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Fenvalerate Hazards to Fish, Wildlife, and Invertebrates: A Synoptic Review

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Abstract

Synthetic pyrethroids are the newest major class of broad-spectrum organic insecticides used in agricultural, domestic, and veterinary applications, and now account for more than 30% of global insecticide use. Fenvalerate [(RS) α-cyano-3-phenoxybenzyl (RS) 2-(4-chlorophenyl)-3-methylbutyrate] is one of the newer synthetic pyrethroid insecticides and the one most widely used. Technical fenvalerate is a mixture of four optical isomers, each occurring in equal amounts, but with different efficacies against insect pests. Insecticidal properties are largely associated with the 2S, αS isomer and, to a minor extent, with the 2S, αR isomer. Isomers with a 2R configuration have negligible biocidal properties; however, tumorlike growths in rodent liver are associated with the comparatively innocuous 2R, αS isomer. Pyrethroid insecticides are potent neurotoxicants that interfere with nerve membrane function by interaction with the sodium channel. Fenvalerate is among the most effective pyrethroid neurotoxicants tested, and the 2S, αS isomer is as much as 15 times more potent than other fenvalerate isomers.

Fenvalerate persists for < 10 weeks in the environment and does not accumulate readily in the biosphere. Time for 50% loss (Tb ½) in fenvalerate-exposed amphibians, birds, and mammals is 6-14 h; for reptiles, terrestrial insects, aquatic snails, and fish it is usually > 14 h-<2 days, and for crop plants it is 2-28 days. In nonbiological compartments, Tb ½ is as long as 6 days in fresh water, 34 days in seawater, 6 weeks in estuarine sediments, and 9 weeks in soils.

At recommended application rates to control pestiferous crop insects, fenvalerate and other synthetic pyrethroids are relatively harmless to birds, mammals, and terrestrial plants; however, certain nontarget species, including bees, crustaceans, and fish, are at considerable risk, especially at low temperatures. Target insect species are usually killed at fenvalerate concentrations of 0.015 µg/insect, 0.11 kg/ha by way of aerial application, 5.4 mg/kg in soil, or 50 mg/kg in diet. Fenvalerate is especially toxic to aquatic organisms (e.g., crustaceans died at 0.003-0.03 µg/L and fish and amphibians at 0.09-1.1 µg/L), and its use in or near aquatic environments now seems contraindicated. Birds and mammals are significantly more resistant than fish and invertebrates. Adverse effects on birds occur at acute oral doses >500 mg/kg body weight (BW), and 750 mg/kg ration; <50 mg fenvalerate per kilogram of feed produced no appreciable residues in eggs and meat of exposed birds. Among sensitive mammals, adverse effects on survival occur at acute oral doses of 50—450 mg/kg BW, dietary loadings of 50-1,000 mg/kg feed, and dermal applications of 1,800 mg/kg BW.

Criteria have not yet been formulated by regulatory agencies for protection of sensitive fish and wildlife resources against fenvalerate. Current guidelines for protection of poultry, livestock, and human health include <50 mg/kg in poultry diets, <5 mg/kg in livestock diets, <3 mg/kg in human diets, and <0. 125 mg/kg BW daily in humans.

Key words: Fenvalerate, insecticide, pyrethroid, crops, aquatic life, birds, wildlife, livestock, invertebrates, ecotoxicology, criteria.

Synthetic pyrethroids, including fenvalerate [(RS) α-cyano-3-phenoxybenzyl (RS) 2-(4-chlorophenyl)-3methylbutyrate]αS isomer (A. Stavola, U.S. Environmental Protectin Agency, personal communication, 28 January 1991.[1], are now broadly recognized as a major class of synthetic organic insecticides (Gray and Soderlund 1985). Introduced commercially less than 20 years ago, synthetic pyrethroids now account for more than 30% of insecticide use worldwide (Flannigan et al. 1985; Gilbert et al. 1989) in household, agricultural, and veterinary applications (Haya 1989; Williamson et al. 1989). More than 1,000 pyrethroids have been synthesized since 1973 (Flannigan et al. 1985); they include compounds containing nitrogen, sulphur, fluorine, chlorine, and bromine, in addition to carbon, hydrogen, and oxygen (Glickman and Casida 1982). The most potent synthetic pyrethroid insecticides are the cyanophenoxybenzyl pyrethroids (Casida and Lawrence 1985); fenvalerate is the most widely used compound in this group (Clark et al. 1985).

Pyrethroid insecticides are synthetic analogs of natural pyrethrins. Natural pyrethrins were widely used in Europe during the 19th century, when few effective insecticides were available (Elliott and Janes 1978). Natural pyrethrins, which contain six insecticidally active components extracted from the dried flower heads of the pyrethrum flower (*Chrysanthemum cinariaefolium*), have high insecticidal properties and low mammalian toxicity; however, they are expensive to produce and have low photostability and high biodegradability (Wouters and Bercken 1978; Gray and Soderlund 1985; Haya 1989; Williamson et al. 1989). Modern synthetic pyrethroids have been designed to provide enhanced residual activity through greater photostability and greater resistance to chemical and biological degradation, greater insecticidal activity, diminished mammalian toxicity, and greater cost effectiveness (Elliott and Janes 1978; Vijverberg and Bercken 1982; Gray and Soderlund 1985; Smith and Stratton 1986; Coats et al. 1989; Haya 1989). The first synthetic pyrethroids, allethrin and cyclethrin, were produced around 1950 but lacked adequate photostability and were not as effective insecticidally as the natural pyrethrins. Tetramethrin was introduced in 1964, but it had inferior insecticidal activity. The first synthetic pyrethroids with greater insecticidal activity than natural pyrethrins were resmethrin and cismethrin, produced in 1968. Photostable pyrethroids were produced in the mid 1970's and included deltamethrin, cypremethrin, fenpropathrion, and fenvalerate (Smith and Stratton 1986).

Pyrethroid insecticides are generally recognized as potent neurotoxicants that interfere with nerve membrane function by interaction with the sodium channel (Elliott and Janes 1978; Vijverberg et al. 1982; Gilbert et al. 1989; Haya 1989). Synthetic pyrethroids are more toxic against insect pests, up to 10 times more potent, in some instances, than other insecticides now in general use (Bradbury and Coats 1989a). However, the stereochemical structure of pyrethroid insecticides greatly influences their toxicity to insects and mammals, and this phenomenon is especially pronounced for fenvalerate (Bradbury et al. 1987b).

As broad-spectrum insecticides, the synthetic pyrethroids are necessarily toxic to a wide range of arthropods. Most insect orders are extremely susceptible, including many types of beneficial predator and parasite species (Bradbury and Coats 1989a). Synthetic pyrethroids are also toxic to fish and nontarget aquatic insects and crustaceans (Muir et al. 1985). Fenvalerate, for example, enters freshwater aquatic environments in runoff from food crop use, in drift from forest-spray procedures, and by direct spraying of water bodies (Haya 1989). Estuarine organisms may be exposed to fenvalerate and other pyrethroids after applications to corn (*Zea mays*), cotton (*Gossypium hirsutum*), rice (*Oryza sativa*), and vegetables in coastal areas or by discharges from pyrethroid manufacturers or formulating and distribution centers (Clark et al. 1989). Fenvalerate has been implicated in kills of coastal organisms in South Carolina, primarily from agricultural runoff into estuarine tidal creeks (Scott et al. 1987).

This report was prepared in response to information requests from environmental contaminant specialists of the U.S. Fish and Wildlife Service. It is part of a continuing series of brief reviews on hazards of chemicals to fish and wildlife resources. Detailed information on ecological and toxicological aspects of fenvalerate and other synthetic pyrethroid insecticides is provided in reviews by Elliott (1977), Elliott and Janes (1978), Wouters and Bercken (1978), Glickman and Casida (1982), Vijverberg and Bercken (1982), Gray and Soderlund (1985), Leahey (1985), Smith and Stratton (1986), Coats et al. (1989), and Bradbury and Coats (1989a).

[1]The technical fenvalerate formation is no longer being manufactured by the Dupont Company, although existing stocks may be used until exhausted. The new fenvalerate formulation will be sold as Asana or Esfenvalerate, and contains only the 2*S*, α*S* isomer (A. Stavola, U. S. Environmental Protection Agency, personal communication, 28 January 1991).

Environmental Chemistry

General

Synthetic pyrethroids now account for at least 30% of the world insecticide market and are rapidly replacing other agricultural chemicals for control of insect pests. Fenvalerate is one of the more recently developed and widely used synthetic pyrethroid insecticides. It is derived from a combination of α-cyano-3-phenoxybenzyl alcohol and α-isopropyl phenylacetate ester. Technical fenvalerate is a mixture of four optical isomers, each occurring in equal amounts but with different efficacies against insect pests. Fenvalerate does not usually persist in the environment for > 10 weeks, and it does not accumulate readily in the biosphere. Time for 50% loss (Tb ½) in fenvalerate-exposed amphibians, birds, and mammals was 6-14 h; for reptiles, terrestrial insects, aquatic snails, and fish it was > 14 h-<2 days; and for various species of crop plants it was 2-28 days. Fenvalerate degradation in water is due primarily to photoactivity and, in soils, to microbial activity. Half-time persistence in nonbiological materials is variable but may last as long as 6 days in fresh water, 34 days in seawater, 6 weeks in estuarine sediments, and 9 weeks in soils.

Chemical Properties

Synthetic pyrethroid insecticides are photostable analogs of the natural pyrethrins of botanical origin; they consist of a series of related esters derived from alcohols and acids that maintain critical isosteric relations with the natural product prototype (Glickman and Casida 1982; Bradbury and Coats 1989a). Small changes in substituents and stereochemistry are sufficient to produce compounds differing in their insecticidal potency, spectrum of activity, and mammalian toxicology (Gray and Soderlund 1985). Halogenated, lipophilic, photostable compounds are exceptionally active against many species of insects; although these compounds are relatively safe to birds and mammals, they are usually extremely toxic to certain freshwater and marine groups, including fish (Leahey 1985; Coats et al. 1989).

The first significant success in creating a photostabilized pyrethroid with high insecticidal activity was achieved through use of the 3-phenoxybenzyl alcohol moiety. A further step was the finding that 2-aryl-3methylbutyric acid esters of pyrethroid alcohols were both photostable and insecticidal (Gray and Soderlund 1985).

Fenvalerate is one of the more recently developed and widely used synthetic pyrethroid insecticides, and it is a highly active phenyl acetate ester of known pyrethroid alcohols—specifically, a combination of isopropyl phenyl acetate ester and α-cyano-3-phenoxybenzyl alcohol (Wouters and Bercken 1978). The phenoxybenzyl group and the halogenated phenyl ring increase the photostability of the molecule. The cyano group, substituted on the benzylic carbon, stabilizes the ester bond against hydrolysis (Coats et al. 1989).

Fenvalerate, like most other synthetic pyrethroids, is a halogenated, lipophilic, stable compound with low solubility in water and high solubility in organic solvents (Table 1). Technical fenvalerate is a racemic mixture of four isomers, composed of equal amounts of dextrorotary and levorotary forms; however, the four optical isomers (Figure) have very different efficacies against pest species. In general, fenvalerate stereoisomers with S configurations in both the acid and alcohol moieties are more active pharmacologically and toxicologically than those with R configurations (Wouters and Bercken 1978).

Uses

Pyrethroids are used primarily for the control of household and agricultural insect pests and secondarily in industrial, stored product, and veterinary applications. They are especially advantageous for use in northern climates because their toxicity is enhanced at low temperatures (Smith and Stratton 1986). Synthetic pyrethroid insecticides, including fenvalerate, are used as alternatives to organochlorine, organophosphorus, carbamate, and natural pyrethrum insecticides because they are highly toxic to insect pests, low to intermediate in persistence, and low in toxicity to warm-blooded organisms, although extremely toxic to many aquatic organisms (Hansen et al. 1983; Coats et al. 1989). By 1982, more than 30% of the world market for insecticides consisted of synthetic pyrethroids, and this percentage is increasing (Smith and Stratton 1986).

Outside of the United States, fenvalerate is used on cotton in Australia, Greece, and South Africa and on apples (*Malus* sp.), pears (*Pyrus* sp.), and potatoes (*Solanum* sp., *Ipomoea* sp.) in Canada (Reed 1981); uses in other countries, including Mexico, are anticipated (Reed 1981), as is increased use against agricultural, poultry, dairy, and household pests (Mumtaz and Menzer 1986). In agricultural use, recommended application rates of

fenvalerate range between 0.055 and 0.224 kg/ha for control of a broad spectrum of pestiferous insects (Bennett et al. 1983).

Domestically, about 6,500 kg of fenvalerate was used in 1979; all of this amount was imported (Reed 1981). In 1980, in addition to registered use, the U.S. Environmental Protection Agency allowed an additional 80,000 kg for crisis and experimental use (Reed 1981). By 1981, fenvalerate had been registered for domestic use on apples, cotton, peanuts (*Arachis* sp.), pears, and potatoes. Additional uses were allowed under various experimental or crisis exemptions on beans (*Phaseolus* spp.); black and white pepper (*Piper* spp.); broccoli, cabbage, and cauliflower (*Brassica* spp.); celery (*Apium* sp.); corn; cucumbers (*Cucumis* sp.); eggplant (*Solanum melongena*); grapes (*Vitis* spp.); lettuce (*Lactuca* sp.); peas (*Pisum* sp.); squash (*Cucurbita* spp.); and tomatoes (*Lycopersicon esculentum*; Reed 1981). By 1989, this list was expanded to include tobacco (*Nicotiana tabacum*); soybeans (*Glycine max*); sugarcane (*Saccharum officinarum*); a wide variety of nuts, fruits, and vegetables; pine seed orchards, forest tree nurseries, mosquitos, biting insects, insect vectors of disease, mite control in poultry, and fly and tick control in cattle (Spehar et al. 1982; Akhtar 1983; Bennett et al. 1983; Hansen et al. 1983; Sine 1988; Clark et al. 1989; Smith et al. 1989).

Table 1. Chemical and other properties of fenvalerate.[a]

Variable	Datum
Chemical name	(RS)-α-cyano-3-phenoxybenzyl (RS)-2-(4-chlorophenyl)-3-methylbutyrate; cyano (3-phenoxyphenyl) methyl 4-chloro-α-(1-methylethyl) benzeneacetate; α-cyano-3-phenoxybenzyl 2-(4-chlorophenyl)-3-methylbutyrate; 4-chloro-α-(l-methyl ethyl) benzeneacetic acid cyano(3-phenoxyphenyl) methyl ester; α-cyano-3-phenoxybenzyl α-(4-chlorophenyl) isovalerate
Alternate names	Agmatrin, Belmark, Ectrin, Fenkill, Phenvalerate, Pydrin, S-5602, Sanmarton, SD 43775, Sumicidin, Sumifly, Sumipower, Sumitox, WL 43775
CAS number	51630-58-1
Chemical formula	$C_{25}H_{22}ClNO_3$
Molecular weight	419.92
Physical state	Clear yellow, viscous, liquid at 23° C
Purity	Technical grade compound is 92% pure; nature and extent of impurities unknown
Vapor pressure at 25° C	1.1×10^{-8} mm mercury
Density at 23° C	1.17 g/mL
Stability	Stable in most solvents except alcohols at ambient temperature. Unstable in alkaline media. No significant breakdown after 100 h at 75° C; gradual degradation occurred in range 150-300° C
Degradation	Cleavage of the ester linkage is the primary route
Formulations	Emulsifiable concentrate, dust, granules, wettable powder
Log octanol-water partition coefficient	6.2
Solubility at 20° C	
Acetone	>450 g/L
Chloroform	>450 g/L
Methanol	>450 g/L
Hexane	77 g/L
Water	2-85 µg/L
Seawater	24 µg/L

[a] References: Elliott 1977; Coats and O' Donnell-Jefferey 1979; Reed 1981; Tagatz and Ivey 1981; Akhtar 1983; Schimmel et al. 1983; Windholz et al. 1983; Clark et al. 1987, 1989; Crofton and Reiter 1988; Sine 1988.

The delivery vehicle of fenvalerate-containing insecticide may account for wide variations in toxic action. For example, fenvalerate microcapsules used to control caterpillar pests (*Plutella xylostella*, *Spodoptera litura*) were most effective with thin-walled capsules and small particles; however, significant protection to nontarget organisms, such as fish, occurred with thicker-walled capsules and larger particles (Ohtsubo et al. 1989). The popularity of commercial synthetic pyrethroids and their widespread replacement of older, more toxic compounds in various settings mandates a thorough understanding of the formulation used and of the active and inert components (Williamson et al. 1989).

Persistence

In nonbiological samples, half-time persistence of fenvalerate was variable but frequently ranged between 2 and 6 days in fresh water, 27 and 34 days in seawater, 3 and 9 weeks in soils, and up to 6 weeks in estuarine sediments (Table 2). Persistence was longer at higher initial application rates and under conditions of reduced light, low microbial activity, and high organic content (Table 2). Fenvalerate is not readily transported from upland field application sites into the aquatic environment. Fenvalerate that directly enters the aquatic environment by way of runoff has limited bioavailability to aquatic organisms owing to rapid adsorption onto soil particles, organic matter, or plants and to chemical hydrolysis and photodecomposition (Ohkawa et al. 1980). Under acidic conditions, fenvalerate in water is stable to hydrolysis for 100 h at 75° C; Tb ½ at elevated recommended application rates is about 21 days, primarily as a result of photodegradation (Reed 1981).

Fenvalerate is one of the more persistent synthetic pyrethroids in soils (Klaassen et al. 1986). In agricultural soils, fenvalerate is tightly adsorbed to soil particles, does not easily move laterally or to lower soil layers with groundwater, and almost always localizes in the application site because of its extremely low solubility in water (Ohkawa et al. 1980; Hill 1981; Miyamoto 1988). Fenvalerate degradation rates from mineral soil surfaces are dependent on soil type, moisture, temperature, and microbial activity. Half-time persistence in soils usually ranged between 2 and 18 days, but 3 months has also been recorded (Harris et al. 1981; Reed 1981; Bennett et al. 1986). Although fenvalerate is susceptible to chemical degradation by hydrolysis and oxidation, most authorities agree that degradation in soils is due primarily to microbial activity, that microbial degradation is most rapid under aerobic conditions, and that transformed products do not persist longer than the parent compound (Ohkawa et al. 1980; Chapman et al. 1981; Bennett et al. 1986).

In biological samples, fenvalerate neither persists for lengthy periods nor is readily accumulated (Smith and Stratton 1986). In general, fenvalerate is rapidly (i.e., Tb ½ of 6-14 h) excreted by amphibians, birds, and mammals; has low persistence in various reptiles, terrestrial insects, aquatic snails, and fish; and has moderate (i.e., Tb ½ of 2-28 days) persistence in various species of target plants (Table 3; Reed 1981; Mumtaz and Menzer 1986; Bradbury and Coats 1989a, 1989b). Animals collected after 5 days from a cotton field sprayed with 0.112 kg/ha, or from the immediate vicinity, had very low fenvalerate residues (Table 3; Bennett et al. 1983). In that study fenvalerate was detected in one of nine bird species sampled, in one of four mammals, in the western ribbon snake (*Thamnophis proximos*), in one of four amphibian species, and in fish and insects. The bird was a male dickcissel (*Spiza americana*) that had established a breeding territory within the sprayed cotton field. Carnivorous ground beetles, found moribund on the ground, contained the highest mean fenvalerate residue of 0.55 mg/kg fresh weight (FW) whole body; large numbers of dead insects were found in the fields during collection. The highest residues (0.32-0.55 mg/kg) in fish and invertebrates were in those collected from a small pool in a drainage ditch, which compares with 0.92 mg/kg found in common carp (*Cyprinus carpio*) after exposure in the laboratory for 7 days to 0.8 µg fenvalerate per liter (Bennett et al.1983).

Fenvalerate is not significantly absorbed or translocated in plants. Cotton, apples, and lettuce treated with fenvalerate contained surface residues of parent fenvalerate 8 weeks after treatment (Reed 1981). In addition to the parent compound, which accounted for 80% of all residues, identified metabolites included 3-phenoxybenzaldehyde, 3-phenoxybenzyl methylbutyric acid, and conjugates of these compounds. Half-time persistence of fenvalerate on plant surfaces is between 2 and 4 weeks, and degradation is primarily a result of weathering (Reed 1981).

Various plants sprayed with 0.25 kg fenvalerate per hectare had measurable residues 7 days after application and nondetectable residues 15-30 days after treatment (Jain et al. 1979). Washing plants in cold water to remove the pesticide was effective only on the initial day of application, removing 30-50%. Afterwards, only 3-13% could be removed by washing. Cooking removed 71-88% of the fenvalerate residues on the initial

day of treatment, but in later samplings, removal was 68-70% in spinach (*Spinacea oleracea*) and tomatoes and 38-40% in okra (*Abelmoschus esculentus*) and cauliflower (*Brassica oleracea botrytis*; Jain et al. 1979).

Adsorption and persistence in plants can be modified by other chemicals or by selected carriers, although mechanisms to account for these phenomena are unclear. The application mixture influences adsorption and persistence of fenvalerate. For example, interception and persistence in sugarcane were increased when fenvalerate was applied in a 25% water to 75% soybean oil mixture versus water or soybean oil alone (Smith et al. 1989). Also, biocidal properties of fenvalerate residues on cotton foliage were increased up to 100% due to enhanced persistence of fenvalerate in the presence of toxaphene (Brown et al. 1982).

Table 2. Fenvalerate persistence in water, sediments, and soils.

Sample and other variables	Persistence	Reference[a]
Fresh water		
Various concentrations	Half-time persistence (Tb ½) of 3.2 days (range 1.9-5.8 days); longer for higher initial doses	1
0.1 µg/L	Tb ½ of 4.1 days; 90% loss in 13.5 days	11
3.9 µg/L	Maximum concentration was 2.3 µg/L 48 h after application; at 168 h it was 0.6 µg/L	1
8.3 µg/L	Concentration declined from 5.3 µg/L at 24 h to 1.8 µg/L at 168 h	1
16.5 µg/L	Concentration declined from 17.6 µg/L at 24 h to 9.1 µg/L at 168 h	1
30.6 µg/L	Concentration declined from 54.4 µg/L at 24 h to 21.2 µg/L at 168 h	1
Seawater	Tb ½ of 8 days in light, >14 days in dark; 27-34 days under alternating light and dark	2,3
Estuarine sediments		
Sterilized	No degradation in 28 days	2
"Low" concentrations	Tb ½ of 4.5-9 days	1,3
"Various" concentrations	Tb ½ of 24-42 days	2,4,5,6
0.1-10 mg/kg dry weight (DW)	73% loss in 8 weeks at initial nominal concentration of 0.1 mg/kg DW, 78% at 1.0 mg/kg, and 96% loss in 8 weeks at 10 mg/kg DW	4
Soils		
Initial concentration of 1.0 mg/kg DW soil		
Natural mineral, pH 8.0-8.1	12% remaining after 8 weeks, about 5% after 16 weeks	7
Sterilized mineral, pH 7.7-8.1	91% remaining after 8 weeks, 87% after 16 weeks	7
Natural organic, pH 7.1-7.2	58% remaining at 8 weeks, about 32% after 16 weeks	7
Sterilized organic, pH 6.5-6.9	100% remaining after 16 weeks	7
Various (clay, silt, sand), dose unknown	Tb ½ of 22-40 h	8
Mineral soils, dose unknown	Tb ½ of 6 weeks	9
Moist sand, dose unknown	Tb ½ of 9 weeks, 88% loss in 48 weeks	9
Lethbridge surface soil, agricultural, British Columbia		

Field conditions, initial application of 150 g/ha	Tb ½ of 6 weeks, 89% loss in 45 weeks	10
Laboratory study, 70 g/ha equivalent	Tb ½ of 5.2 weeks	10

[a] 1. Coulon 1982; 2. Schimmel et al. 1983; 3. Smith and Stratton 1986; 4. Tagatz et al. 1987; 5. Tagatz and Ivey 1981; 6. Hansen et al. 1983; 7. Chapman et al. 1981; 8. Muir et al. 1985; 9. Harris et al. 1981; 10. Hill 1981; 11. Day et al. 1987.

Table 3. Fenvalerate persistence in plants and animals under field conditions.

Sample and othervariables	Persistence	Reference[a]
Alfalfa, *Medicago sativa*	Half-time persistence (Tb ½) of 9 11 days	1
Cotton *(Gossypium hirsutum)* treated with 0.224 kg/ha, residues on foliage 12 days later		
In combination with 2.24 kg/ha toxaphene	Fenvalerate residues were 11.6 mg/kg	2
Fenvalerate alone	Residues were 5.9 mg/kg	2
Cotton, foliage	Tb ½ of 2 days, 96% lost in 17 days	3,7
Cotton field sprayed with 0.112 kg/ha (0.1 pound per acre), Garland, Arkansas, July 1979. Animals collected from field 5 days later		
Mammals		
Deer mouse, *Peromyscus maniculatus*; white-footed mouse, *P. leucopus;* cotton rat, *Sigmodon hispidus*	<0.01 mg/kg whole body fresh weight (FW), less skin and GI tract	3
House mouse, *Mus musculus*	0.01 mg/kg whole body FW, less skin and GI tract	3
Birds		
Cardinal, *Richmondena cardinalis*; red-winged blackbird, *Agelaius phoeniceus*; eastern meadowlark, *Sturnella magna*; brown-headed cowbird, *Molothrus ater*; purple martin, *Progne subis subis*; horned lark, *Eremophila alpestris*; little blue heron, *Florida coerulea*; green-backed heron, *Butorides virescens virescens*	<0.01 mg/kg whole body FW, less skin and GI tract	3
Dickcissel, *Spiza americana*	0.02 mg/kg whole body FW, less skin and GI tract	3
Reptiles		
Western ribbon snake, *Thamnophis proximus*	0.12 mg/kg whole body FW, less skin and GI tract	3
Animals collected from location near cotton field 5 days later		

Insects		
Cicada, Cicadidae	<0.01 mg/kg FW whole body	3
Short-horned Acrididae	0.18-0.24 mg/kg FW whole body	3
Ground beetle, *Calosoma* sp.	0.55 mg/kg FW whole body	3
Molluscs		
Aquatic snail, unidentified	0.53 mg/kg FW soft parts	3
Fish		
Mosquitofish, *Gambusia affinis*	0.3 mg/kg FW whole body	3
Golden shiner, *Notemigonus crysoleucas*	0.47 mg/kg FW whole body	3
Amphibians		
Southern leopard frog, *Rana utricularia*; green frog, *Rana clamitans*; green treefrog, *Hyla cinerea*	<0.01 mg/kg FW whole body, less skin and GI tract	3
Fowler's toad *Bufo fowleri*	0.02 mg/kg FW whole body, less skin and GI tract	3
Old field site, Iowa, O. 112 kg/ha (0.1 pound per acre) applied on 9 June 1980, and again on 5 August 1980, 10 June 1981, and 21 July 1981		
Vegetation	Maximum immediately after each application was 12.1 mg/kg FW; residues after 24 days were always <1 mg/kg FW	1
Short-horned grasshopper, whole		
Applied 9 June 1980	Residues were 0.03 mg/kg FW after 36 days, and nondetectable (ND) in 49 days	1
Applied 5 August 1980	Residues were 0.33 mg/kg FW after 7 days, 0.19 after 14 days, and 0.12 after 21 days	1
Ground beetles, Carabidae, whole		
Applied June 1980	After 10 days, beetles contained 0.12 mg/kg FW; after 17 days residues were ND	1
Applied 5 August 1980	After 6 days, residues were O. 14 mg/kg FW and ND in 17 days	I
Applied 21 July 1981	Maximum residue after 24 days was 0.15 mg/kg FW	1
Deer mice, *Peromyscus maniculatus*, whole		
Applied 21 July 1988	Residues were 0.1 mg/kg FW after 2 days, and 0.01 after 21 days	1
Meadow vole, *Microtus pennsylvanicus*, whole		
Applied 21 July 1988	Residues were variable: 0.07 mg/kg FW after 2 days, O. 12 after 4 days, 0.46 after 8 days, and 0.04 after 21 days	1
Plants, 4 species, sprayed with 0.05% emulsifiable concentrate equivalent to 0.25 kg/ha		
Okra, *Abelmoschus esculentus*, initial	After 5 days residue was 1.6 mg/kg FW, after 7 days it was 0.8, and after 15 days it was ND	4

concentration of 4 mg/kg FW		
Cauliflower, *Brassica oleracea botrytis*, initial deposit of 0.86 mg/kg FW	Initial deposit degraded to 0.3 mg/kg in 7 days and was ND in 15 days	4
Tomato, *Lycopersicon esculentum*, initial residue of 0.85 mg/kg FW	Initial residue degraded to 0.67 mg/kg in 5 days, 0.3 in 15 days, and was ND in 30 days	4
Spinach, *Spinacea oleracea*, initial residue of 9.5 mg/kg FW	Initial residue degraded to 2.8 mg/kg in 15 days and was ND in 30 days	4
Plants, various, foliage	Mean Tb ½ of 8.2 days, range 2.8-14 days	6
Bean, *Phaseolus* sp.	Tb ½ of 14 days, essentially no translocation from leaf surface	1
Sugarcane, *Saccharum officinarum*, initial residue immediately after application was 18.8-28.2 mg/kg dry weight leaf	Residues after 7 days were 2.1-5.4 mg/kg DW; Tb ½ of 2.2-2.4 days	5

[a] 1. Bennett et al. 1986; 2. Brown et al. 1982; 3. Bennett et al. 1983; 4. Jain et al. 1979; 5. Smith et al. 1989; 6. Willis and McDowell 1987; 7. Buck et al. 1980.

Fenvalerate photoproducts merit consideration, as some may be comparatively toxic. Decarboxyfenvalerate is a major degradation product of fenvalerate that is formed by photochemical reactions in water and on plant foliage (Mikami et al. 1985). This photoproduct composes up to 10% of the total residues in forage crops that have been exposed to prolonged sunlight and drying. Decarboxyfenvalerate did not persist in tissues of hens, rats, and cows when consumed with feed for extended periods; its residue levels in ova, milk, and meat were negligible (Mikami et al. 1985).

Photolysis of fenvalerate in various solvents by sunlight yields products resulting from ester cleavage, primarily decarboxyfenvalerate, but also 15 other products. All sunlight photoproducts were relatively harmless to mice; LD50 values were >500 mg/kg body weight (BW; Holmstead et al. 1978). When photolysis was by way of ultraviolet light, however, two of the photoproducts formed (3-phenoxybenzoyl cyanide, 3-phenoxybenzyl cyanide) were considerably more toxic than fenvalerate; LD50 values for intraperitoneal injection in mice were >500 mg/kg BW for fenvalerate, 2 mg/kg BW for 3-phenoxybenzoyl cyanide, and 105 mg/kg BW for 3-phenoxybenzyl cyanide (Holmstead et al. 1978). This finding strongly suggests a need for additional research on fenvalerate photoproduct persistence and toxicity.

Mode of Action

General

Two types of synthetic pyrethroids have been identified, as judged by different behavioral, neurophysiological, chemical, and biochemical profiles: Type I, those pyrethroids lacking the α-cyano group, and Type II, those possessing the α-cyano group (i.e., fenvalerate). Induction of repetitive activity in the nervous system is the principal effect of pyrethroids. Repetitive activity originates from a prolongation of the transient increase in sodium permeability of the nerve membrane associated with excitation. All pyrethroids affect sodium channel gating in a similar manner, although Type II pyrethroids are significantly more neurotoxic than Type I pyrethroids.

Metabolism of fenvalerate proceeds by way of oxidation and hydrolysis to produce metabolites considered pharmacologically inactive or inferior to the parent compound. Insects and fish are extremely susceptible to fenvalerate when compared to mammals and birds; interspecies differences are associated with rates of metabolism, excretion, absorption, esterase activity, and neurosensitivity.

Fenvalerate is neither mutagenic nor teratogenic. Tumorlike growths in rodent tissues, however, were associated with the 2R, αS isomer (heretofore believed innocuous)--specifically, with its cholesterol conjugate.

Types of Pyrethroids

Two distinct types of synthetic pyrethroids have been identified, as judged by different behavioral, neurophysiological, chemical, and biochemical profiles in rodents: Type I, also known as Class 1 or T for tremor; and Type II, also known as Class 2 or CS for choreoathetosis-salivation (Wouters and Bercken 1978; Verschoyle and Aldridge 1980; Glickman and Casida 1982; Gray 1985; Gray and Soderlund 1985; Klaassen et al. 1986; Crofton and Reiter 1988; Bradbury and Coats 1989a; Gilbert et al. 1989; Williamson et al. 1989). In general, these authorities agree that pyrethroids containing both a halogenated acid esterified with the α-cyano-3-phenoxybenzyl alcohol--such as fenvalerate, deltamethrin, and cypermethrin--produce the Type II poisoning syndrome and that pyrethroids lacking either or both of these moieties (i.e., permethrin, resmethrin, cismethrin, allethrin, bromphenothrin, phenothrin, kadethrin, tetramethrin) tend to produce the Type I syndrome. Type I is characterized by sparring, aggressive behavior (in rats, but not mice), rapid onset of tremor in the extremities, increased body temperatures, and whole-body tremors. As toxicity progresses, mice show hyperactivity, whereas rats become prostrate and die with immediate onset of rigor mortis; in mice, death is often associated with spasmodic seizures. The Type I syndrome is very similar to that produced by p,p'-DDT. Type II is characterized by pawing and burrowing behavior, profuse salivation, a decrease in body temperature of rats (due partially to evaporation of saliva), tremors progressing to choreoathetosis (i.e., a sinuous, writhing movement), muscular contractions and seizures, and death. With repeated high doses sufficient to kill some rats, degenerative changes in sciatic and posterial tibial nerves were observed. The same two types of pyrethroid actions are also evident among insects.

Regardless of route of administration, signs of fenvalerate poisoning in rodents were similar. Doses administered by intercerebroventricular injection of comparatively low concentrations were more toxic than higher doses given orally or by intravenous or intraperitoneal injection, suggesting greater central nervous system involvement in Type II than in Type I poisoning. In fact, pyrethroids that produce the Type II syndrome--including fenvalerate--are 5 to 10 times more potent neurotoxicants than Type I pyrethroids, which suggests different sites of action in the central nervous system.

Sodium Gating Kinetics

Pyrethroids have an action at or near the sodium channel in the nerve, resulting in greatly altered ionic currents and disrupted nerve function through membrane depolarization. Based on studies with insects, crustaceans, frogs, and small mammals, there is general agreement that the sodium channel in the nerve membrane is the major target site for all synthetic pyrethroid insecticides (and many other neurotoxicants); that synthetic pyrethroids prolong the transient increase in sodium permeability of the nerve membrane during excitation, resulting in spontaneous depolarization and repetitive discharges; that persistent repetitive discharges lead to muscular fasciculations, acetylcholine depletion, and muscular weakness; that effects are enhanced at lower temperatures; and that α-cyano (Type II) pyrethroids are more potent neurotoxicants than noncyano (Type I) pyrethroids, differences in neurotoxic effects being attributed solely to the α-cyano substituent (Wouters and Bercken 1978; Gammon et al. 1981; Vijverberg and Bercken 1982; Vijverberg et al. 1982; Parker et al. 1984b; Flannigan et al. 1985; Gray and Soderlund 1985; Ruigt and Bercken 1986; Eells and Dubocovich 1988; Flodstrom et al. 1988; Clark and Brooks 1989; Gilbert et al. 1989; Holloway et al. 1989; Salgado et al. 1989). Most of these authorities agree that fenvalerate was the most effective pyrethroid tested for inducing pronounced repetitive activity in nerve fibers and that the 2S, αS isomer was up to 15 times more potent than other fenvalerate isomers. Pyrethroids induce the sodium channels to close more slowly than normal, resulting in a gradually decaying inward sodium current (called a tail current) after termination of membrane depolarization. Type I pyrethroids induce tail currents with time constants of decay in milliseconds, but Type II pyrethroids result in time constants of decay that are orders of magnitude longer and contain thousands of impulses, inducing a quickly reversible, frequency-dependent suppression of the action potential. Depolarization of axons by synthetic pyrethroids was most effective at low temperatures; the negative temperature dependence of the steady state current seems to be due to the stabilizing effect of low temperature on the open-modified channel.

Myelinated nerves of vertebrates are thought to sequester the pyrethroid molecules, known to be soluble in the myelin sheath, thereby preventing a portion of their chemical effect on the nerve axon (Flannigan et al. 1985). Fenvalerate, unlike other α-cyano pyrethroids, had little effect on the electrophysiological function of single myelinated nerve fibers in the frog (*Rana esculenta*), suggesting that additional research is needed on mechanisms other than membrane sodium transport (Tippe 1987).

The role of calcium in pyrethroid interaction with nerve tissue is under active investigation. Fenvalerate affects calcium-ATPase enzyme and calmodulin-activated enzyme activities, such as phosphodiesterase (Flodstrom et al. 1988). Fenvalerate inhibits calcium uptake by nerve cord of crayfish (*Procambarus clarki*) and axon of spiny lobster (*Panulirus japonicus*), an action that seems to be related to its lipophilic properties (Doherty et al. 1986). Fenvalerate enhances the calcium-dependent potassium-stimulated release of norepinephrine from rat brain and could lead to an overall depletion of brain stores of this neurotransmitter, producing a convulsive state typical of Type II pyrethroid poisoning (Brooks and Clark 1987; Clark and Brooks 1989). Fenvalerate evoked a calcium-dependent release of dopamine and acetylcholine from rabbit (*Oryctolagus* sp.) brain that was concentration related and specific for the 2S, αS isomer; release of dopamine and acetylcholine was antagonized completely by tetrodotoxin, a sodium channel blocker (Eells and Dubocovich 1988). The relatively low potency of fenvalerate and other Type II pyrethroids on potassiumstimulated calcium uptake in rat brain and other responses suggests that neither the sodium-calcium exchanger nor the voltage-dependent calcium channels are primary targets for pyrethroid toxicity (Ramadan et al. 1988).

Toxic isomers of Type II pyrethroids usually antagonize -aminobutyric acid (GABA) by interacting with the t-butyl bicyclophosphorothionate-picrotoxin binding site in brain; antagonism of GABA leads to a reduction in inhibition (Casida and Lawrence 1985). Fenvalerate seems to increase inhibition, however, and this may be explained by a differential effect on sodium channel kinetics (Gilbert et al. 1989). Fenvalerate also inhibits perhydrohistrionicotonin binding with electric organ membrane of the electric ray (*Torpedo* sp.; Abbassy et al. 1983) and interacts with binding sites for dihydropicrotoxinin and kainic acid in the brain (Gammon et al. 1982), but the significance of these observations is unclear.

Metabolism

The most important metabolic degradation pathways for synthetic pyrethroids are oxidation on the phenoxy ring, hydrolysis of the ester linkage, and conjugation of metabolites; rates and pathways differ among taxonomic animal groupings resulting in large differences in sensitivity (Holmstead et al. 1978; Kaneko et al. 1981; Akhtar 1983; Miyamoto 1988; Bradbury and Coats 1989a).

All metabolic degradation products of fenvalerate are pharmacologically inactive or inferior to the parent compound, implying that metabolic modifications lead to detoxication (Miyamoto 1988). Fenvalerate and other α-cyano pyrethroids, however, are consistently more resistant to oxidative attack than their noncyano analogs (Gray and Soderlund 1985). Liver is the predominant site of fenvalerate metabolism through hydrolysis by one or more hepatic microsomal esterases; inhibition of these enzymes results in enhanced toxicity (Ghiasuddin and Soderlund 1984). Hydrolysis has also been demonstrated in plasma, kidney, stomach, and brain tissues. Except for brain, however, these tissues were relatively unimportant in the detoxification process (Ghiasuddin and Soderlund 1984; Gray and Soderlund 1985).

Metabolism of the 2S isomers proceeds sequentially: hydroxylation at the phenoxy group, hydrolysis of the cyano group, and cleavage of the ester linkage (Coats et al. 1989). Fenvalerate and the 2S isomers yield two ester metabolites in feces from hydroxylation at the 4' and 2' phenoxy positions. Other significant metabolites were 3-phenoxybenzoic acid and its hydroxy derivatives from the alcohol moiety, 3-(4-chlorophenyl) isovaleric acid and its hydroxy derivatives from the acid moiety, and thiocyanate and carbon dioxide from the cyano moiety (Ohkawa et al. 1979). A slow elimination rate characterizes fenvalerate and other α-cyano pyrethroids when compared with noncyano pyrethroids; it seems to be due to the release of the cyano group during ester cleavage, which is then incorporated into the body thiocyanate pool and retained in the skin and stomach (Gray and Soderlund 1985). Decarboxyfenvalerate, a photolysis product of fenvalerate, is present in water and on plant surfaces, but it is extensively hydroxylated in mammals and excreted rapidly and completely into feces with no apparent toxic effects (Miyamoto 1988).

Signs of fenvalerate intoxication are similar in birds, fish, mammals, and insects, but insects and fish are extremely sensitive when compared with warm-blooded organisms, frequently by one to three orders of magnitude (Bradbury and Coats 1989a, 1989b). Increased resistance to fenvalerate and other synthetic pyrethroid insecticides in mammals and birds, when compared with aquatic organisms and terrestrial insects, is attributed to their higher metabolism, more rapid excretion, lower absorption from diet or the surrounding envirosphere, higher esterase activity, higher fat content, and lower neurosensitivity (Wouters and Bercken 1978; Ohkawa et al. 1979; Glickman and Casida 1982; Flannigan et al. 1985; Gray and Soderlund 1985; Klaassen et al. 1986; Bradbury and Coats 1989a, 1989b; Coats et al. 1989). For example, rainbow trout

(*Oncorhynchus mykiss*)—one of the more sensitive aquatic species—have significantly lower rates of metabolism and elimination of fenvalerate than those reported for birds and mammals (Bradbury et al. 1986; Bradbury and Coats 1989a, 1989b); show little or no esterase activity towards pyrethroids and substantially lower oxidative activity than warm-blooded animals (Bradbury and Coats 1989a, 1989b); efficiently accumulate fenvalerate from the medium (Gray and Soderlund 1985); and show greater intrinsic sensitivity of the central nervous system when compared with birds and mammals (Gray and Soderlund 1985; Bradbury and Coats 1989a).

Fenvalerate effects are antagonized or synergized by various compounds or chemicals. Dermal exposure to fenvalerate in mammals may produce a skin sensory response, most frequently on the face, characterized by itching and tingling. Administration of vitamin E up to 29 h before fenvalerate exposure partially reduced the fenvalerate-mediated skin sensation in guinea pigs (*Cavia* sp.; Malley et al. 1985). The effectiveness of vitamin E may be associated with its membrane stabilizing property, although the exact mode of action is unknown. Fenvalerate skin sensations were also reduced by piperonyl butoxide when applied directly to the skin or in conjunction with fenvalerate (Malley et al. 1985). Delayed toxic effects in rodents and insects were produced with various muscle relaxants, including propranolol and diazepam, perhaps through depolarization of nerve terminals (Gammon et al. 1982; Gray 1985; Gray and Soderlund 1985). Mice given profenofos, an esterase inhibitor, were up to 27 times more susceptible than were nontreated animals (Glickman and Casida 1982).

Mutagenicity, Teratogenicity, Carcinogenicity

Fenvalerate and other synthetic pyrethroids caused no oncogenic, reproductive, mutagenic, or teratogenic effects, as judged by results of 2-year feeding studies with rodents at 250-300 mg/kg diet, three-generation rodent reproduction studies at 250 mg/kg diet, various mutagenicity assays, bone marrow cytogenicity up to 150 mg/kg BW, the dominant lethal bioassay at 100 mg/kg, and a host-mediated bioassay in mice at 50 mg/kg BW (Reed 1981; Pluijmen et al. 1984; Flannigan et al. 1985; Gray and Soderlund 1985). Some chromosomal aberrations and alterations in the mitotic index were noted, however, in bone marrow and testis cells of rats given fenvalerate at 100 mg/kg BW orally, a dose that killed 71% of the rats (Gray and Soderlund 1985). A similar pattern was noted in mice (Flodstrom et al. 1988; Pati and Bhunya 1989), indicating that additional research is needed to establish mutagenicity of fenvalerate.

The carcinogenic potential of fenvalerate is based on negative or inconclusive evidence and centers on its ability to produce microgranulomas in various tissues, especially liver, in dogs (*Canis familiaris*) and rodents. Beagles exposed to fenvalerate at 250, 500, or 1,000 mg/kg diet for 6 months showed treatment-related microscopic effects, including histiocytic cell infiltrates in mesenteric lymph nodes and multifocal microgranulomas in liver (Parker et al. 1984b). Female rats fed a diet containing fenvalerate at 1,000 mg/kg ration for 2 years showed a statistically significant increase in the incidence of mammary tumors; however, this was judged by the authors (Parker et al. 1984a) to be of unlikely biological significance. Their unusual conclusion was based on four points: (1) none of the mammary tumor incidences exceeded those expected or reported on aged female rats of this strain, (2) time and appearance of tumors in control and treated groups were unchanged by treatment, (3) the benign-malignant ratio of mammary tumors was the same in control and treated groups, and (4) the tumors were common in this strain of rat and did not seem to be related to treatment.

Fenvalerate inhibits intercellular communication between fibroblast cells and enhances the development of hepatocyte loci in rat liver at nonheptatotoxic dose levels. Chemicals that possess these properties are likely to be tumor promoters (Flodstrom et al. 1988). Fenvalerate alone induced no hepatoxic effects in rat liver, as judged by transaminase activities and histology. However, some rats that were partially hepatectomized and insulted with nitrosodiethylamine—a carcinogen and tumor initiator—had significantly elevated numbers of liver foci after administrations of fenvalerate. This response suggested that fenvalerate is a potential tumor promoter (Flodstrom et al. 1988).

Linkage of the tumorlike formations in rodents with a specific fenvalerate stereoisomer was an important breakthrough (Kaneko et al. 1986; Okuno et al. 1986; Miyamoto et al. 1986; Miyamoto 1988). Granulatomous cells in spleen, lymph node, and liver of fenvalerate-stressed rats and mice tended to fuse, forming large multinucleated cells called giant cells. Researchers convincingly demonstrated that the 2R, αS isomer, heretofore believed innocuous, was solely responsible for the observed microgranulomas. The residual metabolite in this instance is the cholesterol conjugate [cholesterol (2R)-2-(4- chlorophenol) isovalerate] known as CPIA-cholesterol ester. This lipophilic conjugate forms rapidly, usually peaking within 60 min, and tends to

persist in tissues, especially in adrenal, spleen, liver, and mesenteric lymph node. Of the four fenvalerate isomers, only the 2R, αS isomer yielded CPIA-cholesterol ester in tissue homogenates of mice, rats, dogs, and monkeys. Mouse tissues showed relatively higher activities than those of other animals. Kidney, brain, and spleen of mice showed relatively higher capacities to form CPIA-cholesterol ester when compared with other mouse tissues; in all cases, enzyme activity localized mainly in microsomal fractions.

Researchers concluded that stereoselective formation of the CPIA-cholesterol ester resulted from the stereoselective formation of the CPIA-carboxyesterase complex only from the 2R, αS isomer, which subsequently undergoes cleavage by cholesterol to yield the CPIA-cholesterol ester that produced giant cells in mice (Kaneko et al. 1986; Miyamoto et al. 1986; Okuno et al. 1986; Miyamoto 1988). These findings strongly support the need for more research on carcinogenic potential of fenvalerate stereoisomers.

Effects

General

Fenvalerate is extremely toxic to representative nontarget aquatic organisms and to some beneficial terrestrial arthropods at concentrations substantially lower than those recommended to control pestiferous insects. Toxic effects are associated primarily with the 2S, αS isomer and are exacerbated at low temperatures. Birds, mammals, and terrestrial plants are normally tolerant.

Target insect species are usually killed at fenvalerate concentrations of 0.015 µg whole body, 0.11 kg/ha by way of aerial application, 5.4 mg/kg in the soil, or 50 mg/kg in the diet. Adverse effects on survival of sensitive aquatic organisms occur at 0.003-0.03 µg/L for crustaceans and 0.09-1.1 µg/L for fish and amphibians. Younger stages of sensitive birds had reduced survival at acute oral doses >500 mg/kg BW and reduced growth at diets containing >750 mg/kg ration; poultry diets containing fenvalerate at <50 mg/kg feed produced no appreciable residues in eggs and meat of exposed birds. Among sensitive mammals, adverse effects on survival were noted at acute oral doses of 50-450 mg/kg BW, dietary concentrations of 50-1,000 mg/kg, and dermal applications of 1,800 mg/kg BW.

Terrestrial Plants and Invertebrates

Terrestrial plants are relatively unaffected by fenvalerate at recommended application rates, as judged by negligible uptake of fenvalerate from treated soils, formation of numerous fenvalerate conjugates that are pharmacologically inactive, and metabolism of the liberated cyano group into amino acids and eventually carbohydrate and protein (Miyamoto 1988).

Adverse effects of fenvalerate on survival of terrestrial arthropods were observed at 0.002-0.015 µg whole body topical application, 0.11 kg/ha aerial application, 5.4 mg/kg in the soil, 50 mg/kg in the diet, and 1.4 g per ant mound (Table 4). Synthetic pyrethroids are more effective in biological systems at low temperatures. The relative sensitivity of insects when compared with mammals is attributed in part to this negative temperature coefficient; thus, warm-blooded animals are less affected than insects and other poikilotherms (Klaassen et al. 1986). Fenvalerate, for example, showed a negative correlation between temperature and toxicity to crickets (*Acheta pennsylvanicus*), being up to 1.9 times as toxic at 15° than at 32° C (Harris et al. 1981). A similar case is made for honeybees (Mayer et al. 1987) and for many species of aquatic invertebrates and fish (Mayer 1987).

Signs of lethal pyrethroid poisoning in insects and other arthropods generally include hyperexcitation, tremors, and convulsions, culminating in paralysis and death (Wouters and Bercken 1978). At sublethal doses equivalent to about 10% of a lethal dose, signs of poisoning in sensitive insects include cessation of feeding, wandering, hyperactivity, restlessness, and flushing out of hiding (Bradbury and Coats 1989a). The American cockroach (*Periplaneta americana*) exposed to topical lethal concentrations of fenvalerate had uncoordinated rapid movements followed by inactivity, appearance of water drops under wings and abdomen, and blackening of the abdomen (Yellamma and Reddy 1987). Signs appeared in < 1 h at lethal concentrations and < 3 h at sublethal concentrations. Roaches exposed to sublethal doses began recovery 6 h after exposure, attaining full recovery at 24 h (Yellamma and Reddy 1987).

Field application rates of fenvalerate at 0.05-0.2 kg/ha are recommended for insect control on many food crops. Under these conditions, fenvalerate remained completely effective for 5 days against adults and nymphs of aphids (*Lipaphis erysimi*), jassids (*Amrasca biguttula biguttula*), and white fly (*Bemisia tabaci*; Jain et al.

1979). Fenvalerate, applied as a drench to mounds, shows promise as an effective control agent of the fire ant, *Solenopsis invicta* (Phillips et al. 1984). Foliar applications of fenvalerate sprays at 135 mg/L effectively controlled various pests in pear orchards of northern California, including pear psylla (*Psylla pyricola*), codling moth (*Laspeyresia pomonella*), and pear rust mite (*Epitrimerus pyri*); populations of spider mites increased, especially the two-spotted spider mite, *Tetranychus urticae* (Riedl and Hoying 1980).

A concentration of 2 mg fenvalerate per liter is frequently applied to soils to control insect pests (Schreiber and Brink 1989). However, several species of soil protozoans (*Blepharisma undulans*, *Colpoda cucullus*, *Oikomonas termo*) have LC10 (9 h) values in the range of 0.1-0.18 mg/L, suggesting that some damage occurs to this group under recommended application protocols (Schreiber and Brink 1989). In fact, all fenvalerate treatments applied to control insect pests of crops also reduced populations of beneficial nontarget organisms, including spiders, ground beetles (*Calosoma* sp.), and crickets (Smith et al. 1989). For example, spiders (*Chiracanthium mildei*) exposed for 48 h to grapefruit leaves that had been dipped 1 h previously for 5 s in aqueous emulsions of fenvalerate at field-recommended application rates all died within 2 days postexposure (Mansour 1987).

Fenvalerate-tolerant strains of arthropods include insect vectors of disease, flies and cockroaches, arthropods of veterinary importance, and agricultural pests (Sawicki 1985). But serious control problems are restricted to only a few areas, such as Central America and Thailand, where insecticidal usage is often excessive (Sawicki 1985). The exact mechanisms of resistance are unknown, although tolerance to fenvalerate in the diamondback moth (*Plutella xylostella*), a worldwide pest of cabbage-type crops, is about 20% genetic, involving several genes and multiple loci (Tabashnik and Cushing 1989). Estimates of heritability in tolerance of insects to all biocides ranges between 14 and 47% (Tabashnik and Cushing 1989). Tolerant insect species, such as larvae of the common green lacewing (*Chrysopa carnea*), and resistant strains of houseflies and lepidopterous larvae may hydrolyze fenvalerate faster than sensitive species or susceptible strains (Glickman and Casida 1982). Fenvalerate-resistant strains of domestic houseflies (*Musca domestica*), for example, when compared with susceptible strains, absorbed up to one-third the fenvalerate, had a metabolic rate up to 8 times faster, began excretion of metabolites 5 times faster, and were twice as resistant to piperonyl butoxide, a synergist applied with fenvalerate (Golenda and Forgash 1989).

The alfalfa leaf cutter bee (*Megachile rotundata*) is the most important insect pollinator of alfalfa grown for seed production in France. Alfalfa is parasitized by many insects, including the flower midge (*Contarina medicaginis*). Fenvalerate, at 0.05 kg/ha, controls the flower midge without harm to alfalfa leaf cutter bees (Tasei and Debray 1985). In general, fenvalerate-treated plants were usually nontoxic to bees after 24 h (Mayer et al. 1987). Fenvalerate does not poison bees when they are in contact with contaminated (100 mg/kg) wax in combs (Stoner et al. 1985). Fenvalerate does not pose a serious threat to honeybees except when dietary levels exceed 50 mg fenvalerate per kilogram (Stoner et al. 1984). Field application of fenvalerate at 0.22 kg/ha on blooming alfalfa, pollen-shedding corn, and blooming red raspberry (*Rubus strigosus*) resulted in reduced honeybee visitation and low to moderate adult bee mortality (Mayer et al. 1987). Caged honeybees exposed to an equivalent dose of fenvalerate at 0.11 kg/ha experienced >50% mortality within 24 h (Table 4). However, field studies showed that 0.11 kg/ha caused no observable adverse effects to bee colonies located adjacent to a treated alfalfa field; researchers concluded that fenvalerate temporarily repelled bees, as judged by a 70% reduction in bee visits to the alfalfa field in the afternoon after application when compared with periods 24 h before and after application (Moffett et al. 1982). Impaired response to scent stimuli, in addition to repellency, may account for a reduction in bee visits. Recent studies by Taylor et al. (1987) suggested that bees surviving LD50 doses of fenvalerate were unable to distinguish odor-mediated learned responses for up to 6 days after treatment. This finding indicates that more research is needed on fenvalerate-associated olfactory inhibition.

Table 4. Lethal and sublethal effects of fenvalerate on terrestrial invertebrates.

Organism, dose and other variables	Effect	Reference[a]
Cricket, *Acheta pennsylvanicus*		
5.4 mg/kg mucky soil	LD50 (18 h)	1
6.5 mg/kg moist sand	LD50 (18 h)	1
Mosquito, *Anopheles stephensi*		
0.002 µg whole body	LD50	12
Indian hive bee, *Apis cerana indica*		
0.128-0.14 µg/bee	LD50, topical application	2
Honeybee, *Apis mellifera*		
0.11 kg/ha, caged bees	57% dead in 24 h	3
Bees caged with alfalfa treated previously with 0.22 kg/ha, and held under various photo-thermal regimens for 24 h	Bees held at 10° C in the dark experienced 96% mortality; bees held at 29° C in the dark had 58% dead; those held at 18-35° C with normal photo-period had 40% dead	3
0.22 kg/ha	Repelled bees for 10 h	4
0.4 kg/ha	Increased mortality for 3 days after exposure	4
0.43 kg/ha, caged bees	All dead in 24 h	3
0.9 kg/ha	Hazardous for 2 h after application	5
Fed sucrose syrup for 7-8.5 weeks containing fenvalerate at 0.1, 1, 10, 50, or 100 mg/kg	At 100 mg/kg, survival was lower and honey production declined. At 50 mg/kg diet, bees consumed less syrup, suggesting repellency. No measurable effect at 10 mg/kg diet and lower. Queens were not affected at any dose level	5
Colonies exposed for several weeks to 1, 10, 100, or 1,000 mg/kg incorporated into beeswax foundation	Adverse effects noted only at 1,000 mg/kg, namely, lower egg hatch and survival. Fenvalerate degradation in beeswax was 11% in 15 days, 21% in 75 days, and 81% in 130 days	6
Mite, *Chorioptes bovis*		
0.05% dip (500 mg/L) for 1 min	Kills all mites and their eggs on Angora goats (*Capra* sp.) within 7 days	7
Alfalfa leaf cutting bee, *Megachile rotundata*		
0.05 kg/ha	No effect on survival or reproduction	8
0.11 kg/ha	82% dead in 24 h	3
0.22 kg/ha	92% dead in 24 h	3
0.43 kg/ha	All dead within 24 h	3
Housefly, *Musca domestica*		
Susceptible strain		
0.013-0.015 µg per fly	LD5, topical dose	12,13
0.028 µg per fly	LD30, topical dose	13
Resistant strain		
0.150 µg per fly	LD5, topical dose	13
Alkali bee, *Nomia melanderi*		
0.11 kg/ha	64% dead in 24 h	3
0.43 kg/ha	All dead in 24 h	3
American cockroach, *Periplaneta americana*		
3.5 µg per roach	Nonlethal	9
10.5 µg per roach	LD50, topical	9
100 µg/kg BW	LD50, topical	12
200 µg/kg BW	LD95, topical. Diazepam delayed onset of action	10

Fire ant, *Solenopsis invicta*		
0.73-1.4 g per mound, applied as drench	All mounds viable after 4 weeks; 70-100% of mounds nonviable after 8 weeks	11
112 or 224 g/ha, aerial application	Ineffective control. After 4 weeks, population levels were 29-35% of controls	11

[a] 1. Harris et al. 1981; 2. Lingappa et al. 1985; 3. Mayer et al. 1987; 4. Moffett et al. 1982; 5. Stoner et al. 1984; 6. Stoner et al. 1985; 7. Wright et al. 1988; 8. Tasei and Debray 1985; 9. Yellamma and Reddy 1987; 10. Gammon et al. 1982; 11. Phillips et al. 1984; 12. Abbassy et al. 1983; 13. Golenda and Forgash 1989

Aquatic Organisms

"Supertoxic" compounds are those with LC50 (96 h) values < 10 µg/L (Scott et al. 1987). Fenvalerate is considered supertoxic, as judged by LC50 (96 h) values of < 1.0 µg/L for sensitive aquatic organisms, and < 10 µg/L for representative aquatic species (Table 5).

Table 5. Lethal and sublethal effects of fenvalerate on aquatic organisms.

Taxonomic group, organism, dose or concentration, and other variables	Effect	Reference[a]
Algae		
Alga, *Chlamydomonas reinhardii* 0.109-5.17 µg/L	Up to 93% of all fenvalerate was adsorbed by algae in 48 h in a biomass-dependent manner when cells increased from 100/mL to 2 million/mL. In absence of alga, up to 33% of fenvalerate added to glass containers was adsorbed to container walls in 48 h	1
Marine algae, 4 species: *Isochrysis galbana, Skeletonema costatum, Thalassiosira pseudonana, Nitzschia angularis*		
1,000 µg/L	Insufficient to produce 50% growth inhibition in 96 h	2
Invertebrates		
Mosquito, *Aedes nigromaculis*		
Multiresistant strain, 4th stage larvae		
5.6 g/ha (0.005 pounds per acre)	58% reduction 6 h after treatment	3
11.2 g/ha (0.01 pounds per acre)	81% reduction 6 h after treatment	3
28.0 g/ha (0.025 pounds per acre)	88% reduction 6 h after treatment	3
Mosquito, *Aedes* spp.		
0.9-10.0 µg/L	LC50-LC90 range for 4th stage larvae	4
1.5-4.0 µg/L	LC50-LC90 range for 24 h stage pupae	4
Rhagionid fly, *Atherix* sp.		
0.021 µg/L	LC30 (28 days)	5
0.029 µg/L	LC50 (28 days)	5
0.032 µg/L	LC50 (96 h)	5
Cladoceran, *Ceriodaphnia lacustris*		
0.01 µg/L	Filtration rate of alga *(Chlamydomonas reinhardii)* significantly decreased after 24-h exposure	6
0.05 µg/L	Decreased food assimilation rate, 24-h exposure	6

0.21 µg/L	50% immobilization of adults in 48 h	6
Chironomids		
4.2-18.0 µg/L	LC50 (24 h), 3 species	7
4.2-80.0 g/L	LC50 (24 h), 8 species	7
Midge, *Chironomus tentans,* fourth-instar larvae		
0.015-0.93 µg/L	Normal burrowing behavior	8
Exposed for 24 h in different sediment types containing initial fenvalerate concentration of 50 µg/kg fresh weight (FW) or 48 h in water above sediment; depuration for 96 h in each case		
Sand (water column and sediment interstitial water concentrations after 24 h were 1.02 and 4.82 µg/L, respectively)	Bioconcentration factor (BCF) of x69 for those held in water column and x 102 for those held in sand	8
Silt (water column 0.17 µg/L, interstitial water 0.15 µg/L)	BCF of x74 for water column, x 116 for silt	8
Clay (water column 0.3 µg/L, interstitial water 0.34 µg/L)	BCF of x32 for water column, x 152 for clay	8
Snail, *Cipangopaludina japonica*		
0.4-0.7 µg/L	BCF of x617 in 30 days	9
Sand shrimp, *Crangon septemspinosa*		
0.04 µg/L	LC50 (96 h)	10,11
American oyster, *Crassostrea virginica*		
1.0 µg/L	BCF of x4,700 in 28 days; depuration to non-detectable levels in <7 days	12
> 1,000 µg/L	Abnormal shell growth in 50% of larvae surviving exposure for 48 h	2, 11
Mosquito, 3 species of *Culex*		
1.2-30.0 µg/L	LC50-LC90 range for 24-h stage pupae	4
4.0-10.0 µg/L	LC50-LC90 range for fourth stage larvae	4
Mosquito, *Culex pipiens pipiens*, larvae		
0.45 µg/L	LC50 (24 h), technical grade	13
30.0 µg/L	LC50 (24 h), emulsifiable formulation	13
11.0 mg/kg diet	LC50 (24 h)	13
Mosquito, *Culex quinquefasciatus*		
7-8 µg/L	LC50-LC90 range for 4th stage larvae	3
Daphnid, *Daphnia galeata mendotae*		
0.005 µg/L	Life cycle (28-day) exposure produced increased longevity but decreased production of young	1
0.01 µg/L, and higher	Decreased survival, reproduction, and generation time in lifetime exposure	1
0.042-0.084 µg/L	Whole body fenvalerate residues in presence of alga (*Chlamydomonas reinhardii*) ranged from 0.51 to 1.08 mg/kg FW after 48-h exposure	14
0.05 µg/L	Decreased filtering rate and assimilation rate of algae after exposure for 24 h; decrease in population numbers in 28-day exposure	1,6

0.051-0. 109 µg/L	In absence of algae, whole body residues ranged from 1.46 to 2.66 mg/kg FW after 48 h	14
0.16 µg/L	50% of immatures immobilized in 48 h	6, 15
0.29 µg/L	50% of adults immobilized in 48 h	6, 15
Daphnid, *Daphnia magna*		
0.25 µg/L	No measurable effect after exposure for 21 days	16, 17
0.5 µg/L	After 21 days, reduced survival and inhibited reproduction	16
0.83 µg/L	50% immobilization of immatures in 48 h	6
2.1-2.5 µg/L	50% immobilization of adults in 48 h	6,18
Daphnid, *Daphnia pulex*		
0.4-0.7 µg/L	BCF of x683 in 30 days	19
Copepod, *Diaptomus oregonensis*		
0.05 µg/L	Decreased filtration rate and food assimilation rate after 48-h exposure	6
0.12 µg/L	50% of adults immobilized in 48 h	6
Mayfly, *Ephemerella* sp.		
0.022 µg/L	LC80 (14 days)	5
0.07 µg/L	50% reduction in swimming ability in 96 h	20
0.08 µg/L	LC50 (96 h)	20
0.93 µg/L	LC50 (24 h)	5,20
Amphipod, *Gammarus pseudolimnaeus*		
0.022 µg/L	LC65 (6 days)	5
0.03 µg/L	LC50 (96 h), adults	5
0.05 µg/L	LC50 (96 h), juveniles	5
0.93 µg/L	All dead or immobilized within 5 h	5
Snail, *Helisoma trivolvis*		
0.021 µg/L	BCF of x1,167 in 28 days	5,7
0.054 µg/L	BCF of x592 in 28 days	5,7
0.79 µg/L	BCF of x386 in 28 days; no adverse effects on survival or behavior	5,7
American lobster, *Homarus americanus*		
0.14 µg/L	LC50 (96 h)	10, 11
Mosquito, 4 species, larvae		
0.9-28.0 µg/L	LC50 (24 h)	7,21
Mysid shrimp, *Mysidopsis bahia*		
0.008-0.021 µg/L	LC50 (96 h)	2,11,12,18,22
97-190 µg/kg sediment, equivalent to 0.03 µg/L water column	58% dead in 4 days, 70% dead in 10 days	23
1,200-1,600 µg/kg sediment, equivalent to 0.06-0.17 µg/L water column	All dead in 4 days	23
Copepod, *Nitocra spinipes*		
0.38 µg/L	LC50 (96 h)	23
Rusty crayfish, *Orconectes rusticus*		
20 µg/L	LC100 (96 h)	24
Grass shrimp, *Palaemonetes pugio*		
0.0016 µg/L	No deaths of larvae in 20 days; larval development prolonged by 2 days	25
0.003-0.013 µg/L	LC50 (96 h)	18,26

0.0032 µg/L	Larvae exposed for 20 days had reduced survival and inhibited metamorphosis	25
0.007 µg/L	LC50 (96 h), emulsifiable concentrate, zoeae, 10 ‰ salinity	27
0.02 µg/L	LC50 (96 h), emulsifiable concentrate, zoeae, 20 ‰ salinity	27
0.040 µg/L	LC50 (96 h), adults, emulsifiable concentrate	27
0.044 µg/L	LC50 (96 h), adults, technical grade	27
0.046 µg/L	Maximum tolerated dose in 6-h exposure, adults	27
0.1-0.15 µg/L	LC50, 90 h after 6-h exposure, adults	27
88-200 µg/kg sediment	LC50(96 h)	18,23
1,000-1,200 µg/kg sediment	LC100 (96 h)	18,23
Pink shrimp, *Penaeus duorarum*		
0.84 µg/L	LC50 (96 h)	12,22
1,200-1,600 µg/kg sediment, equivalent to 0.06-0.17 µg/L	None dead in 10 days	23
10,000-13,000 µg/kg sediment equivalent to 0.2-1.9 µg/L water column	All dead in 4 days	23
Red crayfish, *Procambarus clarkii*		
0.37 µg/L	LC50 (24 h), juveniles	28
Mosquito, *Psorophora columbiae*		
28-50 µg/L	LC50--LC90 range for fourth stage larvae	4
53-82 µg/L	LC50-LC90 range for 24-h stage pupae	4
Stonefly, *Pteronarcys dorsata*		
0.11 µg/L	38% immobilized in 72 h	5
0.13 µg/L	50% immobilized in 72 h	5
0.44 µg/L	38% immobilized in 24 h; 25% dead in 72 h	5
1.02 µg/L	All immobilized in <4 h; most dead in 72 h	
Chordates		
Amphioxus, *Branchiostoma caribaeum*		
760 µg/L	LC10 (10 days)	18
1,000 µg/L	No deaths in 96 h	18
1,600 µg/L	LC50 (96 h)	18
2,500 µg/L	LC100 (96 h)	18,23
100-1,000 µg/kg sand	Effectively colonized in 8 weeks	29
10,000 µg/kg sediments	No deaths in 10 days	18
10,000 µg/kg sand	Unable to effectively colonize during 8-week study	29
Vertebrates		
Bleak, *Alburnus alburnus*		
0.3 µg/L	LC50 (96 h)	23
Desert pupfish, *Cyprinodon macularis*		
25 µg/L	LC50 (48 h)	20
Sheepshead minnow, *Cyprinodon variegatus*		
0.3-5.0 µg/L	Whole body BCF values in fish surviving 28-day exposure were x460 (0.31 µg/L), x360 (0.62 µg/L), x500 (1.2 µg/L), x700 (2.5 µg/L), and x820 (5.0 µg/L)	22
0.56 µg/L	No effect on hatchability, survival or growth in 28-day exposure	17,22
2.2 µg/L	Growth reduction in 28-day exposure	22
4.4-5.0 µg/L	LC50 (96 h), flowthrough assay	2, 12,22,30

120 µg/L	LC50 (96 h), static assay	2
Common carp, *Cyprinus carpio*		
0.4-0.7 g/L	BCF of x69-x 117 in 30-day exposure	19
0.8 µg/L	After exposure for 7 days, 50% excreted 5 days after exposure and 87% in 25 days	19
0.9 µg/L	No deaths in 48 h	31
3.8 µg/L	LC10 (48 h)	31,32
10 µg/L	At 48 h, hypoproteinemia and altered enzyme activity in gills	31,32
21-30 µg/L	LC50 (48 h)	31,32
117 µg/L	LC90 (48 h)	31
Mummichog, *Fundulus heteroclitus*		
1.2-1.8 µg/L	LC50 (96 h)	23,26
Mosquitofish, *Gambusia affinis*		
15.0 µg/L	LC50 (48 h)	20
Channel catfish, *Ictalurus punctatus*		
1.8-1.9 µg/L	LC50 (24 h)	19,28
16.5 µg/L, equivalent to 112 g/ha	Muscle residues in dead fish ranged up to 70 µg/kg FW	28
30.6 µg/L, equivalent to 224 g/ha	Muscle residues in dead fish collected 24 h after treatment ranged up to 160 µg/kg FW	28
Bluegill, *Lepomis macrochirus*		
0.3-1.1 µg/L	LC50 (96 h)	19
0.7 µg/L	Elevated whole body calcium content after 48 h	34
0.9-1.9 µg/L	LC50 (48 h) range for water hardnesses between 6 and 309 mg $CaCO_3$/L, or between 4.2 and 13.6 ‰ salinity	35
10 µg/L	LC100 (96 h)	24
Intraperitoneal injection, in mg/kg body weight (BW)		
0.12	LD50 (48 h), 2S, αS isomer	17,36,37
0.67	LD50 (48 h), technical fenvalerate--mixture of all isomers	13,17,36,37
11.5	LD50 (48 h), 2S, αR isomer	17,36,37
216	No deaths in 48 h, 2R, αS isomer	17,36,37
264	No deaths in 48 h, 2R, αR isomer	17,36,37
California grunion, *Leuresthes* tenuis		
0.06 µg/L	No observable effect concentration in 28-day early life history exposure	23
0.3-0.6 µg/L	LC50 (96 h)	2,30
Inland silverside, *Menidia beryllina*		
1.0 µg/L	LC50 (96 h)	30
Atlantic silverside, *Menidia menidia*		
0.062 µg/L	No observable effect concentration in 28-day early life history exposure	23
0.31-0.69 µg/L	LC50 (96 h)	12, 17, 22
Tidewater silverside, *Menidia peninsulae*		
0.083 µg/L	No observable effect concentration in 28-day early life history exposure	23
1.0 µg/L	LC50 (96 h)	30

Striped mullet, *Mugil cephalus*		
0.58 µg/L	LC50 (96 h)	2, 12,22
African catfish, *Mystus vittatus*		
0.13 µg/L	Safe concentration	38
6.3 µg/L	LC50 (96 h)	38
Rainbow trout, *Oncorhynchus mykiss*		
0.00028 µg/L, exposure for 48 h followed by depuration for 48 h	Tissue residues, in µg/kg FW, were 7.06 in bile; 0.2 in fat; 0.02-0.05 in blood, brain, carcass, gill, kidney, liver, muscle, ovary, erythrocytes, and spleen; and <0.02 in heart, plasma, and testes	39
0.23-2.1 µg/L	LC50 (96 h)	17,18,19, 20,41,50
3.6 µg/L	Hyperactivity in 48 h	41
4.7-76 µg/L	LC50 (24 h)	20,42
300 µg/L	All dead in 10 h. At death, brain residues of 150-160 µg/kg FW. Similar brain residues reported through lethal intraperitoneal and intravenous injection routes	13,39,43
412 µg/L	All dead in 11 h. Before death, trout displayed elevated cough rate, tremors, seizures, elevated urine Na and K, and abnormal blood chemistry. At death, gill histopathology evident, and residues, in µg/kg FW, were 160 in brain, 250 in carcass, and 3,620 in liver	40
Steelhead trout, *Oncorhynchus mykiss*		
Steelhead embryos and larvae exposed intermittently (4.5 h daily) or continuously for 70 days after fertilization to nominal concentrations of 0.018, 0.04, 0.08, 0.135, or 0.505 µg/L		
0.018 µg/L	No deaths. Whole body BCF values at 70 days were X 400 for intermittent exposure and x4,100 for continuous exposure	40
0.04 µ g/L, tested at intermittent exposure only	No deaths; BCF of x3,200	40
0.08 µg/L	For continuous exposure, no effect on survival or growth; BCF of x3,000. For intermittent exposure 32% dead, 50% reduction in growth, BCF of x 10,700	40
0.135 µg/L, continuous exposure only	More than 90% dead, with most dying after 56 days; BCF of x 11,800	40
0.505 µg/L, continuous exposure	All dead. Most died after 49 days	40
Steelhead juveniles exposed intermittently (4.5 h daily) or continuously		
0.088 µg/L	LC50 (96 h), intermittent exposure	40
0.172 µg/L	LC50 (96 h), continuous exposure	17,40
Gulf toadfish, *Opsanus tau*		
1.2 µg/L	No observable effect concentration in 28-day	23

	early life history exposure	
2.4-5.4 µg/L	LC50 (96 h)	2,12,23
Fathead minnow, *Pimephales promelas*		
0.14-0.19 µg/L	Whole body residues of larvae in 28-day exposure ranged from 230 to 880 µg/kg FW. BCF values ranged from x 1,643 to x4,631, in a dose dependent manner	21
0.19 µg/L	No effect on larval survival or growth in 30-day exposure	45
0.33 µg/L	50% of larvae exposed for 96 h developed abnormally	45
0.34 µg/L	LC50 (48 h), adults, mixture of 2S, αS and 2S, αR isomers	36,37
0.36-0.43 µg/L	Exposure of eggs and resultant larvae for 30 days had no effect on hatchability, but adversely affected larval growth, survival, and swimming ability	21,45
0.37 µg/L	Whole body residues of survivors at 96 h contained 598 µg/kg FW, equivalent to BCF of x 1,616	46
0.49 µg/L	After 96 h, survivors contained 911 µg/kg whole body, or BCF of x 1,859	46
0.75 µg/L	After 96 h, survivors contained 1,680 µg/kg BW, or BCF of x2,240	46
0.85 µg/L	LC50 (96 h), larvae	45
1.69 µg/L	LC50 (48 h), adults, technical fenvalerate	37
2.5 µg/L	Schooling behavior absent after 48 h exposure, adults	41
2.85 µg/L	Exposure of larvae for 5 h resulted in 50% deformities 96 h later	45
3.6 µg/L	Hyperactivity after 48 h, adults	41
5.4 µg/L	LC50 (96 h), adults	17
>140 µg/L	LC50 (48 h), adults, mixture of 2R, αS and 2R, αR isomers	36,37
1.0 mg/kg FW whole body	Residue at death of fenvalerate-poisoned fish	13
Northern leopard frog, *Rana pipiens pipiens*		
3 µg/L	All dead in 72 h at 4° C	47
9 µg/L	None dead in 72 h at 20° C	47
130 µg/kg BW	LD50 (24 h), subcutaneous (sc) injection	47
1,800 µg/kg BW	LD50 (24 h). Initially pretreated with sc dose of 10 mg diazepam per kilogram BW followed by sc injection dose of fenvalerate	47
Atlantic salmon, *Salmo salar*		
0.8 µg/L	Some deaths during 96-h exposure; BCF of x200	10
1.2 µg/L	LC50 (96 h)	10
2.0-4.1 µg/L	Some deaths during 54-h exposure; BCF about x 125	10
9.3 µg/L	Some deaths during 16-h exposure; BCF of x40	10
Mozambique tilapia, *Tilapia mossambica*		
9 µg/L	No deaths in 20 days, but significant decreases in activity of catalase superoxide dismutase in liver, gill, and muscle, and significant increases in activity (and presumably metabolism) of	48,49

	fructose-1, 6-diphosphate aldolase in liver, gill, kidney, and brain	
45 µg/L	LC50 (48 h)	48,49

a 1, Day and Kaushik 1987a; 2. Mayer 1987; 3. Mulla et al. 1978; 4. Mulla et al. 1980; 5. Anderson 1982; 6. Day and Kaushik 1987c; 7. Anderson 1989; 8. Muir et al. 1985; 9. Ohkawa et al. 1980; 10. McLeese et al. 1980; 1 l. Tagatz and Ivey 1981; 12. Schimmel et al. 1983; 13. Coats et al. 1989; 14. Day and Kaushik 1987b; 15. Day 1989; 16. McKee and Knowles 1986; 17. Bradbury and Coats 1989b; 18. Clark et al. 1987; 19. Mayer and Ellersieck 1986; 20. Smith and Stratton 1986; 21. Spehar et al. 1982; 22. Hansen et al. 1983; 23. Clark et al. 1989; 24. Bills and Marking 1988; 25. McKenney and Hamaker 1984; 26. Scott et al. 1987; 27. Baughman et al. 1989; 28. Coulon 1982; 29. Tagatz et al. 1987; 30. Clark et al. 1985; 31. Jagan et al. 1989; 32. Reddy and Bashamohideen 1988; 33. Trim 1987; 34. Symonik et al. 1989; 35. Dyer et al. 1989; 36. Haya 1989; 37. Bradbury et al. 1987b; 38. Verma et al. 1981; 39. Bradbury et al. 1986; 40. Curtis et al. 1985; 41. Holcombe et al. 1982; 42. Coats and O'Donnell-Jeffery 1979; 43. Bradbury and Coats 1989a; 44. Bradbury et al. 1987a; 45. Jarvinen et al. 1988; 46. Bradbury and Coats1985; 47. Cole and Casida 1983; 48. Radhaiah and Reddy 1989; 49. Radhaiah et al. 1989.

Signs of fenvalerate poisoning in fish include loss of schooling behavior, swimming near the water surface, hyperactivity, erratic swimming, seizures, loss of buoyancy, elevated cough rate, increased gill mucus secretions, flaring of the gill arches, head shaking, and listlessness before death (Bradbury and Coats 1989a, 1989b). Fenvalerate mainly affects the teleost nervous system, as discussed earlier. It also produces osmoregulatory imbalance, as judged by altered calcium uptake (Symonik et al. 1989), abnormal sodium and potassium excretion rates, and elevated urine osmolality (Bradbury et al. 1987a; Bradbury and Coats 1989a, 1989b). Histological damage to gill surfaces by fenvalerate is attributed to high accumulations in gills, irritation due to elevated mucus secretion, increased ventilation volume, and decreased gill-oxygen uptake efficiency (Bradbury et al. 1986, 1987a; Bradbury and Coats 1989a, 1989b). In fish, as in mammals, fenvalerate toxicity is primarily dependent on the 2S, αS component of the technical mixture. Studies with individual isomers and various freshwater fishes indicate that the 2S, αS isomer is 96 times as toxic as the 2S, αR isomer, and at least 1,766 times as toxic as the 2R, αS or 2R, αR isomers (Table 5).

Laboratory studies with fenvalerate and aquatic organisms indicate marked differences in sensitivity among taxonomic groups (Table 5). Crustaceans were the most sensitive group: reduced survival was evident between 0.0032 and 0.03 µg/L, and impaired feeding and reproduction was evident between 0.0016 and 0.01 µg/L. Fish and amphibians were more tolerant to fenvalerate than were crustaceans: increased mortality was evident between 0.088 and 1.1 µg/L, and no adverse effects were demonstrated in several species between 0.062 and 0.083 µg/L, although certain salmonids showed high uptake at concentrations as low as 0.0003 µg/L. Algae, molluscs, and chordates were comparatively resistant to fenvalerate (Table 5). Survival patterns of fenvalerate-stressed aquatic organisms are significantly altered, sometimes by an order of magnitude or greater, by selected biological, chemical, and physical variables. In general, increased mortality was associated with the following: reduced metabolism and excretion (Bradbury et al. 1986; Bradbury and Coats 1989a; Coats et al. 1989; Haya 1989); depleted glycogen stores due to starvation (Haya 1989); larval and juvenile stages of development (Spehar et al. 1982; Bradbury and Coats 1989a; Haya 1989); low concentrations of humic acid and other dissolved materials (Coats et al. 1989); low particulate loadings (Coulon 1982; Coats et al. 1989); increased water hardness (Dyer et al. 1989; Coats et al. 1989); increased exposure time and bioavailability (Spehar et al. 1982; Curtis et al. 1985); emulsifiable formulations (Trim 1987; Haya 1989); low temperatures (Cole and Casida 1983; Bradbury and Coats 1989a; Coats et al. 1989); and the 2S, αS component (Ohkawa et al. 1980; Bradbury and Coats 1989a; Coats et al. 1989; Haya 1989). Fenvalerate-protective agents include diazepam and endosulfan. Diazepam provides up to 14-fold protection to frogs against toxic doses of fenvalerate (Cole and Casida 1983); endosulfan provides limited protection to estuarine fish and shrimp (Scott et al. 1987; Trim 1987).

Bioaccumulation factors for fenvalerate by representative freshwater and estuarine organisms during exposure for 28-30 days to various sublethal doses ranged from 40 to 570 times for fish, 356 to 4,700 times for invertebrates, and 477 to 933 times for algae (Smith and Stratton 1986). Because of its unusually high lipophilicity, fenvalerate is accumulated at only 30% efficiency by aquatic fauna, and uptake is not dose

dependent (Coats et al. 1989). Contamination of algal food of daphnids with fenvalerate does not seem to contribute to an increase in whole body burdens, although reduced filtration rates due to toxicity could also account for a reduced intake of fenvalerate adsorbed to algae (Table 5; Day and Kaushik 1987b, 1987c).

Fenvalerate applications of 0.055-0.220 kg/ha are recommended for control of pestiferous crop insects, but these levels are rapidly fatal to nontarget organisms if introduced accidentally into aquatic environments (Day et al. 1987). In one study, large earthen ponds containing red crayfish (*Procambarus clarki*) were treated with fenvalerate at concentrations equivalent to 28, 56, 112, or 224 g/ha. All crayfish died within 24 h at all concentrations tested (Coulon 1982). After 3 days, ponds dosed with 112 g/ha and lower were not lethal to crayfish exposed for 24 h. The 224 g/ha pond remained toxic to crayfish after 72 h (71% dead) and 120 h (32% dead); mortality was negligible (<10%) after 168 h (Coulon 1982). Fenvalerate applications of 28-112 g/ha (0.025—0.1 pounds per acre) usually control 90-100% of floodwater mosquitos and stagnant water mosquitos. But at 2 -11 g/ha equivalent, the following effects are reported: mayfly naiads are eliminated; populations of diving beetles, cladocerans, and dragonfly naiads are suppressed for up to 3 weeks; zooplankton filtration rates are reduced; colonization processes are altered; and algal and rotifer populations increase due to lack of cladoceran grazing and competition (Mulla et al. 1978, 1980; Tagatz and Ivey 1981; Anderson 1982; Spehar et al. 1982; Hansen et al. 1983; Smith and Stratton 1986; Day et al. 1987; Bradbury and Coats 1989a; Day 1989).

Sediment—water interactions are important to the understanding of fenvalerate toxicokinetics. Addition of soil to fenvalerate-treated waters reduced toxicity to channel catfish (*Ictalurus punctatus*) through adsorption of fenvalerate to clay and organic components of soil; however, crayfish were not protected (Coulon 1982). Chironomid larvae held in water on sand initially spiked with 50 µg fenvalerate per kilogram accumulated up to 15 times as much fenvalerate than did larvae held in water above spiked silt or clay; a similar pattern was evident at an initial concentration of 5 µg/kg (Muir et al. 1985). This phenomenon is attributed to the greater bioavailability of fenvalerate in sand, as judged by elevated sediment interstitial water concentrations in sand when compared with those of silt or clay (Table 5; Muir et al. 1985). Mortality was observed in systems where fenvalerate concentrations in sediments were sufficient to establish lethal concentrations in the overlying water through sediment-water partitioning; lethal effects at nominal sediment concentrations of 0.1 mg fenvalerate per kilogram were observed for mysids (*Mysidopsis bahia*) and grass shrimp (*Palaemonetes pugio*) and at 10 mg/kg for pink shrimp (*Penaeus duorarum*; Clark et al. 1989). Because fenvalerate readily sorbs and binds to organic and inorganic particulate matter, it is difficult to predict its toxic effects on aquatic biota after runoff from agricultural areas or from discharges into particulate-laden habitats (Clark et al. 1989).

Birds

Birds that died of fenvalerate poisoning contained residues of 0.1 to 1.26 mg/kg brain fresh weight (FW) and 0.74 mg/kg liver FW, based on acute oral doses of 500 to 4,000 mg/kg BW (Table 6); juveniles were more sensitive than adults (Bradbury and Coats 1989a). When compared to other synthetic pyrethroids tested in laying hens, fenvalerate provided higher, more persistent residues in tissues (Saleh et al. 1986a). Birds given single oral doses of fenvalerate as low as 250 mg/kg BW experienced significant weight loss (adults) or a reduction in the rate of weight gain (immatures); similar signs were noted at dietary levels of 15,000 mg/kg ration but not at 7,500 mg/kg feed (Bradbury and Coats 1982). Poultry diets that contain fenvalerate at <50 mg/kg feed do not produce an appreciable concentration of residues in eggs or meat of exposed birds (Akhtar et al. 1989).

Adult Japanese quail (*Coturnix japonica*) given a single oral dose of 4,000 mg/kg BW started feeding normally (Mumtaz and Menzer 1986), but in about 90 min they became hyperactive. Hyperactivity increased until 2 h postdosing, at which time feeding ceased. At 4 h, they had convulsions, irregular movements, jerking, and twitching; they became progressively ataxic and uncoordinated. One quail died at 4 h, another at 8 h. By 24 h, most of the survivors had resumed feeding, but they had an odd standing posture: head held high above the body, legs extended as far straight as possible, and wings held in an upright position close to the body. By 48 h the survivors seemed to be feeding and drinking regularly; growth was normal 14 days after exposure (Mumtaz and Menzer 1986). Signs of intoxication in fenvalerate-poisoned northern bobwhites (*Colinus virginianus*) usually appeared within 2 h and included hyperactivity, irregular locomotion, ataxia, and spastic muscle contractions (Bradbury and Coats 1982, 1989a). Bobwhites use croplands for feeding, and insects are an important dietary item of chicks and adults in summer months. Little potential exists for adverse effects of fenvalerate on bobwhite and other gallinaceous bird populations from dietary exposures, however, because

insects from sprayed fields had maximum whole body residues of only 0.5 mg/kg—a level far below that associated with adverse effects (Table 6; Bradbury and Coats 1982).

Table 6. Lethal and sublethal effects of fenvalerate on birds.

Organism, dose, and other variables	Effect	Reference[a]
Northern bobwhite, *Colinus virginianus*		
0.1-1.26 mg/kg fresh weight (FW), brain	Residues in dead birds following single oral exposure; residues increased in dose-dependent manner in dose range of 500-4,000 mg/kg body weight (BW)	1
0.74 mg/kg FW, liver	Mean residue in dead birds following single oral exposure; residue seemingly independent of dose	1
250 mg/kg BW, single oral dose, immatures, age 5 weeks	No deaths in 14 days	1
500 mg/kg BW, single oral dose, immatures	20% dead within 25 h	1
1,785 mg/kg BW, single oral dose, immatures	LD50. All deaths occurred 3 to 25 after dosing	
4,000 mg/kg BW, single oral dose, immatures	70% dead within 24 h; remainder survived at least 14 days	1
4,000 mg/kg BW, single oral dose, adults. age 19 weeks	No deaths in 14 days; all appeared normal 24 h after dosing	1
15,000 mg/kg diet, 5 days of exposure plus 3 days of clean feed	Insufficient to kill 50% of 2-week-old chicks	1
Japanese quail, *Coturnix japonica*		
4 daily treatments of 100 mg/kg BW, oral route	Maximum tissue residues 72 h after the last dose, in mg/kg FW, were 3.1 in fat, 0.9 in skin, 0.7 in liver, 0.2 in heart and kidney, 0.1 in lung, and 0.02 in brain	2
2,000 mg/kg diet, 6-week-old females, 7-day feeding	Increased liver aldrin epoxidase, intestinal cytochrome P-450, and intestinal erthoxyresorufin dealkylase	3
4.000 mg/kg BW, single oral dose. 14-day observation	75% excreted in <6 h, 90% within 24 h. Tissue residues were highest at 3 h in liver (9 mg/kg FW) and gradually declined, while in blood it peaked within 2 h and fell quickly to an equilibrium level of 1.5 mg/L	2
American kestrel, *Falco sparverius*		
Oral dose of 1,000, 2,500, or 4,000 mg/kg BW; maintained at 22° C or -5° C for 10 h after dosing	No deaths. Mild intoxication and elevated plasma alanine amino-transferase activity; holding temperature did not affect toxicity	8
Domestic chicken, *Gallus* sp.		
0.03 mg/kg diet for 32 days	No detectable residues in tissue or eggs	6
5 mg/kg BW, single	Up to 85% of administered dose eliminated	4

oral dose, residues measured in egg albumin and yolk, and various tissues during observation period of 144 h	in 24 h, 88% in 72 h. Maximum residues, in mg/kg FW, were 0.5 in kidney (24 h), 0.48 in yolk (96 h), 0.46 in liver (24 h), 0.25 in plasma (24 h), 0.19 in abdominal fat (96 h), 0.18 in albumin (24 h), 0.14 in blood cells (24 h), 0.07 in both leg muscle and heart at 144 h, and not detectable in subcutaneous fat and breast muscle	
10 mg/kg BW, single oral dose, laying hens, residues measured over 14 days	Maximum residues, in mg/kg FW, were 4.7 in blood (24 h), 4.0 in brain (7 days), 1.0 in kidney (48 h), 1.0 in heart (3 days), 0.3 in egg yolk (5 days), 0.25 in kidney (14 days), 0.23 in egg white (5 days), 0.2 in skin (5 days), 0.18 in liver (48 h), and <0.15 in fat and ovary	5
Oral doses of 1,000 mg/kg BW for 5 days, and again at 21 days	No neurotoxic effects observed in hens	6
1,500 mg/kg BW	Acute oral LD50	7

[a] 1. Bradbury and Coats 1982; 2. Mumtaz and Menzer 1986; 3. Riviere et al. 1983; 4. Akhtar et al. 1989; 5. Saleh et al. 1986a; 6. Reed 1981; 7. Smith and Stratton 1986; 8. Rattner and Franson 1984.

Birds rapidly and efficiently metabolize fenvalerate by hydrolytic cleavage of the ester bond followed by extensive hydroxylation of the acid moiety at the carbon adjacent to the carboxyl group, the methyl group, or both. Major metabolites identified in liver preparations were 2-(4-chlorophenyl)-3-methylbutyric acid, 4-hydroxyfenvalerate, 3-phenoxybenzaldehyde, and 3-phenoxybenzoic acid (Akhtar 1983; Mumtaz and Menzer 1986; Akhtar et al. 1989; Bradbury and Coats 1989a). Liver microsomal drug-metabolizing enzymes usually play an important role in pesticide metabolism; however, fenvalerate and other synthetic pyrethroids are very weak inducers of avian microsomal enzymes (Riviere et al. 1983). Birds are more resistant to fenvalerate than are mammals, as judged by studies with Japanese quail and rats. Quail excreted fenvalerate more rapidly, had lower absorption, and faster metabolism; the oral LD50 for quail was >4,000 mg/kg BW versus 450 mg/kg BW for rat, almost an order of magnitude higher (Mumtaz and Menzer 1986).

Mammals

In general, fenvalerate administered to mammals was rapidly eliminated and had little tendency to accumulate in tissues (Table 7). Fenvalerate killed sensitive species of mammals at a brain injection concentration of 1.0 mg/kg FW brain (equivalent to 14 µg/kg BW), an intraperitoneal injection concentration of 3.9 mg/kg BW, acute oral doses of 50 to 450 mg/kg BW, dietary levels of 50 to 1,000 mg/kg feed, and an acute dermal concentration of 1,800 mg/kg BW; in all cases the 2S, αS isomer was the most toxic (Table 7). Measurable residues of fenvalerate were detected in tissues of sensitive mammals at 0.15 mg/kg diet, 0.15 mg/kg BW applied dermally six times over a 3-week period, and at 2.5 mg/kg BW given orally; in all cases the 2R, αS isomer was taken up 9-16 times over other isomers (Table 7). Behavioral alterations (e. g., change in drinking water preference) occurred in mice after a single oral dose of 0.3 mg/kg BW (Table 7). No significant adverse effects were observed in dogs on diets equivalent to 12.5 mg/kg BW daily for 90 days or in rats on diets containing fenvalerate at 250 mg/kg (equivalent to 12.5 mg/kg BW) for 2 years (Table 7).

At sublethal doses in rodents (i.e., 100 mg/kg BW), fenvalerate produces neurological toxicity but no histological damage; at higher doses, pathological alterations in peripheral nerves occur (Bradbury and Coats 1989a). Rats given acutely toxic doses of fenvalerate showed histopathological changes such as axonal swelling and degeneration and myelin fragmentation of the sciatic nerve; the significance of these findings is unclear (Gray and Soderlund 1985).

Route of administration may account for wide variations in the toxic action of fenvalerate. Most authorities agree that fenvalerate is most toxic to rodents when administered by intercerebroventricular injection relative to other routes—indicating the importance of the brain in the Type II poisoning syndrome; fenvalerate was

decreasingly toxic when administered intravenously, intraperitoneally, orally, and dermally (Lawrence and Casida 1982; Flannigan et al. 1985; Grissom et al. 1985; Bradbury and Coats 1989a; Williamson et al. 1989).

Differences in fenvalerate metabolism occur, even among closely related species such as rats and mice (Kaneko et al. 1981). In both species, regardless of sex, dose level, or chiral isomer, fenvalerate is metabolized primarily by oxidation at the 2'-, 4'-phenoxy positions of the alcohol moiety and at the C-2 and C-3 positions of the acid moiety, by cleavage of the ester linkage, by conversion of the CN group to SCN^- and CO_2, and by conjugation of the resultant carboxylic acids and phenols with glucuronic acid, sulfuric acid, and amino acids. However, the taurine conjugate of 3-phenoxybenzoic acid was found in mice but not in rats; 4'-hydroxylation of the alcohol moiety and the sulfate conjugate of 3-(4'hydroxyphenoxy) benzoic acid occurred to a greater extent in rats than in mice; and more thiocyanate was excreted in mice than in rats (Kaneko et al. 1981). Dogs are remarkably different from rodents in their ability to metabolize fenvalerate (Kaneko et al. 1984). Four major differences have been observed: (1) Rats and mice show hydroxylation of the 2' position of the alcohol moiety, whereas dogs do not; (2) dogs produce 3-phenoxybenzyl alcohol and 3-(4'-hydroxyphenoxy) benzyl alcohol, whereas rodents do not; (3) the predominant conjugate of the alcohol moiety in dogs is 3-phenoxybenzoyl glycine, but this is only a minor conjugate in rodents; and (4) dogs produced more glucuronides of acid moiety and their hydroxy derivatives than did rats and mice. The proposed fenvalerate metabolic pathways in dogs (Kaneko et al. 1984) suggest that species differences and pathways are important and require more research.

Table 7. Lethal and sublethal effects of fenvalerate on mammals.

Organism, route of administration, dose, and other variables	Effect	Reference[a]
Cattle, *Bos* spp.		
Diet		
Fed 0.15 mg/kg feed for 21 days	Residues ranged up to 0.002 mg/L in milk, 0.022 mg/L in cream, 0.014 mg/kg fresh weight (FW) in fat, 0.006 mg/kg FW in liver, and <0.01 mg/kg FW in bone, brain, muscle, kidney, or lung	1
Dairy cows fed 5 or 15 mg/kg ration daily for 4 days; milk and feces collected during exposure and 6 days after exposure	Maximum concentrations of fenvalerate in milk during exposure were 48 µg/L (377 µg/kg dry weight [DW]) in the 5 mg/kg group and 250 µg/L (1,950 µg/kg DW) in the 15 mg/kg group; fenvalerate was not detectable 2 days after exposure in the low dose group and 6 days after exposure in the high dose group. In feces, the maximum concentrations ranged between 34.9 and 50.4 mg/kg DW during exposure; detectable concentrations in both groups were evident 6 days after exposure	2
Fed 10.9 mg/kg feed for 28 days	Maximum residues, in mg/kg FW, were 0.13 in whole milk, 1.0 in cream, 0.8 in fat, and 0.06 in muscle	1
Dermal		
Dairy cows of mean weight 671 kg given 0.1 g topically (0.1 mg/kg body weight [BW]) in six consecutive treatments at intervals of 3 or	After last application, no detectable fenvalerate residues were found in milk after 6 h; maximum residues in milk were 1.14 µg/L after 3 days, 0.42 in 4 days, and not detectable after 7 days	3

4 days (total 0.6 g)		
Dairy cows given three consecutive topical treatments of 0.5 g (0.5 mg/kg BW; total 1.5 g) at 2-week intervals	Maximum residues in milk, in µg/L, after last treatment were 6.8 after 6 h, 2.9 after 3 days, 2.5 at 7 days, 1.3 at 14 days, and <0.2 at 3 weeks. About 0.05% of the applied fenvalerate appears in the milk as the intact insecticide over the 59-day study	3
Dog, *Canis familiaris*		
Oral		
Male beagles, 7 months old, 1.7 mg/kg, single dose	About 84% eliminated from body within 3 days through urine and feces. Half-time persistence of 2 h in blood, and 0.7-1.0 day in whole body	4
Diet		
Fed up to 12.5 mg/kg BW equivalent for 90 days	No evidence of toxicity at any level	1
Groups of 12 beagles (6 males, 6 females 5 months old, fed fenvalerate at 250, 500, or 1,000 mg/kg feed for 6 months	For all groups, dose-dependent increase in emesis, head shaking, biting of the extremities, blood chemistry alterations, ataxia, tremors, and hepatic multifocal microgranulomas. Some males in the 1,000 mg/kg group were killed after 2 weeks while in coma. Sex-related differences were noted: increased cholesterol and alkaline phosphatase in males; poor growth and enlarged adrenals, ovaries, liver, and kidneys in females. Lymph node histopathology was observed in female 500 and 1,000 mg/kg group and in the male 1,000 mg/kg group	5
Hamster, *Cricetus* sp.		
In vitro		
5-40 mg/L	Nontoxic to isolated cells	6
Oral		
12.5 or 25 mg/kg BW for 2 days	No chromosomal aberrations in bone marrow	1
Domestic cat, *Felis domesticus*		
Dermal		
Topical aerosol treatment of fenvalerate plus Deet (N-N-diethyl-m toluamide) to control fleas and ticks	Kitten, 3 months old, died in 6 h following hypersalivation, ataxia, depression, and seizures. No histopathology at necropsy; brain AChE activity normal. Fenvalerate residues, in µg/kg, were 345,000 in skin, 230 in kidney, 150 in liver, 10 in brain. Adult (4 years old) showed signs of toxicosis 4 h after topical application; by 30 h, animal had lowered body temperature, bradycardia, and other signs of fenvalerate poisoning. At death, shortly thereafter, fenvalerate residues were 1,000 µg/kg in skin and 20 µg/kg in liver	7
Domestic mouse, *Mus* spp.		
Intercerebroventricular injection		
0.2 mg/kg BW	95% dead; 50% show signs of poisoning	8

	within 6 min of brain injection	
1.0 mg/kg FW brain, equivalent to 14 µg/kg BW	LD50; 2S, αS isomer	9
Oral, single dose		
0.3, 3, or 30 mg/kg	No deaths in any group. The 30 mg/kg group were hyperactive for 4 h after dosing. All mice preferred 0.3% saccharin solution to water	10
2.5 mg/kg BW of each of the 4 chiral isomers; tissue residues measured 6 days after administration	Residues of the 2R, αS isomer were 9-16 times as high in adrenal as that of the other 3 isomers (2S, αS; 2S, αR; 2R, αR), at least 20 times as high in heart, 6-14 times as high in kidney, 17-28 times as high in liver, at least 15 times in lung, 3-6 times in mesenteric lymph node, and >30 times as high in spleen	11
7 mg/kg BW, residues measured 6 days later	Maximum concentrations, in mg/kg FW, were 7.3 in hair, 0.9 in fat, 0.5 in skin, 0.3 in blood, and 0.08 in liver	12
8.4 mg/kg BW, residues measured 7 days later	Maximum concentrations, in mg/kg FW, were 2.3 in hair, 0.8 in fat, 0.3 in stomach contents, 0.1 in skin, and 0.05 in blood	12
50 mg/kg BW	LD50; 2S, αS isomer	13
72-845 mg/kg BW, various laboratory strains	LD50	1,13,14, 15,16
200 mg/kg BW	Slight increase in frequency of chromosome aberrations in bone marrow cells	17
>600 mg/kg BW	LD50; 2S, αR isomer	13
>5,000 mg/kg BW	LD50; 2R, αR isomer	13
Dermal		
I mg/kg BW, single application	Penetration through skin was 1.9% at 60 min, 2.2% at 6 h, and 9.1% at 24 h. Of penetrated dose, maximum percent distribution was 83% in carcass at 60 min, 1.3% in blood at 6 h, 11.5% in liver at 6 h, 2.2% in kidney at 6 h, 0.7% in fat at 6 h, and 73% in feces at 24 h	18,19
60, 600, or 1,800 mg/kg BW, single application	At 1,800 mg/kg BW, 20% died in 96 h; no deaths in other groups. Survivors in 600 and 1,800 mg/kg groups were hyperactive. All survivors preferred 0.3% saccharin solution to water	10
Intraperitoneal injection		
3.9 mg/kg BW	LD50; 2S, αS isomer	9
62 mg/kg BW	LD50	14
89 mg/kg BW	LD99	14
Diet		
Fed 5, 15, or 50 mg/kg on days 6-15 of gestation	Maternal toxicity at 50 mg/kg BW, but no effect on embryonic development	1
Fed 10, 50, 250, or 1,250 mg/kg feed for 2 years	Increased mortality, reduced growth, disrupted enzyme activity at 1,250 mg/kg. Nonneoplastic microgranulomas in lymph, liver, and spleen of 250 and 1,250 mg/kg male mice; less severe microgranu-	34

	latomous changes in mesenteric lymph node of 50 and 250 mg/kg groups; no observable effect at 10 mg/kg diet	
Fed 50, 250, or 1,250 mg/kg feed for 2 years	Nonneoplastic pathological changes diagnosed as multifocal microganulomas in lymph nodes, liver, and spleen of males at all dose levels, and in females at the 250 and 1,250 mg/kg diet level	20
Fed 100, 300, 1,000, or 3,000 mg/kg feed for 78 weeks	No evidence of carcinogenicity at any does tested. No-observable-effect-level (NOEL) was 100 mg/kg diet (equivalent to 15 mg/kg BW); dose-related effects noted in liver at 300 mg/kg diet and higher	1
125 mg/kg diet, 8 weeks, 2R, αS isomer	No deaths; 70% incidence of microgranulomas in liver	20
Fed 500 mg/kg diet of three isomers (2S, αS; 2R, αS; 2R, αR) for 2 weeks	Residues, in µg/kg FW, of the 2R, αS isomer were significantly higher than that of other isomers tested in adrenal (173 versus 10-21), heart (15 versus 2), kidney (22 versus 9-10), liver (105 versus 13), lung (31 versus 2-5), mesenteric lymph nodes (86 versus 8-12), and spleen (21 versus 1)	11
500 mg/kg diet, 13 weeks	No deaths; 100% incidence of microgranulomas or giant cell infiltration	20
500 mg/kg diet, 52 weeks, 2S, αS isomer	No microgranulomas or giant cell infiltration in liver, spleen, or lymph nodes	20
500 or 1,000 mg/kg diet, 52 weeks, 2S, αR isomer	No deaths; no microgranulomas	20
1,000 mg/kg diet, 2 weeks, 2S, αS isomer	Severe hyperexcitability and tremors and 100% kill. No microgranulomas present	20
1,000 mg/kg diet, 4 weeks, 2R, αS isomer	No deaths; 100% incidence of microgranulomas	20
1,000 mg/kg diet, 13 weeks, 2R, αR isomer	No deaths; no microgranulomas or giant cell infiltration	20
2,000 mg/kg diet, 2 weeks, 2S, αR isomer	All dead; no microgranulomas	20
Intraperitoneal (ip) injection		
40 mg/kg BW, five daily doses (total of 100 mg/kg BW)	Significant increase in frequency of chromosome aberrations induced in bone marrow cells—but frequency lower than single dose ip injection of 200 mg/kg BW	17
Subcutaneous injection		
Given five daily doses totaling 100, 150, or 200 mg/kg BW	After 35 days, incidence of sperm abnormalities was significantly increased over controls: 3.3% abnormal sperm in 100 mg/kg group, 5.9% in 150 mg/kg group, and 6.3% in 200 mg/kg group versus 2.3% in controls	17

Rabbit, *Oryctolagus* sp.		
Dermal		
0.13 mg/cm^2 skin, applied 5 days weekly for 16 weeks	Minor increases in cutaneous blood flow, skin reddening, and skin thickening	22
In vitro		
0.2-10 mg/L, liver and muscle tissues	Synthesis of protein and RNA inhibited in muscle in a dose-dependent manner; maximum inhibition was 0.2 mg/L for RNA synthesis and 10 mg/L for protein. The reverse was observed in liver; maximum stimulation was at 2 mg/L	23
Domestic sheep, *Ovis aries*		
Diet		
3-month-old lambs fed 45 mg/kg feed for 10 days, equivalent to 20 mg daily	Tissue residues, in mg/kg DW, were 3.6-4.4 in renal fat, 0.2 in leg muscle, and 0.1 in liver	24
Laboratory white rat, *Rattus* spp.		
Diet		
Fed 1, 5, 25, or 250 mg/kg ration for up to 2 years	No measurable effect on body weight, food consumption, hematology, clinical chemistry, or organ weights of any diet	25
Fed diets containing 1, 5, 25, or 250 mg/kg feed for three generations	No teratogenic or fetotoxic effects. Females in third generation fed highest dose had reduced growth	1
Fed 1, 5, 25,250, or 500 mg/kg ration for 2 years	NOEL at 250 mg/kg, equivalent to 12.5 mg/kg BW; growth suppression at 500 mg/kg diet	1
Fed 50, 150, 500, or 1,500 mg/kg feed for 15 months	NOEL at 50 mg/kg, equivalent to 2.5 mg/kg BW. Higher doses had adverse effects on growth, food consumption, and behavior	1
Fed 1,000 mg/kg ration for 2 years	Growth inhibited; organ-BW ratios increased in brain, liver, spleen, kidney, heart (females), and testes. Mammary and pituitary tumors commonly observed in treated and in control groups. No statistically significant difference in number or type of neoplasms, except for mammary tumors	25
Oral		
1.7 mg/kg BW daily for 5 consecutive days, or single dose of 8.4 mg/kg BW. Technical fenvalerate and 2S, αS isomer tested separately	No apparent differences in the nature and amount of metabolites and in the pattern of excretion and tissue residues between the racemic mixture and the 2S, αS isomer	26
Single dose, 2.5 mg/kg BW; residues, in µg/kg FW, in tissues measured 6 days after exposure		
2R, αS isomer	Residues in tissues were usually	11

	much higher than those of other isomers tested: adrenal, 371; fat, 304; heart, 40; kidney, 25; liver, 72; lung, 25; mesenteric node, 318; and spleen, 62	
2S, αS isomer	Residues were 511 in fat, 45 in mesenteric lymph node, and <22 in other tissues	11
2S, αR isomer	Fat contained 326, mesenteric lymph node 68, and other tissues <20	11
2R, αR isomer	Fat contained 756, mesenteric lymph node 94, and other tissues <23	11
Single dose of 3 mg/kg BW, individual isomers tested, fat analyzed periodically during 21 -day observation	Half-time persistence of all four isomers in fat ranged between 7 and 10 days; mean residues at 24 h and 21 days after exposure were 0.64 and 0.08 mg/kg FW, respectively	27
Decarboxyfenvalerate, single dose. 4 mg/kg BW	Almost completely eliminated in a few days, mainly by way of the feces; little translocation from GI contents and liver to other tissues; Tb ½ of 10 h in pancreas and <7 h in all other tissues	28
Single dose, 7 mg/kg BW, residues measured 6 days later	Residues, in µg/kg FW, were about 1,250 in blood, 1,200 in fat, 2,300 in hair of females, 37,000 in hair of males, 370 in liver, and 5,800 in skin	12
Single doses between 15 and 200 mg/kg BW	At 90 rain, rats showed a dosage-dependent decrease in locomotor activity and operant response rates	29
Adults given 25 or 75 mg/kg BW, 5 days a week for 10 weeks	At low dose, no signs of neurotoxicity or significant hepatotoxicity. At high dose, neurotoxicity evident only during first week; liver contained significantly elevated number of foci/cm3 and a larger percentage of liver tissue occupied by foci when compared to controls	30
450-3,000 mg/kg BW	LD50; variability due to solvent	1
451 mg/kg B W	LD50	15,21,31
Single dose of 850 mg/kg BW, observed for 7 days	Signs of toxicosis appeared in 2 h; if untreated, 80% died. Intraperitoneal injection of 400 mg/kg BW of methocarbamol followed by repeated doses of 200 mg/kg BW at every onset of signs eliminated signs of poisoning within 17 h and prevented mortality	32
Dermal		
31,155, or 310 mg/kg BW, 5 days weekly for 2 weeks; observed for 2 weeks after last treatment	No deaths. Altered blood chemistry that returned to normal during observation period, except for elevated serum alkaline phosphatase activity	33
Intravenous injection		
50-100 mg/kg BW	LD50	21

[a] 1. Reed 1981; 2. Wszolek et al. 1980; 3. Frank et al. 1984; 4. Kaneko et al. 1984; 5. Parker et al. 1984b; 6. Pluijmen et al. 1984; 7. Dorman et a1. 1990; 8. Gammon et al. 1982; 9. Lawrence and Casida 1982; 10. Mitchell et al. 1988; 11. Kaneko et al. 1986; 12. Kaneko et al. 1981; 13. Bradbury and Coats 1989a; 14. Williamson et al. 1989; 15. Bradbury and Coats 1989b; 16. El-Sewedy et al. 1982; 17. Pati and Bhunya 1989; 18. Grissom et al. 1985; 19. Grissom et al. 1987; 20. Okuno et al. 1986; 21. Gray and Soderlund 1985; 22. Flannigan et al. 1985: 23. El-Sebae et al. 1988; 24. Wszolek et al. 1981a; 25. Parker et al. 1984a; 26. Ohkawa et al. 1979; 27. Marei et al. 1982; 28. Mikami et al. 1985; 29. Crofton and Reiter 1988; 30. Flodstrom et al. 1988; 31. Smith and Stratton 1986; 32. Hiromori et al. 1986; 33. Saleh et al. 1986b; 34. Parker et al. 1983.

Cattle (*Bos* spp.) protected against various insect pests by fenvalerate-impregnated ear tags grow better than unprotected cattle. Beef cattle were protected against horn flies (*Haematobia irritans*) and other blood-sucking dipterans by fenvalerate-impregnated ear tags; during a 115-day grazing period, protected cattle had greater weight gain than unprotected cattle (Haufe 1982). This technique may have application in protecting fly-infested threatened or endangered species of mammals. Dairy cows tagged with 8% fenvalerate ear tags showed a 99.9% reduction in horn flies over a 16-week trial (Block and Lewis 1986). But other species of flies (housefly; stable fly, *Stomoxys calcitrans*; face fly, *Musca autumnalis*) were not controlled to the same extent, and they increased as horn fly populations decreased. Protected cows produced 117 kg more milk in 16 weeks than did unprotected cows; fat and protein percentages in milk were the same for both groups. The higher milk production in the fenvalerate-tagged group was attributed to more uninterrupted forage time, greater forage consumption, and more efficient energy utilization because less energy was expended on avoiding or removing flies (Block and Lewis 1986). Similar results were reported in dairy cows in a 12-week study (Harris et al. 1987). Fenvalerate was adequately distributed over the entire body and persisted for at least 80 days on the hair of cattle with one ear tag containing 10.5 g active ingredients (Yeung et al. 1989). Residues in hair were highest at 14 days (18.4 mg/kg FW) and lowest at 80 days (1.3-3.0 mg/kg FW). All four stereoisomers were present on cattle hair, and no stereoselective degradation occurred. Hair contained 14.8 mg/kg FW fenvalerate after 30 days with two ear tags (Yeung et al. 1989).

Cows fed fenvalerate in grain at 10 mg/kg diet for 4 days excreted most of the fenvalerate, essentially unchanged, in urine (Wszolek et al. 1981b). A secondary excretion route is feces, accounting for about 25% of the ingested dose; milk accounted for 0.44-0.64% of the total excreted (Wszolek et al. 1980). Half-time persistence of fenvalerate in milk of treated cows is about 6.4 days (Frank et al. 1984). Effects of low concentrations (1.14-6.8 μg/L) of fenvalerate in milk of treated cows on newborn suckling calves are unknown and merit additional research (Frank et al. 1984).

Fenvalerate toxicity is antagonized by atropine sulfate or methocarbamol, which may be effective in treating severe cases of poisoning (Hiromori et al. 1986). Conversely, some compounds exacerbate the toxicity of fenvalerate and interfere with a desired use. Domestic cats (*Felis domesticus*) treated with Fendeet (an aerosol mixture of fenvalerate and N-N-diethyl-*m*-toluamide) to control fleas and ticks sometimes show signs of toxicosis, such as tremors, hypersalivation, ataxia, vomiting, depression, and seizures. Signs usually appeared within hours of topical application, and females and juveniles seem to be the most sensitive group. The demonstrated ability of N-N-diethyl-*m*-toluamide to enhance the dermal absorption of fenvalerate is the probable cause of toxicosis (Dorman et al. 1990).

In occupational settings, fenvalerate produces temporary irritation and itching (Bradbury and Coats 1989a). Among human fenvalerate applicators, sensitive individuals complain of a burning and tingling skin sensation after using the insecticide, and sometimes they substitute an insecticide more toxic to nontarget species in order to avoid this uncomfortable sensation (Flannigan et al. 1985). This practice, if widespread, may compromise existing or proposed natural resource management practices.

Recommendations

Fenvalerate is listed under the Class IV Surveillance Index Classification, indicating a low hazard potential to humans from toxicological and exposure standpoints. This classification requires only nominal monitoring (Reed 1981). Monitoring efforts of regulatory agencies to the present, however, have been limited and of marginal worth in evaluating background concentrations of fenvalerate. Additional monitoring is recommended to measure fenvalerate residues in tissues of birds and mammals of U.S. Fish and Wildlife Service concern.

Products that contain fenvalerate and are registered for use on corn, wheat, soybeans, sorghum, oats, barley, rye, or cotton are subject to the provisions of the Endangered Species Act (Sine 1988). The Endangered Species Act requires that actions of federal agencies not jeopardize threatened or endangered species or their habitats. Specifically, the U.S. Environmental Protection Agency, in consultation with the U.S. Fish and Wildlife Service, determines whether use of fenvalerate poses a threat to listed species of animals and plants in various locations (Sine 1988). Clearly, fenvalerate and other synthetic pyrethroid insecticides should be used with extreme caution in habitats of endangered species.

No regulations exist for protection of sensitive natural resources against fenvalerate, although current application rates to control pestiferous crop insects are lethal to many species of nontarget organisms, including bees, fish, and crustaceans (Table 8). Current fenvalerate guidelines for protection of livestock, poultry, and human health are as follows: <5 mg/kg in diets of livestock, <50 mg/kg in diets of poultry, <3 mg/kg in human diets (< 1 mg/kg for vegetables, <0.5 mg/kg for meat, <0.25 mg/kg for milkfat), and <0.125 mg/kg BW for acceptable daily intake in humans (Table 8).

Despite the high toxicity of fenvalerate and other pyrethroids to aquatic organisms, few environmental problems have been documented, presumably due to the very low application levels needed to control insects, adsorption onto soil and organic matter, and comparatively rapid degradation (Gray and Soderlund 1985). Nevertheless, fenvalerate is extremely toxic to aquatic organisms (Table 8), has high bioaccumulation, and is persistent in sediments; these patterns are most pronounced in estuaries and other wetland environments. Fenvalerate use in areas adjacent to estuarine systems poses unacceptable risks to those ecosystems at concentrations not currently detectable by analytical methods (Schimmel et al. 1983). It seems reasonable to prohibit all uses of fenvalerate directly into aquatic environments and to severely restrict usage in areas adjacent to drainage systems.

Additional research is needed on sublethal effects of fenvalerate in the following areas: (1) impaired response to scent stimuli as demonstrated in bees (Taylor et al. 1987); (2) genotoxic potency as shown in positive genotoxic effects on mice bone marrow (Pati and Bhunya 1989); (3)photoproduct formation—especially those formed through ultraviolet irradiation--wherein at least two photoproducts were more toxic than the parent chemical (Holmstead et al. 1978); (4) enhanced tumor formation in rodent liver (Flodstrom et al. 1988); (5) development of analytical procedures to detect minute and short-lived reactive metabolites (Miyamoto 1988); (6) development of simplified and reliable laboratory test systems more representative of total natural ecosystems (Miyamoto 1988); and (7) interaction effects of fenvalerate degradation products with other chemicals (Smith and Stratton 1986). More research is also needed on indirect effects on wildlife due to reductions in nontarget insects and on bioavailability of fenvalerate to aquatic organisms from sediments and the sediment-water interface.

Table 8. Proposed fenvalerate criteria for the protection of natural resources and human health.

Resource and other variables	Criterion	Reference[a]
Bees (*Apis mellifera, Megachile* sp.)		
Adverse effects		
Whole body	>0.1 µg/bee	1
Diet	> 10 mg/kg fresh weight (FW)	2
Aerial application	0.05 >0.11 kg/ha	3,4
Aquatic organisms		
Crustaceans, decreased survival		
Water column	0.003-0.022 µg/L	5,6,7, 8,9,10, 11,12
Sediments	97-190 µg/kg FW	13
Fish		
Water column		
Persistent residues	>0.00028 µg/L	14
No adverse effects on growth survival, or reproduction	0.062-0.083 µg/L	13

Lethal	0.088-0.31 µg/L	5,10, 11, 13,15,16, 17,18,19,20
Brain residues at death	>0.16 mg/kg FW	20
Birds		
Acute oral exposure, single dose		
No deaths	<250 mg/kg body weight (BW)	21
Some deaths	>500 mg/kg BW	21
Persistent residues	>5 mg/kg BW	22
Tissue residues at death		
Brain	0.1-1.26 mg/kg FW	21
Liver	0.74 mg/kg FW	2 I
Dietary exposure		
Sublethal		
No residues in eggs or meat	<50 mg/kg diet	22
Biochemical upset	>2,000 mg/kg diet	24
Lethal	> 15,000 mg/kg diet	2 I
Mammals		
Dietary exposure		
Sublethal		
Persistent residues	0.15-15 mg/kg feed	23,25
Temporary tolerance level, livestock, dried apple pomace	5 mg/kg feed	23
No significant effects	12.5-15 mg/kg BW daily, 100-250 mg/kg diet	23,26
Significant adverse effects	250-1,000 mg/kg diet	27
Lethal	>50 mg/kg BW, >1,250 mg/kg diet	23,28
Single oral exposure		
Sublethal		
Behavioral changes	0.3-30 mg/kg BW	29
Persistent residues	>2.5 mg/kg BW	30
Lethal	50-450 mg/kg BW	20,23,31
Dermal exposure		
Sublethal		
Persistent residues	0.15-1.0 mg/kg BW	32,33,34
No deaths	310 mg/kg BW daily for 2 weeks	35
Lethal	1,800 mg/kg BW, single application	29
Human health		
Permanent tolerance level		
Meat and milk fat	<0.02 mg/kg FW	23
Temporary tolerance level		
Milk fat	<0.25 mg/kg FW	23
Meat	<0.5 mg/kg FW	23
Total diet	<3 mg/kg FW	23
Vegetables, "safe" level	<1 mg/kg FW	36
Acceptable daily intake (ADI), 60 kg person, 1.5 kg food daily	0.125 mg/kg BW	23
Theoretical daily exposure from diet		
Minimum	0.015 mg, 0.00025 mg/kg BW, 0.2% of AD1	23
Maximum	0.334 mg, 0.0056 mg/kg BW, 4.5% of ADI	23

[a] 1. Lingappa et al. 1985: 2. Stoner et al. 1984; 3. Tasei and Debray 1985; 4. Mayer et al. 1987; 5. Clark et al. 1987; 6. Scott et al. 1987; 7. Day and Kaushik 1987c; 8. Day and Kaushik 1987a; 9. Anderson 1982; 10.

Schimmel et al. 1983; 11. Mayer 1987; 12. Tagatz and Ivey 1981; 13. Clark et al. 1989; 14. Bradbury et al. 1986; 15. Curtis et al. 1985; 16. Mayer and Ellersieck 1986; 17. Clark et al. 1985; 18. Holcombe et al. 1982; 19. Hansen et al. 1983; 20. Bradbury and Coats 1989b; 21. Bradbury and Coats 1982; 22. Akhtar et al. 1989; 23. Reed 1981; 24. Riviere et al. 1983; 25. Wszolek et al. 1980; 26. Parker et al. 1984a; 27. Parker et al. 1984b; 28. Parker et al. 1983; 29. Mitchell et al. 1988; 30. Kaneko et al. 1986; 31. Bradbury and Coats 1989a; 32. Frank et al. 1984; 33. Grissom et al. 1985; 34. Grissom et al. 1987; 35. Saleh et al. 1986a; 36. Jain et al. 1979.

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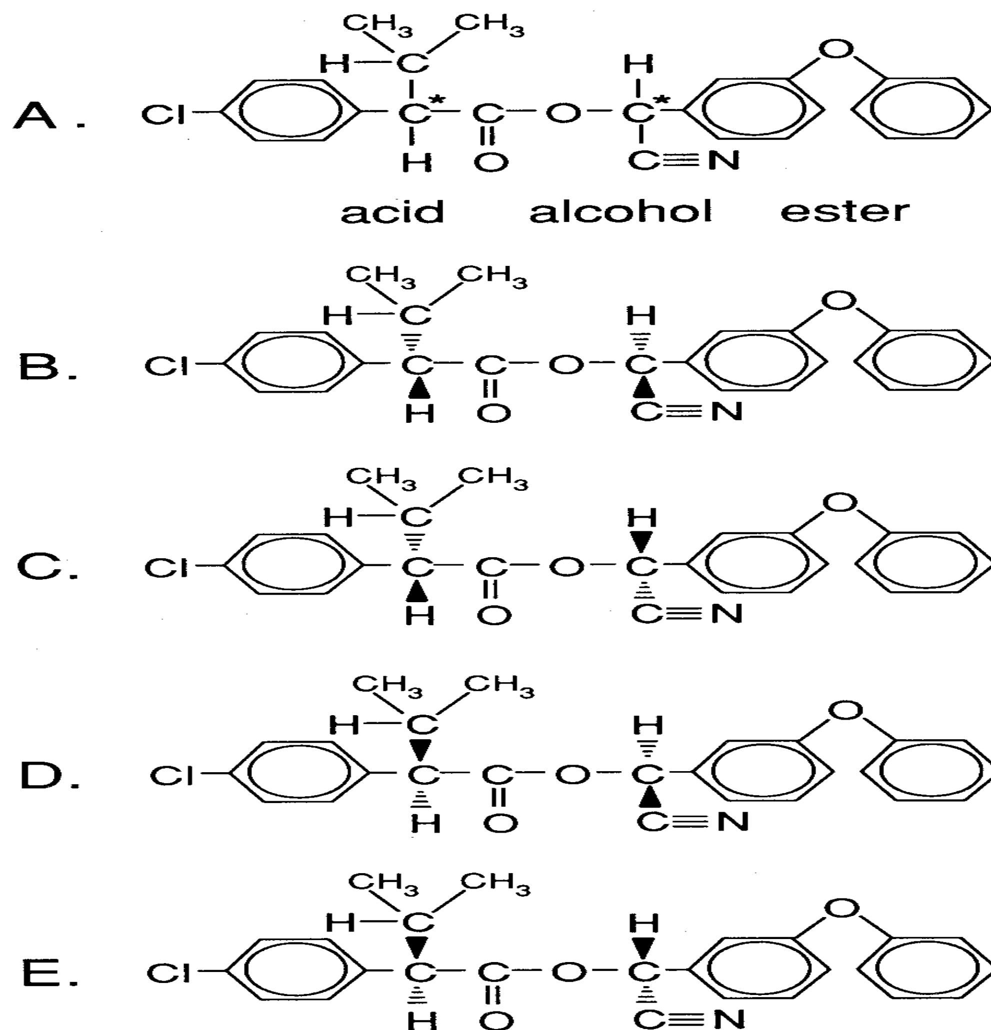

Figure. Fenvalerate and its isomers (Ohkawa et al. 1979; Hill 1981; Kaneko et al. 1981, 1986; Vijverberg and Bercken 1982; Miyamoto et al. 1986; Bradbury et al. 1987b; Bradbury and Coats 1989a, 1989b; Coats et al. 1989).

A. Chemical structure of fenvalerate denoting two asymmetric carbon atoms (*): the 2C position of the acid moiety, and the αC position of the α-cyano-3-phenoxybenzyl alcohol moiety. These two chiral centers, at the 2C and αC positions, yield a mixture of four stereoisomers, in approximately equal amounts but with greatly different biological properties.

B. (2*S*)-α-cyano-3-phenoxybenzyl (α*S*)-2-(4-chlorophenyl)-3-methylbutyrate. The 2*S*, α*S* isomer is extremely toxic to insects and is the most active form of fenvalerate.

C. (2*S*)-α-cyano-3-phenoxybenzyl (α*R*)-2-(4-chlorophenyl)-3-methylbutyrate. The 2*S*, α*R* isomer has markedly reduced insecticidal activity when compared with the 2*S*, α*S* isomer but is greatly elevated in this respect when compared with fenvalerate stereoisomers with an *R* configuration in the acid moiety, that is, the 2*R*, α*S* and the 2*R*, α*R* isomers.

D. The 2*R*, α*S* isomer is the only fenvalerate isomer that caused granulatomous changes in liver, spleen, and mesenteric lymph node in rodents.

E. The 2*R*, α*R* isomer has greatly reduced biological and toxicological properties when compared with other fenvalerate isomers. Isomers with an *R* configuration in the acid moiety degraded slightly faster than the insecticidally active 2*S*, α*S* and 2*S*, α*R* isomers.