# FENVALERATE

## 1. Exposure Data

### 1.1 Chemical and physical data

Fenvalerate is a mixture of four stereoisomers (RR, RS, SR, SS) due to the two asymmetric carbon atoms in the molecule. It has an α-cyanogroup on the 3-phenoxybenzyl alcohol and is a type II pyrethroid. The SS stereoisomer is the most biologically active and is sold as esfenvalerate.

1.1.1 *Synonyms, structural and molecular data*

**Fenvalerate**

*Chem. Abstr. Serv. Reg. No.*: 51630-58-1
*Chem. Abstr. Name*: 4-Chloro-α-(1-methylethyl)benzeneacetic acid, cyano(3-phenoxyphenyl)methyl ester
*IUPAC Systematic Name*: (RS)-α-Cyano-3-phenoxybenzyl (RS)-2-(4-chlorophenyl)-3-methylbutyrate
*Synonyms*: α-Cyano-3-phenoxybenzyl 2-(4-chlorophenyl)isovalerate; α-cyano-3-phenoxybenzyl α-(4-chlorophenyl)isovalerate; α-cyano-3-phenoxybenzyl isopropyl-4-chlorophenylacetate; cyano(3-phenoxyphenyl)methyl 4-chloro-α-(1-methylethyl)benzeneacetate; OMS 2000

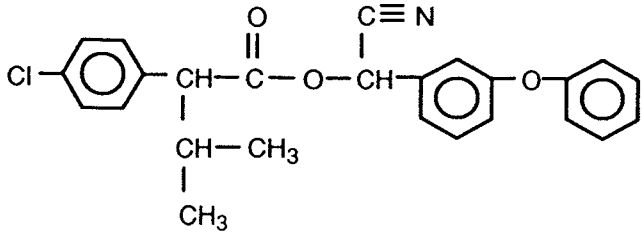
**Fenvalerate β**

*Chem. Abstr. Serv. Reg. No.*: 66267-77-4
*Chem. Abstr. Name*: (R-(R*,S*))-4-Chloro-α-(1-methylethyl) benzeneacetic acid, cyano(3-phenoxyphenyl)methyl ester
*IUPAC Systematic Name*: (R)-α-Cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)-3-methylbutyrate
*Synonyms*: Fenvalerate β; Fenvalerate Aβ; S 5602Aβ

**Esfenvalerate**

*Chem. Abstr. Serv. Reg. No.*: 66230-04-4
*Replaced CAS Reg. No.*: 72650-28-3
*Chem. Abstr. Name*: (S-(R*,R*))-4-Chloro-α-(1-methylethyl) benzeneacetic acid, cyano(3-phenoxyphenyl)methyl ester
*IUPAC Systematic Name*: (S)-α-Cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)-3-methylbutyrate

*Synonyms*: (S)-α-Cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)isovalerate; fenvalerate α; fenvalerate Aα; OMS 3023



$C_{25}H_{22}ClNO_3$ Mol. wt: 419.91

1.1.2 *Chemical and physical properties*

**Fenvalerate**

(*a*) *Description*: Viscous yellow or brown liquid, sometimes partly crystalline at room temperature (Worthing & Walker, 1987; WHO, 1990)
(*b*) *Boiling-point*: 300°C at 37 mm Hg [4.9 kPa] (WHO, 1990)
(*c*) *Density*: 1.175 (25/25°C) (Worthing & Walker, 1987)
(*d*) *Solubility*: Slightly soluble in water (< 1 mg/l at 20°C); readily soluble in most organic solvents (acetone, chloroform, cyclohexanone, ethanol, xylene; all > 1 kg/kg at 23°C) (Worthing & Walker, 1987; Royal Society of Chemistry, 1989)
(*e*) *Volatility*: Vapour pressure, $2.8 \times 10^{-7}$ mm Hg [$0.37 \times 10^{-7}$ kPa] at 25°C (Royal Society of Chemistry, 1989; WHO, 1990)
(*f*) *Stability*: Stable to light, heat and moisture; relatively stable in acidic media, but rapidly hydrolysed in alkaline media, with optimal stability at pH 4 (Worthing & Walker, 1987; Royal Society of Chemistry, 1989; WHO, 1990)
(*g*) *Octanol/water partition coefficient (P)*: log P, 6.2 (WHO, 1990)
(*h*) *Half-time*: Four to 15 days (natural water); eight to 14 days (on plants); one to 18 days (on soil); 15 days to three months (in soil) (WHO, 1990)
(*i*) *Conversion factor for airborne concentrations*[1]: $mg/m^3 = 17.17 \times ppm$

**Esfenvalerate**

(*a*) *Description*: White crystalline solid (Budavari, 1989)
(*b*) *Melting-point*: 59-60.2°C (Budavari, 1989)
(*c*) *Solubility*: Practically insoluble in water; soluble in most organic solvents (acetone, acetonitrile, chloroform, dimethyl formamide, dimethyl sulfoxide, ethyl acetate, ethyl cellosolve, α-methylnaphthalene, xylene); slightly soluble in *n*-hexane, kerosene and methanol (Budavari, 1989; Royal Society of Chemistry, 1989)
(*d*) *Volatility*: Vapour pressure, $5 \times 10^{-7}$ mm Hg [$0.67 \times 10^{-7}$ kPa] at 25°C (Budavari, 1989)

---

[1]Calculated from: $mg/m^3$ = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg [101.3 kPa])

(*e*) *Stability*: Stable at normal temperatures; incompatible with alkaline substances such as soda ash and lye (Du Pont, 1988a)
(*f*) *Octanol/water partition coefficient (P)*: log P, 4.42 (Verschueren, 1983)

### 1.1.3 *Trade names, technical products and impurities*

Some trade names include:

*Fenvalerate*: Aqmatrine; Belmark; Ectrin; Evercide 2362; Fenkill; Fenval; Phenvalerate; Pydrin®; S-5602; Sanmarton; SD 43775; Sumibac; Sumicidin; Sumifleece; Sumifly; Sumipower; Sumitick; Sumitox; WL 43775

*Esfenvalerate*: Asana; Halmark; S-1844; S 5602Aα; Sumi-alfa; Sumi-alpha; Sumicidin Aα

Fenvalerate is a synthetic pyrethroid with no cyclopropane ring in the molecule. Technical-grade fenvalerate is 90-94% pure and consists of equal portions of the four stereoisomers (RR, RS, SR, SS). It may be formulated as emulsifiable concentrates, ultra-low volume concentrates, dusts or wettable powders (WHO, 1990).

Fenvalerate formulations currently registered in the USA, Europe and India are emulsifiable concentrates (Royal Society of Chemistry, 1986; Du Pont, 1988b; E.I. duPont de Nemours & Co., 1988a, 1989a; Roussel Bio Corp., 1989; All India Medical Corp., undated). Xylene (see IARC, 1989) may be present in the concentrates (E.I. duPont de Nemours & Co., 1988a).

Esfenvalerate is available in the USA as a technical-grade product with a purity of 75%. It is formulated in the USA as an emulsifiable concentrate (Du Pont, 1988a; E.I. duPont de Nemours & Co., Inc., 1988b,c, 1989b,c; Du Pont, 1990). The concentrate may contain xylene (E.I. duPont de Nemours & Co., Inc., 1988b,c, 1989b,c) or ethylbenzene (DuPont, 1990).

Fenvalerate is also formulated in combination with oxydemeton-methyl (Royal Society of Chemistry, 1986).

### 1.1.4 *Analysis*

Selected methods for the analysis of fenvalerate in various matrices are given in Table 1. Residues and environmental samples of fenvalerate can be analysed by gas chromatography with electron capture detection, with a minimum detection level of 0.005 mg/kg; products can be analysed by gas chromatography with flame ionization detection (WHO, 1990). Additional methods for formulation and residue analysis have been reviewed (Baker & Bottomley, 1982; Papadopoulou-Mourkidou, 1983; Shell Development Co., 1984).

A method has been described that allows detection of the presence of fenvalerate (as its separate diastereoisomers) in commercially available insecticidal preparations using high-pressure liquid chromatography with a normal-phase system (Mourot *et al.*, 1979). A gas chromatographic method is available for determination of the chemical purity and diastereoisomers of fenvalerate (Horiba *et al.*, 1980), and a gas chromatographic method for the determination of esfenvalerate in technical preparations has been described (Sakaue *et al.*, 1987).

**Table 1. Methods for the analysis of fenvalerate**

| Sample matrix | Sample preparation | Assay procedure[a] | Limit of detection | Reference |
|---|---|---|---|---|
| Animal tissues, crops (oily) | Extract with hexane:isopropanol (3:1); remove isopropanol by water partitioning; partition with acetonitrile; exchange to hexane; clean-up on Florisil column | GC/ECD | 0.01 ppm (mg/kg) | US Food and Drug Administration (1989) |
| Cream, milk, milk fat | Extract with dichloromethane; extract solids with acetone; exchange to hexane; combine hexane and dichloromethane extracts; remove solvent; solubilize fat with hexane and partition with acetonitrile; wash with hexane; backwash with acetonitrile; combine acetonitrile extracts and dilute with sodium chloride; extract with hexane; concentrate; clean-up on Florisil column | GC/ECD | Not reported | US Food and Drug Administration (1989) |
| Crops (non-oily) | Extract with hexane:isopropanol (3:1); remove isopropanol by water partitioning; exchange to hexane; clean-up on Florisil column | GC/ECD | 0.01 ppm (mg/kg) | US Food and Drug Administration (1989) |
| Eggs | Extract with hexane:acetonitrile; wash acetonitrile phase with hexane; backwash with acetonitrile; combine acetonitrile extracts and dilute with sodium chloride; extract with hexane; concentrate; clean-up on Florisil column | GC/ECD | Not reported | US Food and Drug Administration (1989) |
| Formulations | Dissolve in hexane; filter; analyse directly | HPLC/UV | Not reported | Papadopoulou-Mourkidou (1985) |
| Gauze patches | Extract with acetone:hexane (1:1); evaporate to dryness; dissolve residue in hexane; clean-up on Florisil column | GC/ECD | Not reported | US Food and Drug Administration (1989) |
| Hair | Extract with 5% (v/v) ethyl acetate in hexane; inject directly | GC/ECD | Not reported | US Food and Drug Administration (1989) |
| Soil | Extract by high frequency vibration in acetone:hexane (1:1); exchange to hexane; clean-up on Florisil column | GC/ECD | 0.01 ppm (mg/kg) | US Food and Drug Administration (1989) |
| Water | Extract by partitioning with hexane; clean-up on Florisil column | GC/ECD | 0.05 ppm (mg/l) | US Food and Drug Administration (1989) |

[a]Abbreviations: GC/ECD, gas-liquid chromatography/electron capture detection; HPLC/UV, high performance liquid chromatography/ultraviolet detection

## 1.2 Production and use

### 1.2.1 *Production*

Fenvalerate was first marketed in 1976. Approximately 1000 tonnes were produced annually worldwide in 1979-83 (WHO, 1990); annual production is now believed to be about 2000 tonnes. The history of the development, manufacture and commercialization of fenvalerate has been reviewed in detail (Yoshioka, 1978; Rogosheske *et al.*, 1982; Yoshioka, 1985). It is produced currently in India, Japan, the United Kingdom and the USA (Meister, 1990).

Fenvalerate can be prepared by esterification of 3-phenoxybenzaldehyde cyanohydrin with 2-(4-chlorophenyl)isovaleroyl chloride, or by condensation of 3-phenoxy-α-halobenzyl cyanide with the isovaleric acid in the presence of a base such as potassium carbonate. More conveniently, fenvalerate can be provided by the Francis reaction using the isovaleroyl chloride, the aldehyde and sodium cyanide.

The most active isomer, esfenvalerate, can be derived from (S)-2-(4-chlorophenyl)-isovaleroyl chloride and (S)-3-phenoxymandelic acid. It can be prepared most efficiently, however, from the (R,S) alcohol ester of the (S) acid through preferential precipitation (Yoshioka, 1978).

### 1.2.2 *Use*

Fenvalerate is a highly active contact insecticide that is effective against a wide range of pests, including strains resistant to organochlorine, organophosphorus and carbamate insecticides (Worthing & Walker, 1987). It is used mainly in agriculture, with about 90% used on cotton. It is also used on other crops, such as vines, tomatoes, potatoes, pomes, other fruit and a wide variety of other crops (WHO, 1990). It is also used in public health and animal husbandry, e.g., for controlling flies in cattle sheds (Worthing & Walker, 1987).

It is used in homes and gardens for insect control and around the foundations of buildings to control termites and carpenter ants (Roussel Bio Corp., 1989; WHO, 1990).

## 1.3 Occurrence

### 1.3.1 *Food*

Of a total of 946 samples analysed in the 1984-89 Canadian national surveillance programme, seven were found to contain fenvalerate residues, at levels of 0.02-0.096 mg/kg. Most were in pears (6/114 samples) and one in lettuce (1/11 samples) (Government of Canada, 1990). In Sweden, 163 of 165 samples of imported fruit and vegetables contained residues up to 0.2 mg/kg; one had a residue of 0.54 mg/kg (FAO/WHO, 1985)

Of 19 851 food and feed samples analysed in the USA during 1982-86, only 25 had fenvalerate residues; one sample had a level of 1 mg/kg, and the rest were lower (Luke *et al.*, 1988).

In stored grain treated with 1 mg/kg, over 70% of an applied dose remained in wheat after 10 months. White bread contained the same residue levels as the white flour from which it was prepared (WHO, 1990).

When fenvalerate was applied to peanuts in the USA at rates up to 0.45 kg active ingredient/ha, the residues in whole nuts were < 0.1 mg/kg; those in nut meat did not exceed the detection limit of 0.01 mg/kg (FAO/WHO, 1982).

Trials in the USA and Canada on lettuce, spinach, celery and Brassica vegetables showed residue levels of less than 1 mg/kg seven days after treatment at rates of 0.05-0.45 kg/ha. In cabbage, the maximum residue seven days or more after application was 4.3 mg/kg for an application rate of 0.45 kg/ha. Treatments with 0.45 and 0.22 kg/ha fenvalerate gave residue levels of 4.3 and 1.7 mg/kg, respectively, in lettuce (FAO/WHO, 1982).

In apples, following application at rates up to 1.12 kg/ha, residues at day 0 or after were < 2.0 mg/kg. In another trial in the USA, residues of 2.2 mg/kg were found after 42 days following four treatments with 0.67 kg/ha. The residue found in pears in the USA was 4.3 mg/kg 20 days after a second treatment of 0.45 kg/ha. In other countries, residues in pears did not exceed 2 mg/kg 14 days after treatment (FAO/WHO, 1982).

Grapes treated in the USA, Canada and Japan at rates up to 0.22 kg/ha generally contained residues of less than 1 mg/kg 14 days after application; the maximum residue found was 3.8 mg/kg. Wine made from grapes containing up to 3.44 mg/kg fenvalerate contained no detectable residue seven days after treatment (FAO/WHO, 1982).

Apples treated with fenvalerate were processed into apple sauce, juice, pomace and peels plus cores. The sauce and juice contained essentially no residue; whole apples contained about 0.4 ppm (mg/kg), pomace contained about 2 ppm (mg/kg) and peels plus cores, 1.5 ppm (mg/kg) (Spittler *et al.*, 1982).

Fenvalerate-treated tomatoes were processed into chopped fresh tomatoes, canned quarters, juice, paste and by-product skins and seeds. The fresh produce contained 0.26 ppm (mg/kg) and skins and seeds, 1.9 ppm (mg/kg). Residues averaged 0.12 ppm (mg/kg) in the paste but were barely detectable in other products (Spittler *et al.*, 1984).

### 1.3.2 *Occupational exposure*

At a fenvalerate packing plant in China, workers were reported to be exposed to 12-55 $\mu g/m^3$ in the air, with resulting skin contact (He *et al.*, 1988).

## 1.4 Regulations and guidelines

Maximum residue levels have been established by the Codex Alimentarius Commission for fenvalerate (fat-soluble residue) in or on the following agricultural commodities (in mg/kg): alfalfa fodder, 20; kale, 10; Brussels' sprouts, kiwifruit, peaches and wheat bran (unprocessed), 5; cabbages (head), 3; broccoli, cauliflower, celery, cereal grains, cherries, citrus fruit, lettuce (head), pome fruit and wheat wholemeal, 2; beans (except broad and soya beans), berries and other small fruit, Chinese cabbage (pak-choi), meat (fat) and tomatoes, 1; squash (summer, winter), sweet peppers and watermelon, 0.5; cotton seed, cucumbers, melons (except watermelon), tree nuts and wheat flour, 0.2; beans (shelled), cotton-seed oil (crude, edible), milks, peanuts (whole), peas (shelled), soya beans (dried), sunflower seeds and sweet maize (on-the-cob), 0.1; vegetables (root, tuber), 0.05; edible offal (mammalian), 0.02 (Codex Committee on Pesticide Residues, 1990).

Fenvalerate was evaluated by the Joint Meeting of the FAO/WHO Expert Committee on Pesticide Residues in 1979, 1981, 1982, 1984, 1985, 1986, 1987 and 1988 (FAO/WHO, 1980, 1982, 1983, 1985, 1986a,b, 1988a,b). In 1986, the Committee established an acceptable daily intake for humans of 0.02 mg/kg bw (Codex Committee on Pesticide Residues, 1990; WHO, 1990).

The US Environmental Protection Agency (1987) calculated an acceptable daily intake of 0.025 mg/kg per day for fenvalerate and a maximum permissible intake of 1.5 mg/kg per day for a 60-kg human.

National and regional pesticide residue limits for fenvalerate in foods are presented in Table 2. Additionally, the US Environmental Protection Agency (1989c) established a food additive tolerance of 0.05 ppm (mg/kg) for residues of fenvalerate in or on all food items (other than those already covered by a higher tolerance as a result of use on growing crops) in food handling establishments where food and food products are held, processed or prepared.

**Table 2. National and regional pesticide residue limits for fenvalerate in foods[a]**

| Country or region | Residue limit (mg/kg) | Commodities |
|---|---|---|
| Argentina | 2 | Citrus fruit, peaches, sunflower seeds without husks |
| | 1 | Apples, flax, peas (fresh), soya beans, sunflowers |
| | 0.5 | Pears |
| | 0.25 | Peas (dried) |
| | 0.2 | Cotton, sorghum |
| | 0.1 | Sweet maize, tomatoes |
| | 0.05 | Soya seeds without husks |
| | 0.02 | Maize |
| Australia | 5 | Wheat bran |
| | 2 | Celery, cereal grains |
| | 1 | Cole crops, pome fruit, stone fruit, strawberries |
| | 0.5 | Fat of meat of goats and sheep, oilseeds, pod vegetables, seed vegetables |
| | 0.2 | Fat of meat of cattle, milk (fat basis), milk products (fat basis), tomatoes |
| | 0.05 | Sweet maize |
| Austria | 2 | Fruit, vegetables |
| | 0.5 | Other foodstuffs of vegetable origin |
| | 0.05 | Meat |
| Belgium | 1 | Cabbage and related plants, pome fruit |
| | 0.5 | Other fruit |
| | 0.05 | Potatoes |
| | 0 (0.05)[b] | Other foodstuffs of vegetable origin |
| Brazil | 1.0 | Kale, rice |
| | 0.2 | Lard, meat (in fat), meats |
| | 0.1 | Coffee beans, cottonseed, soya beans, tomatoes |
| | 0.04 | Wheat |
| | 0.01 | Maize, field beans |
| Canada | Negligible | Apples, Brussels' sprouts, cabbages, cattle, cauliflower, pears, peanuts, potatoes |
| Chile | 10 | Cabbages, lettuce, peaches |
| | 2 | Apples, pears |
| | 1.5 | Sheep carcasses |
| | 1.0 | Beef carcasses, milk, tomatoes |
| | 0.25 | Dried beans |
| | 0.05 | Hog carcasses |
| | 0.02 | Goat carcasses, potatoes |

**Table 2 (contd)**

| Country or region | Residue limit (mg/kg) | Commodities |
|---|---|---|
| Denmark | 2 | Fruit (citrus, pome, stone), leafy vegetables |
| | 1 | Berries and small fruit, other vegetables |
| | 0.05 | Carrots, other root vegetables and onions, potatoes |
| Finland | 2 | Citrus fruit |
| | 1.0 | Grapes |
| | 0.5 | Other foodstuffs (excluding cereal grains) |
| France | 0.5 | Fruit (pome, stone), grapes |
| Germany | 2 | Berries, stone fruit (except plums) |
| | 1.0 | Cabbages, grapes, pome fruit |
| | 0.5 | Plums |
| | 0.05 | Maize, meat, meat products, potatoes, rape, sugar beets |
| | 0.02 | Other foodstuffs of plant origin |
| | 0.01 | Dairy products, milk |
| Hungary | 1.0 | Not specified |
| Italy | 1.5[c] | Apples, grapes, oranges, peaches, pears |
| Japan | 20 | Exocarp of summer oranges |
| | 1 | Fruit (except exocarp of summer oranges) |
| | 0.5 | Sugar beets, vegetables |
| | 0.1 | Pulses |
| | 0.05 | Potatoes, etc. |
| Netherlands[c] | 1 | Cabbage species, leafy vegetables, pome fruit |
| | 0.05[d] | Cereals, meat, milk, potatoes |
| | 0 (0.05)[e] | Other foodstuffs |
| New Zealand[c] | 5 | *Brassica* vegetables |
| | 3 | Kiwifruit |
| | 1.0 | Legume vegetables, pome fruit |
| | 0.2 | Tomatoes |
| South Africa | 0.5 | Apples, cottonseed, mealies (green), pears |
| | 0.3 | Beans |
| | 0.2 | Sorghum, sunflower seeds |
| | 0.1 | Peas, potatoes, tomatoes |
| | 0.05 | Grapes, mangoes |
| Spain[c] | 10 | Alfalfa |
| | 5 | Beetroot tops, maize, sorghum |
| | 2 | Citrus fruit, drupes, pomes |
| | 1.00 | Grapes |
| | 0.50 | Straw of cereals |
| | 0.20 | Cucumbers |
| | 0.05 | Other plant products |
| Sweden[c] | 1.0 | Fruit, vegetables |
| | 0.05[f] | Potatoes |

**Table 2 (contd)**

| Country or region | Residue limit (mg/kg) | Commodities |
|---|---|---|
| Switzerland | 0.5 | All foodstuffs (except fruit and milk) |
| | 0.4 | Fruit |
| | 0.01 | Milk |
| Taiwan | 2 | Leafy vegetables with small leaves |
| | 1.0 | Nut fruit |
| | 0.5 | Leafy vegetables with large wrapper leaves |
| | 0.1 | Rice, root vegetables |
| USA[g] | 50 | Maize (fodder, forage) |
| | 20 | Dried apple pomace (animal feed), sugar-cane bagasse (animal feed), turnip tops |
| | 15 | Almond hulls |
| | 10 | Cabbage, collards, dried tomato pomace (animal feed), stone fruit |
| | 8 | Radish tops |
| | 7 | Milk (fat) |
| | 3 | Blueberries, caneberries, currants, elderberries, gooseberries, huckleberries |
| | 2 | Apples, beans (snap), broccoli, pears, sugar-cane, sunflower hulls (animal feed) |
| | 1.5 | Cattle, goats, hogs, horses, sheep (fat, meat, meat by-products) |
| | 1.0 | Cantaloupes, eggplants, honeydew melons, muskmelons, peas, peppers, pumpkins, soya bean hulls (animal feed), sunflower seeds, tomatoes, watermelons, winter squash |
| | 0.5 | Carrots, cauliflower, cucumbers, summer squash, turnip roots |
| | 0.3 | Milk, radish roots |
| | 0.25 | Beans (dried), peas (dried) |
| | 0.2 | Almonds, artichokes, cottonseed, English walnuts, filberts, pecans |
| | 0.1 | Maize (sweet, kernels, cob), okra (Florida only), peanut hulls |
| | 0.05 | Soya beans |
| | 0.02 | Maize (grain), peanuts, potatoes |
| Yugoslavia | 1.0 | Fruit, grapes |
| | 0.5 | Other foodstuffs |
| | 0.1 | Rape |

[a]From Health and Welfare Canada (1990)

[b]The figure in parentheses is the lower limit for determining residues in the corresponding product according to the standard method of analysis.

[c]Sum of steroisomers

[d]A pesticide may be used on an eating or drinking ware or raw material without a demonstrable residue remaining; the value listed is considered to be the highest concentration at which this requirement is deemed to have been met.

[e]Residues shall be absent; the value in parentheses is the highest concentration at which this requirement is still deemed to have been met.

[f]Limit of determination with current analytical methodology

[g]From US Environmental Protection Agency (1989a,b)

## 2. Studies of Cancer in Humans

No data were available to the Working Group.

## 3. Studies of Cancer in Experimental Animals

### Oral administration

*Mouse*: Groups of 50 male and 50 female B6C3F$_1$ mice, 7-9 weeks old, were fed 10, 50, 250 or 1250 mg/kg of diet fenvalerate (95.8% pure) for two years. Two control groups of 50 males and 50 females were fed basal diet. The experiment was terminated after 104-105 weeks. There was a significant increase in mortality in male mice that received 10 and 1250 mg/kg and increased mortality in females that received the highest dose of fenvalerate. There was no significant increase in the incidence of tumours at any site in treated animals (Parker *et al.*, 1983).

Groups of 50 male and 50 female C57Bl/6 mice six weeks old were administered 40 or 80 mg/kg bw fenvalerate (99% pure) in arachis oil daily by gavage on five days a week for 104 weeks. Two groups of 50 males and 50 females were given arachis oil alone or were untreated. The experiment was terminated when the mice were 120 weeks of age, when the number of surviving high-dose females was slightly less (34%) than that among controls (40-44%). There was no significant increase in the incidence of tumours at any site in treated animals (Cabral & Galendo, 1990).

In a study designed to evaluate the effect of fenvalerate treatment on the onset of malignant lymphomas in female SJL/ola mice, groups of 24-26 females eight weeks of age, were given 0 or 80 mg/kg bw fenvalerate (92% pure) or 80 mg/kg bw fenvalerate (99% pure) in arachis oil by gavage once a week for 12 weeks and were observed for an additional 40 weeks, at which time the experiment was terminated. A slight increase in mortality was noted in the group that received 92% fenvalerate. Malignant lymphomas developed in all groups, and there was a shortening of the latent period in mice treated with 92% fenvalerate (Cabral & Galendo, 1990). [The Working Group noted that the statistical significance of the finding could not be determined.]

*Rat*: Groups of 93 male and 93 female Sprague-Dawley rats, 7-8 weeks of age, were fed 1, 5, 25 or 250 mg/kg of diet fenvalerate (95.8% pure) dissolved in hexane for up to 104 weeks. Control rats (183 males and 183 females) were maintained on a basal diet. Ten rats from each experimental group and 20 rats from each control group were killed at three, six, 12 and 18 months; the remaining rats were killed at 104 weeks. In a second study, groups of 50 males and 50 females were fed 0 or 1000 mg/kg of diet fenvalerate for 104 weeks. No significant difference in mortality was observed between experimental and control groups. In the first experiment, a significant [trend test: $p = 0.002$] increase in the incidence of benign mammary tumours was observed in females: 25/102 controls, 16/49 at 1 mg/kg, 18/51 at 5 mg/kg, 21/51 at 25 mg/kg and 20/48 at 250 mg/kg. No such increase was observed in the second experiment (20/49 and 16/50 in treated and control animals, respectively). Subcutaneous spindle-cell sarcomas developed in 5/51 males that received 1000 mg/kg fenvalerate; one intrathoracic spindle-cell sarcoma developed in 50 control males [$p > 0.05$]

(Parker *et al.*, 1984). [The Working Group noted the variable historical incidence of benign mammary tumours in this strain of rats.]

## 4. Other Relevant Data

### 4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

For a general introduction to the toxicokinetics of pyrethroids, see the monograph on permethrin. The metabolic pathways of fenvalerate in mammals are depicted in Figure 1 (WHO, 1990). These have mainly been studied using racemic fenvalerate.

Following its oral administration to rats and mice, fenvalerate is apparently rapidly absorbed. After a single oral administration of labelled fenvalerate to rats, excretion of radiolabel from the acid or benzoyl moieties was fairly rapid; the total recovery of radiolabel in the urine, faeces and expired air was 93-99% in six days. Excretion of radiolabel from the cyanogroup was relatively slower and the label was retained as thiocyanate, particularly in the hair, skin and stomach contents (Kaneko *et al.*, 1981).

A lipophilic metabolite, cholesteryl[2R]-2-(4-chlorophenyl)isovalerate (CPIA-cholesterol ester), has been detected in several tissues, notably the adrenal glands, liver and mesenteric lymph nodes, of rats and mice (Kaneko *et al.*, 1986). This metabolite has been indicated as the causative agent for microgranulomatous changes (see below) following administration of fenvalerate (Okuno *et al.*, 1986a). *In vitro* in homogenates from various tissues of mice, rats, dogs and monkeys, only the [2R, αS] isomer gave CPIA-cholesterol ester as a major metabolite. Mouse tissues were more efficient in producing the metabolite than those of other species (Miyamoto *et al.*, 1986), and microsomes from mouse liver produced less CPIA-cholesterol ester than did those from brain, kidney and spleen (Takamatsu *et al.*, 1987).

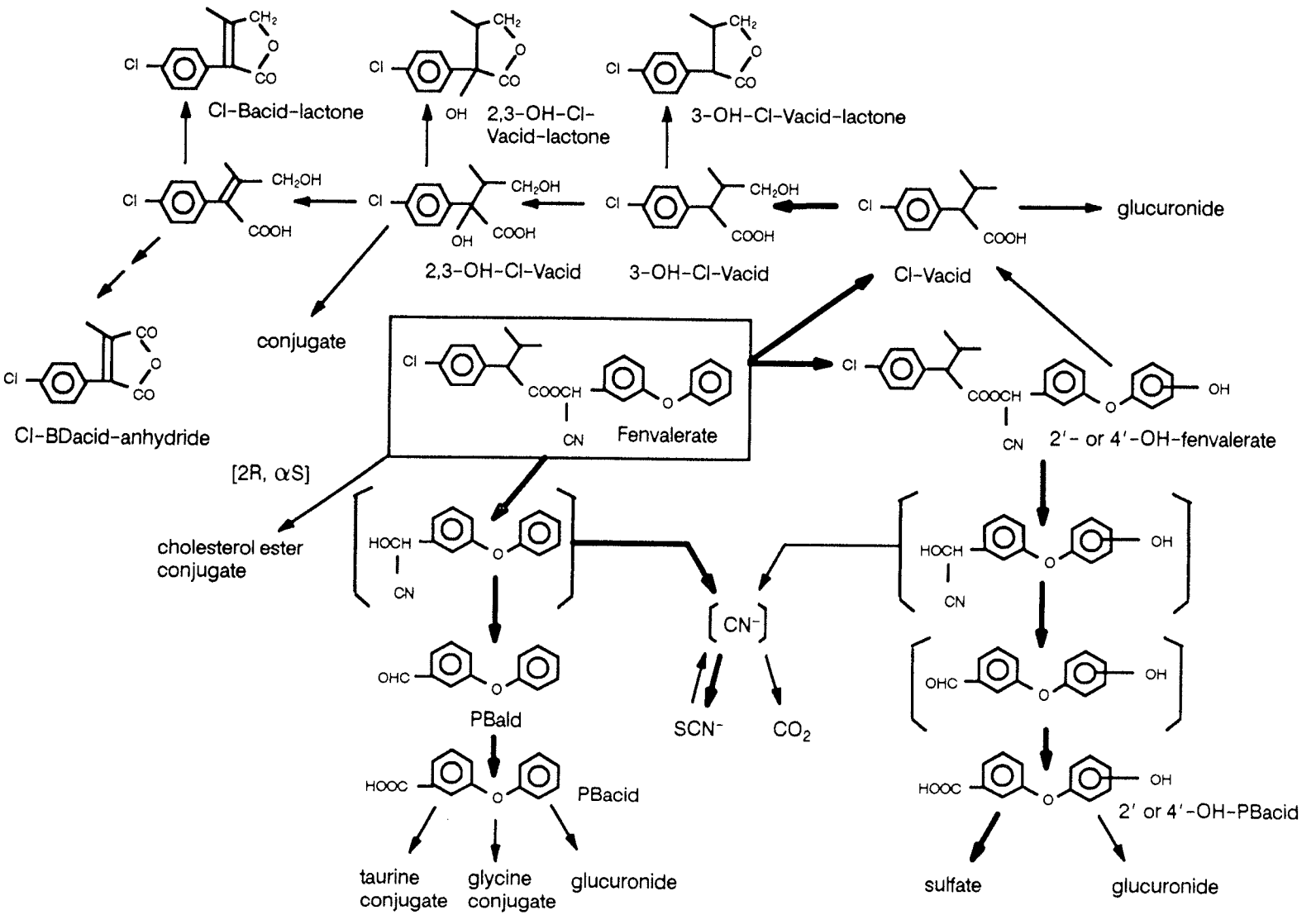
### 4.2 Toxic effects

The toxicity of fenvalerate has been reviewed (FAO/WHO, 1980, 1982, 1985; WHO, 1990).

4.2.1 *Humans*

Thirty-six adult volunteers received topical applications of fenvalerate on each ear lobe (0.081 mg/cm$^2$, approximately the field concentration of fenvalerate, in 0.05 ml of vehicle). Numbness, itching, burning, stinging, pricking and warmth were the most frequently reported sensations, and these occurred intermittently or continuously (Knox *et al.*, 1984). Similar results were obtained in another study (Flannigan *et al.*, 1985) and after occupational exposures (Tucker & Flannigan, 1983). Electrophysiological studies were performed on the arms and legs of subjects who had experienced paraesthesia after exposure to fenvalerate and other pyrethroids; there was no abnormal finding (Le Quesne *et al.*, 1980).

**Fig. 1. Metabolic pathways of fenvalerate in mammals[a]**




[a]From WHO (1990); Cl-Vacid, 2-(4-chlorophenyl)isovaleric acid; Cl-BDacid, 2-(4-chlorophenyl)-*cis*-2-butenedioic acid; Cl-Bacid-lactone, 2-(4-chlorophenyl)-3-methyl-2-butene-4-olide; PBacid, 3-phenoxybenzoic acid; PBald, 3-phenoxybenzaldehyde

He *et al.* (1989) reviewed 196 cases of fenvalerate intoxication from the Chinese medical literature. Common findings included paraesthesia, particularly involving the face, dizziness, headache, nausea, anorexia and fatigue. Less common findings included chest tightness, palpitations, blurred vision, increased sweating and low-grade fever. Muscular fasciculations, convulsions and coma were reported among some of the more severely poisoned cases. Five deaths (two from combined exposures) were reported.

4.2.2 *Experimental systems*

The oral $LD_{50}$ of technical-grade fenvalerate was reported to be 451 mg/kg bw in rats and 100-300 mg/kg bw in mice, when given in dimethyl sulfoxide; when polyethylene glycol/water was used as the vehicle, the $LD_{50}$s were much higher. Signs of intoxication reported in rats were restlessness, tremors, piloerection, occasional diarrhoea and an abnormal gait following oral administration; surviving rats recovered rapidly and were asymptomatic after three to four days. It has been reported that comparative studies of the acute toxicity of several metabolites of fenvalerate in mice following intraperitoneal administration indicated a lower toxicity of the metabolites than that of the parent compound (WHO, 1990).

Absolute and relative increases in liver weight were noted in a 13-week study in Fischer 344 rats fed decarboxyfenvalerate (one major photodegradation product of fenvalerate) in the diet at 300, 3000 or 10 000 mg/kg diet. Hepatocellular hypertrophy and focal necrosis were found in animals fed 3000 or 10 000 mg/kg diet (Parker *et al.*, 1986). The incidence and severity of hepatic multifocal microgranulomas were increased in a dose-dependent way in male and female beagle dogs fed 250, 500 or 1000 mg/kg diet technical-grade fenvalerate for six months (Parker *et al.*, 1984). Multifocal microgranulomas were also observed in liver and spleen of mice fed technical-grade fenvalerate in the diet for two years at concentrations of 250-1250 mg/kg and in lymph nodes of mice fed 50-1250 mg/kg (Parker *et al.*, 1983). Microgranulomas were also observed in liver, spleen and lymph nodes of mice given 20-160 mg/kg bw fenvalerate for 10 weeks. Under similar conditions, hamsters showed slight hepatocyte hypertrophy at 80 and 160 mg/kg but no microgranulomas at any dose level (Cabral & Galendo, 1990). The causative agent of these changes has been reported to be the metabolite CPIA-cholesterol ester (Okuno *et al.*, 1986a).

The pathological changes were caused only by feeding the 2R,αS isomer of fenvalerate, i.e., the only isomer that can be metabolized to CPIA-cholesterol (Okuno *et al.*, 1986a). In another study, Wistar rats and ddY mice were fed diets containing 10-3000 ppm (mg/kg) technical-grade fenvalerate for 24-28 and 17-20 months, respectively. The no-observed-effect level for the development of microgranulomas was found to be 150 and 30 ppm (mg/kg) for rats and mice, respectively. A study in which ddY mice were exposed for six weeks to a diet containing 1000 or 3000 ppm (mg/kg) technical-grade fenvalerate and then to a control diet up to 12 months indicated that the microgranulomatous changes are reversible with time (Okuno *et al.*, 1986b).

It has been reported that, at very high doses of fenvalerate, surviving rats may show neuropathology of the sciatic nerve that might be reversible (WHO, 1990). In mice and rats given single oral doses of technical-grade fenvalerate, reversible ataxia and incoordination

were observed at 56-320 mg/kg bw and sparse axonal damage in peripheral nerves at 180-1000 mg/kg bw (Parker *et al.*, 1985).

Technical-grade fenvalerate (in arachis oil) given by gavage (75 mg/kg bw per day, on five days a week for 10 weeks) induced significantly more γ-glutamyl transpeptidase-positive enzyme-altered foci per cubic centimetre and a larger percentage of liver tissue occupied by focus tissue in partially hepatectomized, *N*-nitrosodiethylamine-initiated male Sprague-Dawley rats than in a vehicle control group. Analysis of the size distribution of foci in fenvalerate- and vehicle-treated rats showed elevated incidences of foci in fenvalerate-treated rats at all focus sizes. Fenvalerate did not increase serum transaminase activities or cause other histopathological changes (Flodström *et al.*, 1988).

In contrast, fenvalerate given in the diet (at up to 1500 ppm [mg/kg]) for six weeks, two weeks after a single intraperitoneal dose of *N*-nitrosodiethylamine (200 mg/kg bw), to male Fischer rats that were also subjected to a two-thirds partial hepatectomy three weeks after the start of the study, did not increase the number or area of glutathione *S*-transferase (placental form)-positive liver-cell foci at eight weeks; positive controls treated with 2-acetylaminofluorene or sodium phenobarbital after *N*-nitrosodiethylamine initiation showed these changes. Neurological signs, including altered response to sensory stimuli, staggering gate and tremors, were observed in rats given 1500 mg/kg fenvalerate in the diet, and relative liver weights were increased in animals administered 500 mg/kg or more in the diet (Hagiwara *et al.*, 1990).

### 4.3 Reproductive and prenatal effects

#### 4.3.1 *Humans*

No data were available to the Working Group.

#### 4.3.2 *Experimental systems*

In a review of reproductive and developmental toxicology studies in mice, rats and rabbits, no adverse effect was reported (WHO, 1990).

### 4.4 Genetic and related effects (see also Table 3 and Appendices 1 and 2)

#### 4.4.1 *Humans*

No data were available to the Working Group.

#### 4.4.2 *Experimental systems*

Several unpublished reports are cited in a recent review (WHO, 1990).

Fenvalerate did not cause mutation in bacteria or in *Drosophila melanogaster*, but weak induction of aneuploidy was observed in *D. melanogaster*. A weak induction of sister chromatid exchange and induction of chromosomal aberrations were observed in cultured human lymphocytes.

*In vivo*, there was evidence of clastogenic effects of fenvalerate in mouse bone marrow; significant effects were reported following a single oral or intraperitoneal administration, yet a single subcutaneous administration had no significant effect. In mice, fenvalerate increased the frequency of micronucleated polychromatic erythrocytes in bone marrow and the frequency of sperm with abnormal morphology.

## Table 3. Genetic and related effects of fenvalerate

| Test system | Result[a] | | Dose[b] LED/HID | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| SA0, *Salmonella typhimurium* TA100, reverse mutation (fluct. test) | – | – | 10.0000 | Pluijmen *et al.* (1984) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 1750.0000 | Herrera & Laborda (1988) |
| SA4, *Salmonella typhimurium* TA104, reverse mutation | – | – | 1750.0000 | Herrera & Laborda (1988) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation (spot test) | – | – | 500.0000 | Herrera & Laborda (1988) |
| SA7, *Salmonella typhimurium* TA1537, reverse mutation (spot test) | – | – | 500.0000 | Herrera & Laborda (1988) |
| SA8, *Salmonella typhimurium* TA1538, reverse mutation (spot test) | – | – | 500.0000 | Herrera & Laborda (1988) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation (fluct. test) | – | – | 10.0000 | Pluijmen *et al.* (1984) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | – | – | 1750.0000 | Herrera & Laborda (1988) |
| SAS, *Salmonella typhimurium* TA97, reverse mutation | – | – | 1750.0000 | Herrera & Laborda (1988) |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation | – | 0 | 20.0000 adult feeding | Batiste-Alentorn *et al.* (1987) |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation | – | 0 | 25.0000 larval feeding | Batiste-Alentorn *et al.* (1987) |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation | – | 0 | 20.0000 adult injection | Batiste-Alentorn *et al.* (1987) |
| DMC, *Drosophila melanogaster*, chromosome breakage | – | 0 | 10.0000 adult feeding | Batiste-Alentorn *et al.* (1987) |
| DMC, *Drosophila melanogaster*, chromosome breakage | – | 0 | 50.0000 larval feeding | Batiste-Alentorn *et al.* (1987) |
| DMC, *Drosophila melanogaster*, chromosome breakage | – | 0 | 20.0000 adult injection | Batiste-Alentorn *et al.* (1987) |
| DMN, *Drosophila melanogaster*, aneuploidy | (+) | 0 | 5.0000 adult feeding | Batiste-Alentorn *et al.* (1987) |
| DMN, *Drosophila melanogaster*, aneuploidy | – | 0 | 50.0000 larval feeding | Batiste-Alentorn *et al.* (1987) |
| DMN, *Drosophila melanogaster*, aneuploidy | – | 0 | 20.0000 adult injection | Batiste-Alentorn *et al.* (1987) |
| SHL, Sister chromatid exchange, human lymphocytes *in vitro* | (+) | 0 | 10.0000 | Puig *et al.* (1989) |
| CHL, Chromosomal aberrations, human lymphocytes *in vitro* | + | 0 | 4.0000 | Puig *et al.* (1989) |
| MVM, Micronucleus test, mouse bone marrow *in vivo* | + | 0 | 150.0000 × 2 i.p. | Pati & Bhunya (1989) |
| CBA, Chromosomal aberrations, mouse bone marrow *in vivo* | + | 0 | 150.0000 × 1 i.p. | Pati & Bhunya (1989) |
| CBA, Chromosomal aberrations, mouse bone marrow *in vivo* | + | 0 | 200.0000 × 1 p.o. | Pati & Bhunya (1989) |
| CBA, Chromosomal aberrations, mouse bone marrow *in vivo* | – | 0 | 200.0000 × 1 s.c. | Pati & Bhunya (1989) |
| ICR, Inhibition of intercellular communication, V79 cells *in vitro* | + | 0 | 4.0000 | Flodström *et al.* (1988) |
| SPM, Sperm abnormalities, mice *in vivo* | + | 0 | 20.0000 × 5 i.p. | Pati & Bhunya (1989) |

[a] +, positive; (+), weakly positive; –, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)
[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

Fenvalerate and a major metabolite, 2-(4-chlorophenyl)isovaleric acid, inhibited gap-junctional intercellular communication in Chinese hamster V79 cells (Flodström *et al.*, 1988).

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Fenvalerate is a highly active contact insecticide. It has been used since 1976, mostly in agriculture but also in public health programmes, in homes and gardens and on cattle, alone or in combination with other insecticides. It has been formulated as concentrates, dusts and wettable powders.

Exposure to fenvalerate can occur during its production and application and, at much lower levels, from consumption of foods containing residues.

### 5.2 Carcinogenicity data in humans

No data were available to the Working Group.

### 5.3 Carcinogenicity in experimental animals

Fenvalerate was tested for carcinogenicity in two experiments in mice and in two experiments in rats by oral administration. There was no increase in the incidence of tumours in mice. In rats, there was an increased incidence of benign mammary tumours in females in one study. In another study at a higher dose, no increase in tumour incidence was seen in animals of either sex.

### 5.4 Other relevant data

In one study, fenvalerate increased the frequency of enzyme-positive foci in rat liver.

Administration of fenvalerate to mice *in vivo* induced chromosomal aberrations and micronuclei in bone marrow and morphological abnormalities in sperm. Induction of chromosomal aberrations and sister chromatid exchange was observed in cultured human cells, and aneuploidy was seen in insects. Fenvalerate inhibited gap-junctional intercellular communication in cultured mammalian cells. It did not induce mutation in insects or bacteria.

### 5.5 Evaluation[1]

No data were available from studies in humans.

There is *inadequate evidence* for the carcinogenicity of fenvalerate in experimental animals.

**Overall evaluation**

Fenvalerate *is not classifiable as to its carcinogenicity to humans (Group 3).*

---

[1]For definition of the italicized terms, see Preample, pp. 26-28.

## 6. References

All India Medical Corp. (undated) *Data Sheet: Fenvalerate 20% E.C.—Sumitox 20% E.C.—Synthetic Pyrethroid Insecticide*, Bombay, AIMCO Pesticides

Baker, P.G. & Bottomley, P. (1982) Determination of residues of synthetic pyrethroids in fruit and vegetables by gas-liquid and high-performance liquid chromatography. *Analyst, 107*, 206-212

Batiste-Alentorn, M., Xamena, N., Velázquez, A., Creus, A. & Marcos, R. (1987) Non-mutagenicity of fenvalerate in *Drosophila*. *Mutagenesis, 2*, 7-10

Budavari, S., ed. (1989) *The Merck Index*, 11th ed., Rahway, NJ, Merck & Co., p. 629

Cabral, J.R.P. & Galendo, D. (1990) Carcinogenicity study of the pesticide fenvalerate in mice. *Cancer Lett., 49*, 13-18

Codex Committee on Pesticide Residues (1990) *Guide to Codex Maximum Limits for Pesticide Residues*, Part 2, (CAC/PR 2—1990; CCPR Pesticide Classification No. 119); The Hague

Du Pont (1988a) *Material Safety Data Sheet: Asana® Insecticide Technical*, Wilmington, DE

Du Pont (1988b) *Material Safety Data Sheet: Pydrin® Insecticide Technical*, Wilmington, DE

Du Pont (1990) *Material Safety Data Sheet: Asana® XL Insecticide*, Wilmington, DE

E.I. duPont de Nemours & Co. (1988a) Material safety data sheet: Pydrin insecticide 2.4 emulsifiable concentrate. In: *MSDS Reference for Crop Protection Chemicals*, New York, Chemical and Pharmaceutical Press, pp. 454-456

E.I. duPont de Nemours & Co. (1988b) Material safety data sheet: Asana insecticide 1.9 emulsifiable concentrate. In: *MSDS Reference for Crop Protection Chemicals*, New York, Chemical and Pharmaceutical Press, pp. 300-302

E.I. duPont de Nemours & Co. (1988c) Material safety data sheet: Asana XL insecticide 0.66 emulsifiable concentrate. In: *MSDS Reference for Crop Protection Chemicals*, New York, Chemical and Pharmaceutical Press, pp. 303-305

E.I. duPont de Nemours & Co. (1989a) Sample label: Pydrin® insecticide 2.4 emulsifiable concentrate. In: *Crop Protection Chemical Reference CPCR®*, 5th ed., New York, Chemical and Pharmaceutical Press, pp. 964-972

E.I. duPont de Nemours & Co. (1989b) Sample label: Asana® insecticide 1.9 emulsifiable concentrate. In: *Crop Protection Chemical Reference CPCR®*, 5th ed., New York, Chemical and Pharmaceutical Press, pp. 724-730

E.I. duPont de Nemours & Co. (1989c) Sample label: Asana® XL insecticide 0.66 emulsifiable concentrate. In: *Crop Protection Chemical Reference CPCR®*, 5th ed., New York, Chemical and Pharmaceutical Press, pp. 730-737

FAO/WHO (1980) *Pesticide Residues in Food: 1979 Evaluations* (FAO Plant Production and Protection Paper 20 Sup.), Rome

FAO/WHO (1982) *Pesticide Residues in Food—1981 Evaluations* (FAO Plant Production and Protection Paper 42), Rome

FAO/WHO (1983) *Pesticide Residues in Food—1982 Evaluations* (FAO Plant Production and Protection Paper 46), Rome

FAO/WHO (1985) *Pesticide Residues in Food—1984 Evaluations* (FAO Plant Production and Protection Paper 67), Rome

FAO/WHO (1986a) *Pesticide Residues in Food—1985 Evaluations* (FAO Plant Production and Protection Paper 68), Rome

FAO/WHO (1986b) *Pesticide Residues in Food—1986 Evaluations* (FAO Plant Production and Protection Paper 77), Rome

FAO/WHO (1988a) *Pesticide Residues in Food—1987 Evaluations* (FAO Plant Production and Protection Paper 86/1), Rome

FAO/WHO (1988b) *Pesticide Residues in Food—1987 Evaluations* (FAO Plant Production and Protection Paper 93/1), Rome

Flannigan, S.A., Tucker, S.B., Key, M.M., Ross, C.E., Fairchild, E.J., II, Grimes, B.A. & Harrist, R.B. (1985) Synthetic pyrethroid insecticides: a dermatological evaluation. *Br. J. ind. Med.*, *42*, 363-372

Flodström, S., Wärngård, L., Ljungquist, S. & Ahlborg, U.G. (1988) Inhibition of metabolic cooperation *in vitro* and enhancement of enzyme altered foci incidence in rat liver by the pyrethroid insecticide fenvalerate. *Arch. Toxicol.*, *61*, 218-223

Government of Canada (1990) *Report on National Surveillance Data from 1984/85 to 1988/89*, Ottawa

Hagiwara, A., Yamada, M., Hasegawa, R., Fukushima, S. & Ito, N. (1990) Lack of enhancing effects of fenvalerate and esfenvalerate on induction of preneoplastic glutathione *S*-transferase placental form positive liver cell foci in rats. *Cancer Lett.*, *54*, 67-73

He, F., Sun, J., Han, K., Wu, Y., Yao, P., Wang, S. & Liu, L. (1988) Effects of pyrethroid insecticides on subjects engaged in packaging pyrethroids. *Br. J. ind. Med.*, *45*, 548-551

He, F., Wang, S., Liu, L., Chen, S., Zhang, Z. & Sun, J. (1989) Clinical manifestations and diagnosis of acute pyrethroid poisoning. *Arch. Toxicol.*, *63*, 54-58

Health and Welfare Canada (1990) *National Pesticide Residue Limits in Foods*, Ottawa, Bureau of Chemical Safety, Food Directorate, Health Protection Branch

Herrera, A. & Laborda, E. (1988) Mutagenic activity of synthetic pyrethroids in *Salmonella typhimurium*. *Mutagenesis*, *3*, 509-514

Horiba, M., Kitahara, H., Takahashi, K., Yamamoto, S. & Murano, A. (1980) Gas chromatographic determination of fenvalerate (S-5602) in technical preparations. *Agric. biol. Chem.*, *44*, 1197-1199

IARC (1989) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 47, *Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting*, Lyon, pp. 125-156

Kaneko, H., Ohkawa, H. & Miyamoto, J. (1981) Comparative metabolism of fenvalerate and the [2S,αS]-isomer in rats and mice. *J. Pestic. Sci.*, *6*, 317-326

Kaneko, H., Matsuo, M. & Miyamoto, J. (1986) Differential metabolism of fenvalerate and granuloma formation. I. Identification of cholesterol ester derived from a specific chiral isomer of fenvalerate. *Toxicol. appl. Pharmacol.*, *83*, 148-156

Knox, J.M., Tucker, S.B. & Flannigan, S.A. (1984) Parasthesia from cutaneous exposure to a synthetic pyrethroid insecticide. *Arch. Dermatol.*, *120*, 744-746

Le Quesne, P.M., Maxwell, I.C. & Butterworth, S.T.G. (1980) Transient facial sensory symptoms following exposure to synthetic pyrethroids: a clinical and electrophysiological assessment. *Neurotoxicology*, *2*, 1-11

Luke, M.A., Masumoto, H.T., Cairns, T. & Hundley, H.K. (1988) Levels and incidences of pesticide residues in various foods and animal feeds analyzed by the Luke multiresidue methodology for fiscal years 1982-1986. *J. Assoc. off. anal. Chem.*, *71*, 415-433

Meister, R.T., ed. (1990) *Farm Chemicals Handbook '90*, Willoughby, OH, Meister Publishing Co., pp. C25-C26, C131-C132, C273

Miyamoto, J., Kaneko, H. & Takamatsu, Y. (1986) Stereoselective formation of a cholesterol ester conjugate from fenvalerate by mouse microsomal carboxyesterase(s). *J. biochem. Toxicol.*, *1*, 79-94

Mourot, D., Delépine, B., Boisseau, J. & Gayot, G. (1979) High-pressure liquid chromatography of a new pyrethroid insecticide, sumicidin. *J. Chromatogr.*, *168*, 277-279

Okuno, Y., Seki, T., Ito, S., Kaneko, H., Watanabe, T., Yamada, T. & Miyamoto, J. (1986a) Differential metabolism of fenvalerate and granuloma formation. II. Toxicological significance of a lipophilic conjugate from fenvalerate. *Toxicol. appl. Pharmacol.*, *83*, 157-169

Okuno, Y., Ito, S., Seki, T., Hiromori, T., Murakami, M., Kadota, T. & Miyamoto, J. (1986b) Fenvalerate-induced granulomatous changes in rats and mice. *J. toxicol. Sci.*, *11*, 53-66

Papadopoulou-Mourkidou, E. (1983) Analysis of established pyrethroid insecticides. *Residue Rev.*, *89*, 179-208

Papadopoulou-Mourkidou, E. (1985) Direct analysis of fenvalerate isomers by liquid chromatography. Application to formulation and residue analysis of fenvalerate. *Chromatographia*, *20*, 376-378

Parker, C.M., McCullough, C.B., Gellatly, J.B.M. & Johnston, C.D. (1983) Toxicologic and carcinogenic evaluation of fenvalerate in the $B6C3F_1$ mouse. *Fundam. appl. Toxicol.*, *3*, 114-120

Parker, C.M., Piccirillo, V.J., Kurtz, S.L., Garner, F.M., Gardiner, T.H. & Van Gelder, G.A. (1984) Six-month feeding study of fenvalerate in dogs. *Fundam. appl. Toxicol.*, *4*, 577-586

Parker, C.M., Albert, J.R., Van Gelder, G.A., Patterson, D.R. & Taylor, J.L. (1985) Neuropharmacologic and neuropathologic effect of fenvalerate in mice and rats. *Fundam. appl. Toxicol.*, *5*, 278-286

Parker, C.M., Wimberley, H.C., Lam, A.S., Gardiner, T.H. & Van Gelder, G.A. (1986) Subchronic feeding study of decarboxyfenvalerate in rats. *J. Toxicol. environ. Health*, *18*, 77-90

Pati, P.C. & Bhunya, S.P. (1989) Cytogenetic effects of fenvalerate in mammalian in vivo test systems. *Mutat. Res.*, *222*, 149-154

Pluijmen, M., Drevon, C., Montesano, R., Malaveille, C., Hautefeuille, A. & Bartsch, H. (1984) Lack of mutagenicity of synthetic pyrethroids in *Salmonella typhimurium* strains and in V79 Chinese hamster cells. *Mutat. Res.*, *137*, 7-15

Puig, M., Carbonell, E., Xamena, N., Creus, A. & Marcos, R. (1989) Analysis of cytogenetic damage induced in cultured human lymphocytes by the pyrethroid insecticides cypermethrin and fenvalerate. *Mutagenesis*, *4*, 72-74

Rogosheske, S.E., Baker, G.J. & Preiss, F.J. (1982) Fenvalerate—its development and application for domestic and industrial use. *Chem. Times Trends*, *5*, 42-44, 64

Roussel Bio Corp. (1989) *Specimen Label: Gold Crest® Tribute® Termiticide/ Insecticide Concentrate*, Englewood Cliffs, NJ

Royal Society of Chemistry (1986) *European Directory of Agrochemical Products*, Vol. 3, *Insecticides, Acaricides, Nematicides*, Cambridge, pp. 4-10

Royal Society of Chemistry (1989) *The Agrochemicals Handbook* [Dialog Information Services (File 306)], Cambridge

Sakaue, S., Kida, S. & Doi, T. (1987) Gas chromatographic determination of esfenvalerate (Sumi-alpha®) in technical preparations. *Agric. Biol. Chem.*, *51*, 1671-1673

Shell Development Co. (1984) Pydrin®: insecticide. In: Zweig, G. & Sherma, J., eds, *Analytical Methods for Pesticides and Plant Growth Regulators*, Vol. XIII, *Synthetic Pyrethroids and Other Pesticides*, New York, Academic Press, pp. 121-131

Spittler, T.D., Argauer, R.J., Lisk, D.J., Mumma, R.O. & Winhett, G. (1982) Gas-liquid chromatographic determination of fenvalerate insecticide residues in processed apple products and by-products. *J. Assoc. off. anal. Chem.*, *65*, 1106-1111

Spittler, T.D., Argauer, R.J., Lisk, D.J., Mumma, R.O., Winnett, G. & Fen, D.N. (1984) Gas chromatographic determination of fenvalerate insecticide residues in processed tomato products and by-products. *J. Assoc. off. anal. Chem., 67*, 834-836

Takamatsu, Y., Kaneko, H., Abiko, J., Yoshitake, A. & Miyamoto, J. (1987) In vivo and in vitro stereoselective hydrolysis of four chiral isomers of fenvalerate. *J. Pestic. Sci., 12*, 397-404

Tucker, S.B. & Flannigan, S.A. (1983) Cutaneous effects from occupational exposure to fenvalerate. *Arch. Toxicol., 54*, 195-202

US Environmental Protection Agency (1987) *Pesticide Fact Sheet Number 145: Fenvalerate*, Washington DC, Office of Pesticide Programs

US Environmental Protection Agency (1989a) Cyano(3-phenoxphenyl)methyl 4-chloro-*alpha*-(methylethyl)benzeneacetate; tolerances for residues. Part 180—Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities. *US Code fed. Regul., Title 40*, Part 180.379, pp. 357-358

US Environmental Protection Agency (1989b) Cyano(3-phenoxphenyl)methyl 4-chloro-*alpha*-(methylethyl)benzeneacetate. Part 186—Tolerances for pesticides in animal feeds. *US Code fed. Regul., Title 40*, Part 186.1300, p. 444

US Environmental Protection Agency (1989c) Cyano(3-phenoxphenyl)methyl 4-chloro-*alpha*-(methylethyl)benzeneacetate. Part 185—Tolerances for pesticides in food. *US Code fed. Regul., Title 40*, Part 185.1300, p. 473

US Food and Drug Administration (1989) Cyano(3-phenoxyphenyl)methyl 4-chloro-*alpha*-(1-methylethyl)benzeneacetate. In: *Pesticide Analytical Manual*, Vol. II, *Methods Which Detect Multiple Residues*, Washington DC, US Department of Health and Human Services

Verschueren, K. (1983) *Handbook of Environmental Data on Organic Chemicals*, 2nd ed., New York, Van Nostrand Reinhold Co., p. 670

WHO (1990) *Fenvalerate* (Environmental Health Criteria 95), Geneva

Worthing, C.R. & Walker, S.B., eds (1987) *The Pesticide Manual—A World Compendium*, 8th ed., Thornton Heath, British Crop Protection Council, pp. 395-396

Yoshioka, H. (1978) Development of fenvalerate, a new and unique synthetic pyrethroid containing the phenylisovaleric acid moiety. *Rev. plant Prot. Res., 11*, 39-52

Yoshioka, H. (1985) Development of fenvalerate. *Chemtech, 15*, 482-486