronic exposure studies have also measured effects on the adrenals, spleen, pituitary and testes.[3]

Depending on the pyrethroid and the test organisms, other possible effects include suppression of the immune system[9,25] and damage to the nervous system.[2,5,19,26] Effects on reproduction have been observed with several pyrethroids and pyrethrins.[3,5,23,25,27]

Mutagenicity and Carcinogenicity

In a number of separate mutagenicity studies (studies of the ability to cause genetic damage), cypermethrin, allethrin, cismethrin, permethrin and fenpropathrin have shown some mutagenic effects.[3,25,28] Only in the case of permethrin was the response (changes in mice bone marrow) found to be significant. Despite these positive results, the mutagenic potential of pyrethroids is considered to be very low if not nonexistent.

Mutagenicity studies have also been done for deltamethrin, phenothrin, resmethrin, tetramethrin, and fenvalerate; no positive results were found.[3] One degradation product, an epoxide produced when allethrin and terallethrin are exposed to light, is mutagenic.[5]

Carcinogenicity studies of permethrin, resmethrin, fenvalerate and deltamethrin have shown increases in various kinds of cancers.[3,27,29-32] Only permethrin has been determined to be a potential or weak carcinogen by the U.S. Environmental Protection Agency.[29] Carcinogenicity studies have also been done on phenothrin, allethrin, and cypermethrin; none were carcinogenic.[3]

Human Exposure

A study of synthetic pyrethroids' effects on persons engaged in packaging fenvalerate and deltamethrin in China documented burning sensations, tightness or numbness on the face, sniffles, and sneezes. Other symptoms included abnormal facial sensations, dizziness, fatigue, and skin rashes.[26] In the five years (1983-1988) after pyrethroids began to be used in China, 573 cases (299 occupational and 344 accidental) of acute pyrethroid poisoning were reported. Of those, five resulted in death.[33] At the time the study was published, only one other case of fatal pyrethroid (cypermethrin) poisoning had ever been reported in the literature.[3] The occupational poisonings in China were attributed to inappropriate handling.[33]

Effects on Other Non-target Organisms: Birds

Pyrethroid's acute toxicity to birds is moderate, with most LD_{50} values being greater than 1000 mg/kg. Yet birds can be indirectly affected by pyrethroids if the pesticides decimate or substantially change their food supply. Waterfowl, which feed almost exclusively on aquatic invertebrates, and small insectivorous or young birds are especially vulnerable.[5,34] Both pyrethrins and deltamethrin have been shown to be teratogenic (causing birth defects) in certain birds. Sublethal studies have indicated behavioral effects on quail.[35]

Effects on Other Non-target Organisms: Aquatic Organisms

Pyrethroids have a devastating effect on aquatic invertebrates with most LC_{50}* values less than 1.0 parts per billion (ppb). These LC_{50}s are similar to those for mosquito, blackfly, and tsetse fly larvae, for which pyrethroids are often used in vector control.[35]

The most sensitive organisms are surface-dwelling insects, mayfly nymphs and some of the larger crustaceans; zooplankton and benthic (bottom-dwelling) organisms are also significantly affected by pyrethroids. Even at low (non-lethal) concentrations, there are significant behavioral changes in aquatic invertebrates, e.g., in their ability to respond to tactile stimuli, which may affect their survival. Lobster and shrimp are susceptible to all pyrethroids.[5,35]

Pyrethroids are highly toxic to most fish; about 40 percent of the LC_{50} values for fish are less than 1.0 ppb. Deltamethrin is one of the most toxic; allethrin is one of the least toxic; and cypermethrin, permethrin and fenvalerate are intermediately toxic. Emulsifiable concentrate formulations of pyrethroids are usually two to nine times more toxic than the technical grade, most likely due to synergistic interactions.[35] Resmethrin synergized with piperonyl butoxide is much more toxic to the white sucker fish than is the technical grade product.[34] Pyrethroids are more toxic to fish at lower temperatures and appear to be more toxic to smaller fish than larger fish.[37]

Field studies indicate that pyrethroids are more toxic to fish in laboratory studies than in natural waters because pyrethroids adhere to sus-

* LC_{50} is the concentration of a chemical in water that will kill 50 percent of a population of aquatic test animals.

Table 1
Bioaccumulation Factors

Pyrethroid	Organism	Bioaccumulation Factor[a]	Reference
permethrin	fish[b]	183	5
	mollusc[b]	6302	5
	Daphnia[b]	334	5
	fathead minnow	100-3300	37
cypermethrin	fish[b]	125	5
	mollusc[b]	612	5
	Daphnia[b]	1234	5
fenvalerate	fish[b]	1148	5
	mollusc[b]	3338	5
	Daphnia[b]	1160	5
	snail	116-356	35
	salmon	40-200	35
	carp	24-122	7
	minnow	50	35
	crustacean	68-683	35
flucythrinate	fathead minnow	3000-5000	35

[a] The ratio of the pyrethroid concentration in the animal to the concentration in the water in which the animal lives.
[b] Model predictions.

pended organic matter in the water and bottom sediment.[5,36,37] Nevertheless, sublethal effects of pyrethroids on fish include damage to gills and behavioral changes. Because they are highly lipophilic (attracted to the non-water soluble components of cells), pyrethroids are likely to be strongly absorbed by the gills, even from water containing low levels of pyrethroids (see Table 1).[35]

Pyrethroids can indirectly affect fish due to diminished and contaminated food supplies.[5,34,36] Another indirect effect of pyrethroid contamination of still waters is massive increases of a green filamentous alga, which can lead to a progressive reduction of dissolved oxygen.[5,38]

Though less tolerant than most mammals, amphibians and molluscs are much more tolerant of pyrethroids than fish and crustacea.[5]

Effects on other Non-target Organisms: Terrestrial Invertebrates

Pyrethroids are toxic to insects whether the insects are beneficials or pests; they initially cause knockdown (the inability of the insect to maintain its normal position) followed by recovery or death. Pyrethroids can also repell the insect or inhibit feeding behavior.[37] Field studies have shown that pyrethroids affect flying and vegetation- inhabiting arthropods (predatory beetles, for example) much more than soil-dwelling arthropods.[5,39] Soil applications of pyrethroids have been shown to decrease the number of predatory mites and at high rates pyrethroids cause significant reductions in earthworm populations.[37,40]

Predator-prey relationships can also be upset by pyrethroids. For example, a black fly predator, the caddisfly, is susceptible to permethrin at rates lower than those necessary to control blackfly. The same is true for a group of spider mite predators, the phytoseiid mites. These mites have an LD_{50} 15 times lower than the spider mite pest.[35] Chronic exposure from residual deposits on vegetation could have an effect on beneficial arthropod behavior and physiology.[2,41]

Pyrethroids are highly toxic to bees, with the exception of fluvalinate, which is used to control mites in bee hives.[37,42] The LD_{50} for the honey bee can be as low as 0.03 micrograms per bee. Field studies indicate that under natural conditions, the hazard to bees is reduced because the worker bees are repelled by pyrethroids; this reduces their contact with plant surfaces recently sprayed with pyrethroids and decreases their chances of receiving a lethal dose. Pyrethroid repellency can also can reduce foraging activity of bees.[35]

Table 2 summarizes the acute toxicity of 21 pyrethroids to some non-target organisms.

Table 2
Acute Effects of Pyrethroids and Pyrethroid Formulations on Non-target Organisms[3,23,37,57-60]

Pyrethroid	birds [a]	fish	bees
pyrethrins	—	highly toxic	—
allethrin	2030 [b]	toxic	—
s-bioallethrin (Esbiol)	680	highly toxic	—
resmethrin	—	toxic	highly toxic
bioresmethrin	—	highly toxic	highly toxic
tetramethrin	>1000	toxic	toxic
permethrin	>13500 [b]	highly toxic	highly toxic
fenvalerate	9932	highly toxic	—
d-phenothrin	>2500 [b]	toxic	toxic
cypermethrin	—	extremely toxic	toxic
esfenvalerate	—	highly toxic	—
bifenthrin	>2150	toxic	—
fenpropathrin	1089	toxic	—
tefluthrin	4190	highly toxic	—
cyfluthrin	4450	toxic	toxic
fluvalinate	>5620	toxic	non-toxic
tralomethrin	7716	extremely toxic	highly toxic
deltamethrin	>4640	toxic	highly toxic
cyhalothrin	>5000	highly toxic	—
kadethrin	—	toxic	toxic
alphacypermethrin	—	toxic	toxic
lambda-cyhalothrin	>3950	toxic	toxic

[a] mallard oral LD_{50} (mg pyrethroid/kg body weight), unless otherwise indicated
[b] quail oral LD_{50} (mg pyrethroid/kg body weight)

Residues in Food and Water

California and U.S. pesticide monitoring programs between 1982 and 1985 found permethrin residues on cabbage, lettuce, and tomatoes.[43] U.S. Food and Drug Administration (FDA) monitoring between 1985 and 1990 consistently found permethrin, fenvalerate, and cypermethrin residues in over 45 different vegetable, fruit, and meat products. Up to 6 parts per million (ppm) permethrin were regularly found on leafy vegetables such as spinach, lettuce, kale, collards, and turnip greens.[44] The maximum residue level set by the FDA for permethrin on leafy vegetable is 20 ppm.[45] Tolerance levels (legal limits) have not yet been established for pyrethroid residues on many of these products.

Recently, FDA has reported levels of fluvalinate in honey 22 times higher than the established tolerances.[46] One study found that resi-

Pyrethroid Mode of Action

Like DDT and many other insecticides, naturally occurring pyrethrins and the synthetic pyrethroids are nerve poisons. Pyrethroids' principal mechanism of action is believed to be disruption of the permeability of nerve membranes to sodium atoms. The site of action is not known, but pyrethroids and DDT probably act on both the central (the brain and spinal chord) and the peripheral nervous system (nerves in other parts of the body). Other major groups of insecticides (carbamates and organophosphates, for example) are nerve poisons but do not act on the peripheral nervous system.[3,18]

dues (10-20 percent of the amount initially applied) of cyfluthrin, deltamethrin, cypermethrin, fenvalerate, and permethrin remain effective for a long period of time in grains (over 10 months), with minimal losses even after milling and baking.[47]

There is no evidence of pyrethroid residues in groundwater in the U.S. or in Europe as a result of agricultural use.

Fate in Plants, Soil and Water

In the environment, pyrethroids are usually degraded by one or more biotic and abiotic processes: metabolic degradation by plants, animals, and microorganisms and degradation by light (photolysis). There are three main routes of degradation by light in pyrethroids: ester cleavage (splitting the molecule where a carbon atom and an oxygen atom are connected with a double bond), reductive dehalogenation (removal of chlorine, flourine, or bromine atoms), and isomerization (conversion from one isomer to another). A main product of pyrethroid photolysis is 3-phenoxybenzoic acid.[5]

Degradation of pyrethroids in the soil is mostly by chemical and microbial action. The rate of degradation depends on the pyrethroid, soil type, climate, the species of microbes present, and the size of their populations.

Fenvalerate and deltamethrin are the most persistent pyrethroids in commercial use, especially in soil containing a high proportion of organic matter. Both can accumulate to levels ten times over the initial concentration if they are repeatedly applied in a single season at rates higher than the rate at which they are degraded.[5]

Since pyrethroids are highly lipophilic, they adhere strongly to any organic matter in water, are easily absorbed into the waxy layer of plants, and are strongly adsorbed by soil particles.[5,48] Once adsorbed, pyrethroids are relatively immobile; leaching through the soil into groundwater is improbable and translocation through a plant is uncommon.[5] Except for tefluthrin, most pyrethroids will stay in the top one to four inches of soil after field applications.[5,49,50] However, several principal pyrethroid degradation products (3-phenoxybenzoic acid and dichlorovinyl acid, for example) leach readily.[5,25]

Pyrethroids are also removed from the site of application by drift, soil erosion, and volatilization (evaporation). Spray drift from heavy agricultural pyrethroid applications can cause contamination in neighboring surface water. Detectable residues have been reported up to several months after application. Erosion of contaminated soil could be a key consideration for protecting aquatic environments; one study found that pyrethroid runoff from a cotton field after heavy rains affected invertebrates in an adjacent pond.[5]

The persistence of residues in soil, water, and plant tissues varies considerably. The half-life (time required for 50 percent of a compound to degrade) of pyrethroids in soils ranges from 1 day to 16 weeks. Pyrethroids that are not light-stable usually degrade much more quickly than those that are light-stable, and degradation is usually much faster in aerobic (oxygen-containing) soils than anaerobic (not oxygen-containing) soils.[51]

Missing Data

There are significant data gaps for the older, less persistent pyrethroids such as allethrin, resmethrin and phenothrin, as well as for pyrethrins. The gaps include data on many aspects of acute and chronic toxicity.[3,52-55] These are some of the most widely used insecticides in homes and gardens.

The data profiles on the newer light-stable pyrethroids are much more complete. Yet, the one area where there is still substantial lack of information on the light-stable pyrethroids (permethrin, fenvalerate, flucythrinate, cypermethrin and tralomethrin, for example) is on their behavior in the environment.[56]

There are also inadequate data on inhalation toxicology of many pyrethroids, even though inhalation is the most common route of human exposure.

In general, very little information exists on the chronic toxicity, especially carcinogenicity, of pyrethroid degradation products and metabolites.[5]

The available information on pyrethroids indicates that they may pose an serious hazard to non-target organisms, especially aquatic and terrestrial invertebrates, and possibly fish. Therefore, the lack of data on the impact of pyrethroids in the environment and on wildlife is a critical gap in our knowledge of pyrethroids. ■

Human Exposure to Naturally Occurring Pyrethrums

The most common manifestation of pyrethrum poisoning is a rash on skin exposed to the chemicals, which may be made worse by exposure to the sun and temperatures high enough to cause sweating.[3,24,61] Allergic responses and asthma following exposure to naturally occurring pyrethrins have also been reported.[5,62] Only two serious poisonings caused by pyrethrum, one fatal, have been recorded in the literature and both were in the nineteenth century.[3,24]

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