IPCS International Programme on Chemical Safety

Environmental Health Criteria 95

Fenvalerate

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The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors that may have occurred to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone No. 7988400 - 7985850).

* * *

The proprietary information contained in this document cannot replace documentation for registration purposes, because the latter has to be closely linked to the source, the manufacturing route, and the purity/impurities of the substance to be registered. The data should be used in accordance with paragraph 82-84 and recommendations paragraph 90 of the Second FAO Government Consultation [39].

ENVIRONMENTAL HEALTH CRITERIA FOR FENVALERATE

A WHO Task Group on Environmental Health Criteria for Fenvalerate, Permethrin, and d-Phenothrin met in Tokyo from 4 to 8 July 1988. This meeting was convened with the financial assistance of the Ministry of Health and Welfare, Tokyo, Japan, and was hosted by the National Institute of Hygienic Sciences (NIHS) in Tokyo.

Dr T. Furukawa and Dr K. Shirota opened the meeting on behalf of the Ministry of Health and Welfare, and Dr A. Tanimura, Director-General of the NIHS welcomed the participants to the institute. Dr M. Mercier, Manager of the IPCS, welcomed the participants on behalf of the three IPCS cooperating organizations (UNEP/ILO/WHO). The group reviewed and revised the draft monograph and made an evaluation of the risks for human health and the environment from exposure to fenvalerate.

The first draft of this document was prepared by Dr J. MIYAMOTO and Dr M. MATSUO of the Sumitomo Chemical Company, Japan, with the assistance of the staff of the National Institute of Hygienic Sciences, Tokyo, Japan. Dr I. Yamamoto of the Tokyo University of Agriculture and Dr M. Eto of Kyushu University, Japan, assisted with the finalization of the draft.

The second draft was prepared by Dr J. SEKIZAWA, NIHS, Tokyo, incorporating comments received following circulation of the first draft to the IPCS contact points for Environmental Health Criteria documents. Dr K.W. Jager and Dr P.G. Jenkins, both members of the IPCS Central Unit, were responsible for the technical development and editing, respectively, of this monograph.

The assistance of the Sumitomo Chemical Company in making available to the IPCS and the Task Group its toxicological proprietary information on fenvalerate is gratefully acknowledged. This allowed the Task Group to make its evaluation on the basis of more complete data.

The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

ABBREVIATIONS

ai	active ingredient
Cl-Vacid (= CPIA)	2-(4-chlorophenyl)isovaleric acid
ECD-GC	gas chromatography with electron capture detector
FID-GC	gas chromatography with flame ionization detector
GLC	gas-liquid chromatography
HPLC	high-performance liquid chromatography
NOEL	no-observed-effect level
PBacid	3-phenoxybenzoic acid
PBalc	3-phenoxybenzyl alcohol
PBald	3-phenoxybenzaldehyde
PCB	polychlorinated biphenyl
TOCP	tri-*ortho*-cresyl phosphate

INTRODUCTION

SYNTHETIC PYRETHROIDS - A PROFILE

1. During investigations to modify the chemical structures of natural pyrethrins, a certain number of synthetic pyrethroids were produced with improved physical and chemical properties and greater biological activity. Several of the earlier synthetic pyrethroids were successfully commercialized, mainly for the control of household insects. Other more recent pyrethroids have been introduced as agricultural insecticides because of their excellent activity against a wide range of insect pests and their non-persistence in the environment.

2. The pyrethroids constitute another group of insecticides in addition to organochlorine, organophosphorus, carbamate, and other compounds. Pyrethroids commercially available, to date include allethrin, resmethrin, d-phenothrin, and tetramethrin (for insects of public health importance), and cypermethrin, deltamethrin, fenvalerate, and permethrin (mainly for agricultural insects). Other pyrethroids are also available, including furamethrin, kadethrin, and tellallethrin (usually for household insects), fenpropathrin, tralomethrin, cyhalothrin, lambda-cyhalothrin, tefluthrin, cufluthrin, flucythrinate, fluvalinate, and biphenate (for agricultural insects).

3. Toxicological evaluations of several synthetic pyrethroids have been performed by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR). The acceptable daily intake (ADI) has been estimated by the JMPR for cypermethrin, deltamethrin, fenvalerate, permethrin, d-phenothrin, cyfluthrin, cyhalothrin, and flucythrinate.

4. Chemically, synthetic pyrethroids are esters of specific acids (e.g., chrysanthemic acid, halo-substituted chrysanthemic acid, 2-(4-chlorophenyl)-3-methylbutyric acid) and alcohols (e.g., allethrolone, 3-phenoxybenzyl alcohol). For certain pyrethroids, the

asymmetric centre(s) exist in the acid and/or alcohol moiety, and the commercial products sometimes consist of a mixture of both optical (IR/IS or d/l) and geometric (*cis/trans*) isomers. However, most of the insecticidal activity of such products may reside in only one or two isomers. Some of the products (e.g., d-phenothrin, deltamethrin) consist only of such active isomer(s).

5. Synthetic pyrethroids are neuropoisons acting on the axons in the peripheral and central nervous systems by interacting with sodium channels in mammals and/or insects. A single dose produces toxic signs in mammals, such as tremors, hyperexcitability, salivation, choreoathetosis, and paralysis. The signs disappear fairly rapidly, and the animals recover, generally within a week. At near-lethal dose levels, synthetic pyrethroids cause transient changes in the nervous system, such as axonal swelling and/or breaks and myelin degeneration in sciatic nerves. They are not considered to cause delayed neurotoxicity of the kind induced by some organophosphorus compounds. The mechanism of toxicity of synthetic pyrethroids and their classification into two types are discussed in the Appendix.

6. Some pyrethroids (e.g., deltamethrin, fenvalerate, flucythrinate, and cypermethrin) may cause a transient itching and/or burning sensation in exposed human skin.

7. Synthetic pyrethroids are generally metabolized in mammals through ester hydrolysis, oxidation, and conjugation, and there is no tendency to accumulate in tissues. In the environment, synthetic pyrethroids are fairly rapidly degraded in soil and in plants. Ester hydrolysis and oxidation at various sites on the molecule are the major degradation processes. The pyrethroids are strongly adsorbed on soil and sediments, and hardly eluted with water. There is little tendency for bioaccumulation in organisms.

8. Because of low application rates and rapid degradation in the environment, residues in food are generally low.

9. Synthetic pyrethroids have been shown to be toxic for fish, aquatic arthropods, and honey bees in laboratory tests. But, in practical usage, no serious adverse effects have been noticed because of the low rates of application and lack of persistence in the environment. The toxicity of synthetic pyrethroids in birds and domestic animals is low.
10. In addition to the evaluation documents of FAO/WHO, there are several good reviews and books on the chemistry, metabolism, mammalian toxicity, environmental effects, etc., of synthetic pyrethroids, including those by Elliott [36], Miyamoto [126], Miyamoto & Kearney [127], and Leahey [101].

1. SUMMARY, EVALUATION, CONCLUSIONS, AND RECOMMENDATIONS

1.1 Summary and Evaluation

1.1.1 Identity, physical and chemical properties, analytical methods

Fenvalerate is a potent insecticide that has been in use since 1976. It is an ester of 2-(4-chlorophenyl)-3-methylbutyric acid and α-cyano-3-phenoxybenzyl alcohol, but lacks a cyclopropane ring. However, in terms of its insecticidal behaviour, it belongs to the pyrethroid insecticides. It is a racemic mixture of four optical isomers with the configurations [2S, αS], [2S, αR], [2R, αS], and [2R, αR]. The [2S, αS] isomer is the most biologically active, followed by the [2S, αR] isomer.

Technical grade fenvalerate is a yellow or brown viscous liquid having a specific gravity of 1.175 at 25 °C. The vapour pressure is 0.037 mPa at 25 °C and it is relatively non-volatile. It is practically insoluble in water (approximately 2 μg/litre), but soluble in organic solvents such as acetone, xylene, and kerosene. It is stable to light, heat, and moisture, but unstable in alkaline media due to hydrolysis of the ester linkage.

Residue and environmental analysis can be carried out using a gas chromatograph equipped with an electron capture detector, the minimum detectable concentration being 0.005 mg/kg. A gas chromatograph with a flame ionization detector is used for product analysis.

1.1.2 Production and use

Approximately 1000 tonnes per year of fenvalerate are used worldwide (1979-1983 figures). It is mostly employed in agriculture but also for insect control in homes and gardens and on cattle, alone or in combination with other insecticides. It is formulated as emulsifiable concentrate, ultra-low-volume concentrate, dust, and wettable powder.

1.1.3 *Human exposure*

Exposure of the general population to fenvalerate is mainly via dietary residues. Residue levels in crops grown by good agricultural practice are generally low. The resulting exposure of the general population is expected to be very low, but data from total-diet studies are lacking.

Analysis of residues in stored grain showed that over 70% of the applied dose remained on wheat after 10 months at 25 °C. Following milling and baking, white bread has about the same residue level as white flour (approximately 0.06-0.1 mg/kg).

Information on occupational exposure to fenvalerate is very limited.

1.1.4 *Environmental fate*

In soil, degradation occurs via ester cleavage, diphenyl ether cleavage, ring hydroxylation, hydration of the cyano group to amide, and further oxidation of the fragments formed to yield carbon dioxide as a major final product. Studies to investigate the leaching potential of fenvalerate and its degradation products showed that very little downward movement will occur in soils.

In water and on soil surfaces, fenvalerate is photo-degraded by sunlight. Ester cleavage, hydrolysis of the cyano group, decarboxylation to yield 2-(3-phenoxyphenyl)-3-(4-chlorophenyl)-4-methylpentane-nitrile (decarboxy-fenvalerate), and other radical-initiated reactions have been shown to occur.

On plants, fenvalerate has a half-life of approximately 14 days. Ester cleavage is a major reaction, followed by oxidation and/or conjugation of the fragments formed. Decarboxylation to yield decarboxy-fenvalerate also occurs.

In general, the degradative processes which occur in the environment lead to less toxic products.

The degradation of fenvalerate in the environment is rather rapid. Half-lives are 4-15 days in river water,

8-14 days on plants, 1-18 days by photodegradation on soil and 15 days-3 months in soil.

There is virtually no leaching of fenvalerate in soil. Thus, it is unlikely that the compound will attain significant levels in the aquatic environment.

1.1.5 *Kinetics and metabolism*

The fate of fenvalerate in rats and mice has been studied using fenvalerate radiolabelled in the acid moiety or benzyl or cyano groups. The administered radioactivity, except that of the cyano-labelled compounds, is readily excreted (up to 99% in 6 days). The major metabolic reactions are ester cleavage and hydroxylation at the 4′ position. Various oxidative and conjugation reactions that lead to a complex mixture of products have been shown to occur. When studies were carried out with fenvalerate radiolabelled in the cyano group, elimination of the radioactive dose was less rapid (up to 81% in 6 days). The remaining radioactivity was retained mainly in the skin, hair, and stomach as thiocyanate. A minor, but very important, metabolic pathway is the formation of a lipophilic conjugate of [2R]-2-(4-chlorophenyl)isovalerate. This conjugate, which is implicated in the formation of granuloma, has been detected in the adrenals, liver and mesenteric lymph nodes of rats, mice, and some other species.

1.1.6 *Effects on organisms in the environment*

In laboratory tests, fenvalerate is highly toxic for aquatic organisms. The LC_{50} values range from 0.008 μg/litre for newly hatched mysid shrimps to 2 μg/litre for a stonefly. The no-observed-effect level in life-cycle tests using *Daphnia galeata mendotae* is less than 0.005 μg/litre. Fenvalerate is also highly toxic for fish. The 96-h LC_{50} values range from 0.3 μg/litre for larval grunion to 200 μg/litre for adult *Tilapia*. The no-observed-effect level, over 28 days, for early-life stages of the sheepshead minnow is 0.56 μg/litre. Fenvalerate is less toxic for aquatic algae and molluscs, with 96-h LC_{50} values > 1000 μg/litre.

In field tests and in the use of the compound under practical conditions, the potentially high toxicity to aquatic organisms is not manifested. Some aquatic invertebrates are killed when water is oversprayed, but the effect on populations is temporary. There have been no reports of fish kills. This reduced toxicity in field use is related to the strong adsorption of the compound to sediments.

Fenvalerate is highly toxic to honey bees. The topical LD_{50} is 0.41 μg/bee, but there is a strong repellent effect of fenvalerate to bees, which reduces the effect in practice. There is no evidence of significant kills of honey bees under normal use. Fenvalerate is more toxic to predator mites than to the target pest species.

Fenvalerate has very low toxicity to birds when given orally or applied to the diet. LD_{50} values are > 1500 mg/kg body weight for acute oral dosage and an LD_{50} value for dietary exposure of Bobwhite quail has been reported at > 15 000 mg/kg diet.

Fenvalerate is readily taken up by aquatic organisms. Bioconcentration factors ranged from 120 to 4700 for various organisms (algae, snail, Daphnia and fish) in model ecosystem studies. The fenvalerate taken up by aquatic organisms is rapidly lost on transfer to clean water. The compound can, therefore, be regarded as having no tendency to bioaccumulate in practice.

.1.7 *Effects on experimental animals and* in vitro *test systems*

Fenvalerate has moderate to low acute oral toxicity. However, LD_{50} values differ considerably (82 to > 3200 mg/kg) according to animal species and vehicle of administration. The acute clinical signs of poisoning appear rapidly but survivors become asymptomatic within 3-4 days. The toxic signs of the racemic mixture, as well as of its [2S, αS] isomer, include restlessness, tremors, pilo-erection, diarrhoea, abnormal gait, choreo-athetosis, and salivation (CS-syndrome); it is classified as a Type II pyrethroid. Electrophysiologically it produces bursts of spikes in the cercal motor nerve of the cockroach. There is, however, no clear-cut link between electro-physiological findings in insects and toxicity to mammals.

Rats fed fenvalerate at 2000 mg/kg diet for 8-10 days showed typical signs of acute intoxication. Reversible morphological changes in the sciatic nerve were observed in rats administered fenvalerate at 3000 mg/kg diet. Histopathological changes in sciatic nerves were also observed in rats and mice treated with a single oral does of fenvalerate at lethal or sublethal levels.

Hens administered fenvalerate orally at 1000 mg/kg per day for 5 days did not show any clinical or morphological signs of delayed neurotoxicity.

The acute intraperitoneal toxicity of fenvalerate metabolites in mice was no greater than that of fenvalerate itself.

In subacute and subchronic toxicity studies, mice, rats, dogs, and rabbits were treated with fenvalerate by oral, dermal, and inhalational routes for 3 weeks to 6 months. In 4-week mouse and rat inhalation studies, a no-observed-effect level (NOEL) of 7 mg/m^3 was established in both species. The NOEL in a 90-day rat study was 125 mg/kg diet, in a 2-year feeding study it was 250 mg/kg diet (12.5 mg/kg body weight), and in a 24-28 month study it was 150 mg/kg diet, (7.5 mg/kg body weight). The NOEL in a 2-year mouse study was 50 mg/kg diet, corresponding to 6.0 mg/kg body weight, and 30 mg/kg diet, corresponding to 3.5 mg/kg body weight, in a 20-month feeding study. For dogs the NOEL was 12.5 mg/kg body weight in a 90-day feeding study. Some fenvalerate formulations have caused skin and eye irritation. However, technical fenvalerate is non-irritant and has no sensitizing effects.

In long-term toxicity studies, microgranulomatous changes were observed in mice, specifically when treated with the [2R, αS] isomer of fenvalerate (125 mg/kg diet) for 1 to 3 months. These changes were reversed when fenvalerate was eliminated from the diet. The causative agent for this change was the cholesterol ester of 2-(4-chlorophenyl)isovaleric acid, a lipophilic metabolite of fenvalerate from the [2R, αS] isomer. The NOEL for these microgranulomatous changes in mice was 30 mg fenvalerate per kg diet.

In a long-term toxicity study, microgranulomatous changes were also observed in rats at a dose level of

500 mg/kg diet, the NOEL for these changes being 150 mg/kg diet.

Fenvalerate was not carcinogenic to mice, when fed at dietary levels up to 3000 mg/kg for 78 weeks or 1250 mg/kg for 2 years. It was also not carcinogenic to rats when fed at dietary levels up to 1000 mg/kg for 2 years.

Fenvalerate did not show any mutagenic or chromosome-damaging activity in several *in vitro* and *in vivo* assays.

Fenvalerate is not teratogenic to mice or rabbits at dose levels of up to 50 mg/kg body weight per day, nor did it show any toxic effects (at up to 250 mg/kg diet) on reproductive parameters in a 3-generation rat reproduction study.

'.1.8 Effects on human beings

Fenvalerate can induce numbness, itching, tingling, and burning sensations in exposed workers, which develop after a latent period of approximately 30 min, peak by 8 h, and disappear within 24 hours. Some poisoning cases have resulted from occupational exposure, owing to over-exposure due to neglect of safety precautions.

There are no indications that fenvalerate will have an adverse effect on human beings, provided it is used as recommended.

.2 Conclusions

.2.1 General population

The exposure of the general population to fenvalerate is expected to be very low. It is not likely to present a hazard provided it is used as recommended.

2.2 Occupational exposure

With reasonable work practices, hygiene measures, and safety precautions, fenvalerate is unlikely to present a hazard to those occupationally exposed to it.

1.2.3 Environment

It is unlikely that fenvalerate or its degradation products will attain levels of environmental significance provided that recommended application rates are used. Under laboratory conditions fenvalerate is highly toxic to fish, aquatic arthropods, and honey bees. However, lasting adverse effects are not likely to occur under field conditions provided it is used as recommended.

1.3 Recommendations

Although dietary levels arising from recommended usage are considered to be very low, confirmation of this through inclusion of fenvalerate in monitoring studies should be considered.

Fenvalerate has been used for many years and only a few cases of temporary effects from occupational exposure have been reported. Nevertheless, it would be wise to maintain observations of human exposure.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Fenvalerate is a synthetic pyrethroid having no cyclopropane ring in the molecule. It is prepared by the esterification of (2RS)-2-(4-chlorophenyl)-3-methylbutyric acid (also known as (2RS)-2-(4-chlorophenyl)isovaleric acid, CPIA, or Cl-Vacid) with (αRS)-α-cyano-3-phenoxybenzyl alcohol [137]. It has four stereoisomers as a result of the two chiral centres in the acid and alcohol moieties (Fig. 1).

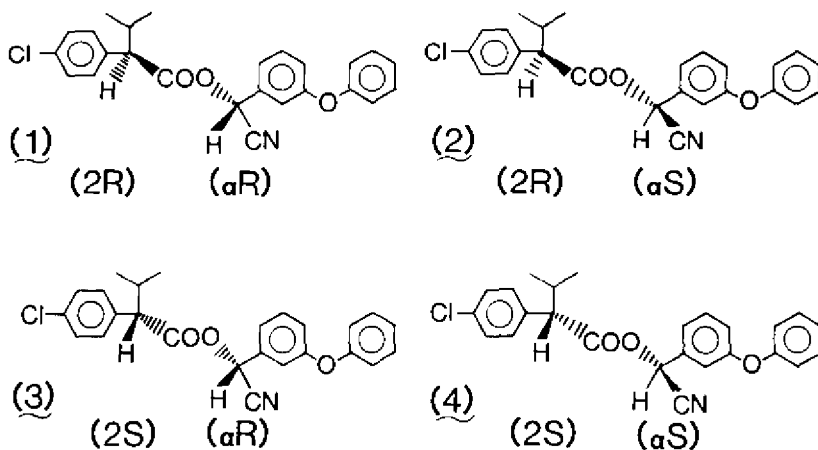


Fig. 1. Chemical structure of the four stereoisomers of fenvalerate.

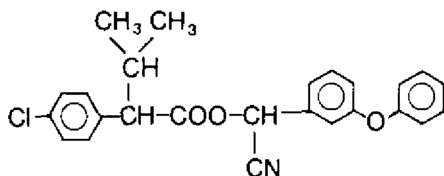
The composition of the product is a racemic mixture of the four isomers in equal proportions (Table 1). Technical grade fenvalerate contains 90-94% of fenvalerate [41]. The molecular formula is $C_{25}H_{22}ClNO_3$.

Table 1. Chemical identity of fenvalerate and its various stereoisomers

Common name/ CAS Registry no./ NIOSH Accession no.[a]	CAS Index name (9CI) / Stereospecific name[b]	Stereoisomeric composition[c]	Synonyms and trade names
Fenvalerate 51630-58-1 CY1576350	Benzeneacetic acid, 4-chloro-*alpha*-(1-methylethyl)-, cyano(3-phenoxyphenyl)methyl ester (RS)-*alpha*-cyano-3-phenoxybenzyl (RS)-2-(4-chlorophenyl)-3-methylbutyrate	(1):(2):(3):(4) = 1:1:1:1	Sumicidin, Belmark, Pydrin, S-5602 SD43775, WL43775
alpha-Fenvalerate 66230-04-4	Same as fenvalerate Benzeneacetic acid, 4-chloro-*alpha*-(1-methylethyl)-, cyano-3-phenylbenzyl ester, [S-(R*,R*)]-		
beta-Fenvalerate 66267-77-4	Same as fenvalerate Benzeneacetic acid, 4-chloro-*alpha*-(1-methylethyl)-, cyano-3-phenoxybenzyl ester, [R-R*, S*)]-		
(S,S)-Fenvalerate CY1576350			

a Registry of Toxic Effects of Chemical Substances (1981-1982 edition).
b (2S), d, (+) or (2R), 1, (-) in the acid part of fenvalerate signify the same stereospecific conformation, respectively.
c Numbers in parantheses identify the structures shown in Fig. 1.

Structural formula:



2.2 Physical and Chemical Properties

Some physical and chemical properties of fenvalerate are given in Table 2. It is stable to heat and moisture and is relatively stable (compared with natural pyrethrins) when exposed to light. It is more stable in acidic than in alkaline media, optimum stability being at pH 4 [41, 117, 207].

Table 2. Some physical and chemical properties of fenvalerate

Physical state	viscous liquid
Colour	yellow or brown
Odour	mild "chemical" odour
Relative molecular mass	419.9
Boiling point	300 °C at 4.93 kPa (37 mmHg)
Water solubility	2 µg/litre
Solubility in organic solvents	soluble[a]
Relative density (25 °C)	1.175
Vapour pressure (25 °C)	0.037 mPa
Log octanol-water partition coefficient (log P_{OW})	6.2

[a] Acetone (>1 kg/kg), hexane (155 g/kg), xylene (>1 kg/kg), ethanol, cyclohexanone, ether, kerosene, chloroform.

2.3 Analytical Methods

Methods for the analysis of fenvalerate are summarized in Table 3. This table includes the procedures for (a) extraction with solvent, (b) liquid-liquid partition, (c) chromatographic separation (clean up), and (d) quantitative and qualitative determination by suitable analytical instruments, and also includes minimum detectable concentration (MDC) and percentage recovery data.

The separation of the cis and trans isomers of fenvalerate has been carried out using a commercially available Pirkle type 1-A chiralphase HPLC with, as solvent system, 0.025% propen-2-ol in hexane (1 ml/min) [24].

Fenvalerate can be determined by gas-liquid chromatography with a flame ionization detector (FID-GC) (3% OV-17 glass column with temperature programming) [11].

A laminar flow, microwave-induced plasma torch has been evaluated for its use in gas chromatography [19]. The detection limit of fenvalerate on the carbon channel was 0.054 μg/ml.

To analyse technical grade fenvalerate, the product is dissolved in chloroform together with 2-(4-biphenyl)-5-phenyl-1,3,4-oxadiazole (an internal standard), and the solution is injected into an FID-GC system [79].

The Joint FAO/WHO Codex Alimentarius Commission has published recommendations for methods for the analysis of fenvalerate residues [48].

Table 3. Analytical methods for fenvalerate

Sample	Sample preparation				Determination	MDC[b]	% Recovery	Reference
	Extraction solvent	Partition	Clean-up		GLC or HPLC; detector, carrier flow, column, temperature, retention time		(fortification level) (mg/kg)[c]	
			Column	Elution				
Residue analysis								
apple pear cabbage potato	*n*-hexane acetone (1/1)	ext.sol.[a] $/H_2O$	silica gel	CH_2Cl_2	ECD-GC, N_2, 50 ml/min, 1 m, 3% OV-7, 235 °C	0.01	89-108 (0.1-1.0)	6
grape pepper	acetone	saturated NaCl/ petroleum ether	Florisil	acetone/ petroleum ether (1/99)	ECD-GC, N_2, 30 ml/min, 1.1 m, 2% XE-60, 215 °C, 7 min	0.005	94-99 (0.005-1.0)	67
cabbage lettuce	CH_3CN	1% NaCl/ petroleum ether	Florisil silica gel	benzene/*n*-hexane (1/1) benzene/ acetone (3/1)	ECD-GC, argon/methane (95/5), 45 ml/min, 1.8 m, 4% SE-30/6% QF-1 or 15% OV-101, 225 °C, 25-30 min	0.005	88-104 (0.012-1.2)	103
beef muscle egg yolk milk	CH_3CN/ H_2O (85/15) or CH_3CN	*n*-hexane/ 2% NaCl solution	Florisil	CH_3CN/ CH_2Cl_2/ *n*-hexane (0.35/50/50)	ECD-GC, N_2, 100 ml/min, 1.8 m, Ultra-Bond 20M, 220 °C, 11.5, 14.2 min	0.005	82-94 (0.01-1.0)	16

Table 3 (contd).

Sample	Sample preparation				Determination	MDC[b]	% Recovery	Reference
	Extraction solvent	Partition	Clean-up		GLC or HPLC; detector, carrier flow, column, temperature, retention time		(fortification level) (mg/kg)[c]	
			Column	Elution				
Environmental analysis								
soil	acetone, *n*-hexane/ acetone (1/1), hexane	2% NaCl/ ext.sol.[a]	alumina	ether/ *n*-hexane (1/9)	ECD-GC, argon/methane (95/5), 60 ml/min, 0.97 m, 6% OV-210, 230 °C, 10.6, 11.8 min		78-105 (0.005-1.0)	74
Product analysis								
Technical grade	$CHCl_3$				FID-GC, He, 60 ml/min, 1.0 m, 2% Apiezon L, 245 °C			79

[a] extraction solvent.
[b] minimum detectable concentration (mg/kg).
[c] fortification level indicates the concentration of fenvalerate added to control samples for the measurement of recovery.

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE: ENVIRONMENTAL LEVELS

3.1 Industrial Production

Fenvalerate was first marketed in 1976 and the estimated production was 1000 tonnes in 1979 and 889 tonnes in 1982 [203]. Recent world-wide production figures are listed in Table 4.

Table 4. World-wide production of fenvalerate

Year	Production (tonnes)	Reference
1979	1016	200
1980	1067	201
1981	914	202, 203
1982	903	203
1983	1280	204
1984	919	9

3.2 Use Patterns

Of the total world-wide consumption of 473 tonnes of fenvalerate in 1980 [8], 271 tonnes were used in the USA, 103 tonnes in Latin America, 43 tonnes in Africa, 28 tonnes in Western Europe, and 26 tonnes each in Australia and Turkey. It was mostly used on cotton (90.3% of the consumption) but some was used on other crops such as vines, tomatoes, potatoes, pomes, and other fruit.

Fenvalerate has also been used for homes and gardens and for the control of cattle insect infestation [8]. It is formulated in emulsifiable concentrates (25-300 g/litre), ultra-low volume concentrates (25-75 g/litre), dusts, and wettable powder, and is also used in combination with other pesticides (e.g., fenitrothion).

3.3 Residues in Food

Supervised trials have been carried out on a wide variety of crops and comprehensive summaries of the results of residue analysis in these trials are contained in the evaluation reports of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) [41, 43, 45, 47, 50]. A comprehensive list of Maximum Residue Limits (MRLs) for a large number of commodities resulted from these evaluations [51].

In one study, apples in the USA were treated four times with 30% emulsifiable concentrate at a rate of 0.67 kg active ingredient/ha. The residue levels were 2.2 mg/kg in whole apples, 7.3 mg/kg in peel, and 0.03 mg/kg in peeled fruits 6 weeks after the last application [41].

When wheat grain treated with fenvalerate at a rate of 1.01 mg/kg was stored at 25 °C, the residue levels were 0.86 mg/kg after 6.5 months of storage and 0.74 mg/kg after 10 months[a].

Three lactating cows were fed ^{14}C-(acid-labelled)-fenvalerate at a dose level of 0.11 mg/kg diet daily for 21 days and sacrificed 12 h after receiving the last dose. The recovery of ^{14}C in the milk was less than 1% and the levels ranged from < 0.0006 to 0.0019 µg/litre, with a plateau occurring after 1 week of feeding. No ^{14}C was detectable in fat (< 0.02 mg/kg) or muscle (< 0.01 mg/kg). In another study, fenvalerate was sprayed on cows at a rate of 0.2, 0.4, or 2 g/animal. The residue level did not exceed 0.01 mg/kg muscle. Maximum residues were 0.22 mg/kg in fat and 0.02 mg/kg in milk at the dose rate of 2 g/cow [132, 154].

When wheat containing 0.6 mg fenvalerate/kg was subjected to milling and baking, white bread was found to

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[a] *M. Bengston (1979), personal communication from final report on silo-scale experiments 1977-1978 to the Australian Wheat Board Working Party on grain protectants. Queensland Department of Primary Industries (unpublished report cited from FAO/WHO [41].*

have about the same residue level as white flour, i.e., about 0.06-0.1 and 0.08-0.09 mg/kg, respectively[b].

3.4 Residues in the Environment

Data on actual levels of fenvalerate residues in air, water, or soil are not available. Residues in air would not be expected for a compound with a vapour pressure of 0.037 mPa at 25 °C.

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b *B.W. Simpson (1979), draft report to be published by Queensland Department of Primary Industries Analytical Chemical Branch, Brisbane, Australia (unpublished report cited in FAO/WHO [41].*

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

Appraisal

The major photodegradation routes for fenvalerate are decarboxylation to yield 3-(4-chlorophenyl)-4-methyl-2-(3-phenoxyphenyl)-valeronitrile, ester and ether cleavage, hydrolysis of the cyanide group, and other radical-initiated reactions. Ester cleavage and some photo-initiated reactions are the major routes of decomposition on plants. In soils, the formation of bound material and the evolution of carbon dioxide are the major processes observed under both aerobic and anaerobic conditions.

The degradation pathways of fenvalerate are summarized in Fig. 2.

4.1 Transportation and Distribution Between Media

Hill [74] investigated the distribution of fenvalerate residues in soil under field conditions using a microplot technique. The microplots (20 x 20 cm) were treated with fenvalerate at a rate of 150 g/ha. After 45 weeks, 11% of the applied fenvalerate was located in the 0-2.5 cm soil layer and less than 0.5% in the 2.5-5 cm soil samples. Less than 0.1% of the applied fenvalerate was detected in any of the soil samples taken after 3 or 4 weeks, despite a rainfall of 95.4 mm during the first 4 weeks (including a 25.9 mm downpour 15 days after application). These results indicate that fenvalerate does not readily leach downward and that lateral surface movement is very limited.

A similar conclusion was obtained from laboratory soil-leaching studies. More than 95% of the applied fenvalerate remained in the treated portion of soil columns when leaching was started immediately or 30 days after treatment of the soil [133]. The possibility of fenvalerate accumulating in orchard soils was assessed by monitoring soil and leaf litter in an orchard in the Okanagan valley, British Columbia, Canada, following

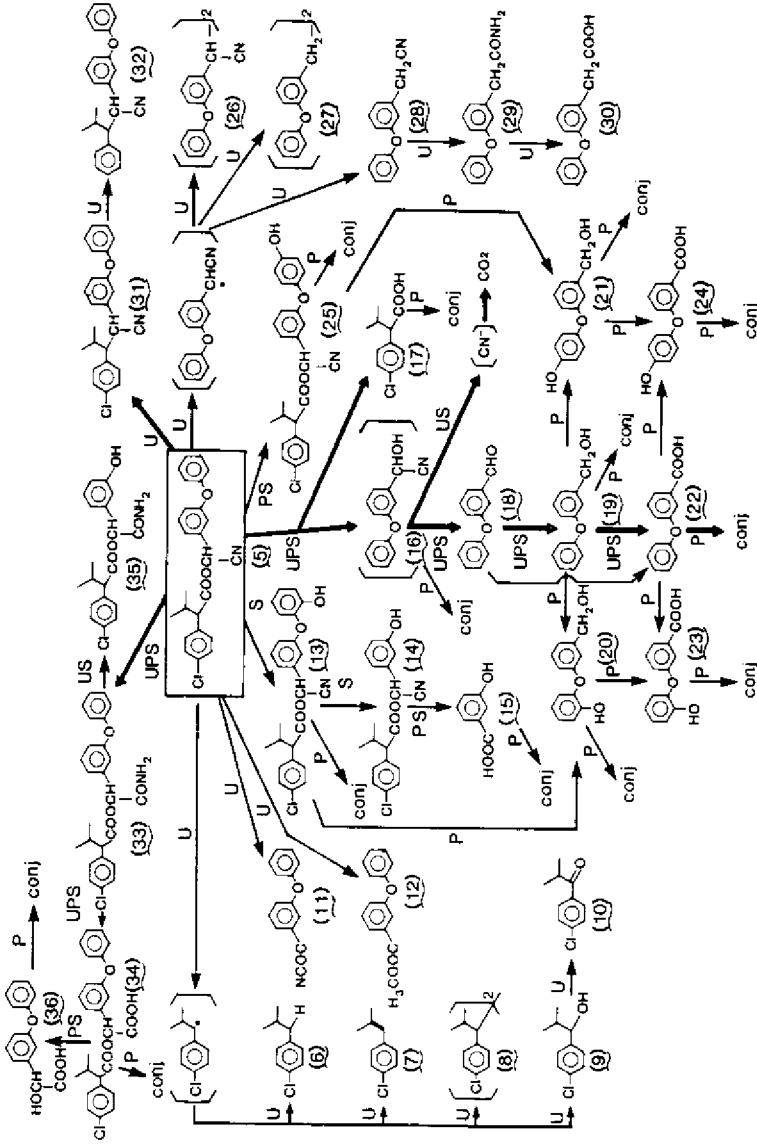

Fig. 2. Degradation pathways of fenvalerate in plants and soil and under the action of UV light.
U = UV light, P = plant, conj = sugar conjugate, S = soil and soil microorganisms.

multiple annual application of the pesticide. Belmark 300 (30% fenvalerate EC formulation) had been sprayed at a rate of 188-500 ml/ha (one to three times per year) for more than three years. To obtain initial concentration, organic litter samples were sprayed at a rate of 450 ml/ha and samples were collected 2 h later. While the initial concentration thus obtained in the litter was 0.214 mg/kg (average value), orchard litter samples contained 0.30-0.63 mg/kg while samples from a non-treated block contained < 0.002 mg/kg. Orchard soil samples (0-15 cm depth) in two orchards contained fenvalerate residues of < 0.0035-0.006 mg/kg and 0.0063-0.024 mg/kg [188].

4.2 Photodecomposition[a]

In studies by Holmstead et al. [78], fenvalerate (5), at a concentration of 0.01 mol/litre in methanol, hexane, or acetonitrilewater (60:40), underwent rapid photodegradation under the action of UV light (290-320 nm) with a half-life of 16-18 min (Fig. 2). With 90-95% conversion after 60 min, 2-(3-phenoxyphenyl)-3-(4-chlorophenyl)-4-methyl-pentanenitrile (31) (decarboxy-fenvalerate) was the major photoproduct, amounting to 54-57% of the total reaction mixture. There were smaller amounts of the dechlorinated analogue (32) of decarboxy-fenvalerate and the dimer (8) of 2,2-dimethyl-4-chlorostyrene. 3-Phenoxybenzoyl cyanide (4), 3-phenoxybenzaldehyde (18) (PBald), 4-chloro-isobutylbenzene (6), and 2,2-dimethyl-4-chlorostyrene (7) were detected in small amounts in hexane or methanol. 3-Phenoxybenzyl cyanide (28), its dimer (26), and 1,2-*bis*-(phenoxyphenyl)ethane (27) were found only in hexane, and methyl 3-phenoxybenzoate (12) was detected only in methanol. Products found uniquely in acetonitrile-water were 2-(4-chlorophenyl)-3-methylbutyric acid (17) (CPIA), 3-phenoxybenzoic acid (22) (PBacid) and 1-(4-chlorophenyl)-2-methylpropanol (9). Several unknown compounds were observed in the remaining 5-10%. Fenvalerate, in a thin film (1 mg/cm^2) on glass, decomposed in sunlight with a half-life of approximately 4 days. About 10% of the applied

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[a] *The numbers in brackets following chemical names refer to the numbers given in Fig. 2.*

material remained after 43 days. In addition to the photoproducts formed in solution, small amounts of 3-phenoxybenzyl alcohol (19) (PBalc) and isopropyl 4-chlorophenylketone (10) were detected.

On exposure to autumn sunlight in Japan, the [2S, αS] isomer of fenvalerate in distilled water decomposed with a half-life of approximate 10 days. This isomer photodecomposed via pathways that included decarboxylation, hydration of the CN group to a carbamoyl ($CONH_2$) group, hydrolysis of the $CONH_2$ group to a carboxyl (COOH) group, and cleavage of the ester or diphenyl ether linkage. Cleavage of the ester linkage was a major photochemical reaction and led to the formation of 2-(4-chlorophenyl)-3-methylbutyric acid (17) (17.3% of the applied ^{14}C, 10 days after exposure). There was no significant difference between fenvalerate and the [2S, αS] isomer in the rates and routes of photodegradation [179].

The photodegradation of fenvalerate (0.3-0.4 ng/cm^2) on two kinds of soil in natural sunlight was compared with that of the [2S, αS] isomer. Fenvalerate and its isomer photodecomposed with half-lives of 1.4-2.4 days and 1.1-2.5 days, respectively. The pathways included hydration of the cyano group to the carbamoyl group (19.2-48.4% at 10 days) with subsequent hydrolysis to the carboxyl group (0.9-2.0% at 10 days), ester-bond cleavage (3.4-4.5% at 10 days), and decarboxylation (0.3-0.9% at 10 days). Little 2S/2R and αS/αR isomerization (as determined by HPLC) occurred on the soils. There was no significant difference between the two compounds in the rates and pathways of photodegradation [89].

Holmstead & Fullmer [77] investigated the photodecarboxylation of several cyanohydrin esters in methanol and hexane under artificial light as models for pyrethroid photodecomposition. The cyanohydrin esters gave rise to decarboxylated products, to a greater or lesser extent, whereas the analogous compounds without the cyano group did not produce the photodecarboxylated compounds. α-Cyanobenzyl phenylacetate, which yielded the stable benzyl radical, gave substantially larger amounts of the decarboxylated product than α-cyanobenzyl benzoate, which produced the unstable phenyl radical.

The photodegradation of fenvalerate in water and on soil was investigated using compounds labelled with ^{14}C at the following positions: carbonyl group (CO-fenvalerate), α-carbon in the benzyl group (Cα-fenvalerate), and cyano group (CN-fenvalerate) [118]. On exposure to sunlight, fenvalerate in very dilute solution in distilled water, in 2% aqueous acetone, in filter-sterilized river water, or in sea water underwent rapid photolysis with half-lives of approximately 4 days in summer and 13-15 days in winter. The quantum yield was calculated at 6.6×10^{-3} (at 313 nm in water) and the half-life of disappearance at latitude 40°N was calculated at 4.1 days in summer and 12.4 days in winter, values which were close to the experimental ones. Photodegradation of ^{14}CN-fenvalerate resulted in the formation of greater amounts of $^{14}CO_2$ than $^{14}CN^-$. After 6 weeks irradiation, approximately 30% (in aqueous acetone or river water) or approximately 55-60% (in distilled water or sea water) of the ^{14}C was recovered as $^{14}CO_2$, while the corresponding figures for $^{14}CN^-$ were 5% and 30%. One of the major photodegradation products was decarboxy-fenvalerate (31), which increased to approximately 20% (in distilled water) in summer after 1 week and decreased thereafter. In winter, the amount was approximately 20% after 6 weeks. Other major products were PBacid (22) and CPIA (17), derived from the ester bond cleavage, amounting to 43% and 58%, respectively, of the applied radioactivity after 6 weeks in winter. In addition, small amounts of α-carbamoyl-3-phenoxybenzyl-2-(4-chlorophenyl)-3-methylbutyrate (33) ($CONH_2$-fenvalerate), α-carboxy-3-phenoxybenzyl-2-(4-chlorophenyl)-3-methylbutyrate (34) (COOH-fenvalerate), 3-phenoxybenzyl cyanide (28), 3-phenoxyphenylacetamide (29), 3-phenoxyphenylacetic acid (30), PBalc, and PBald were detected.

Fenvalerate, as a deposit (5.5-5.9 $\mu g/100\ cm^2$) on Kodaira light clay, Azuchi sandy clay loam, and Katano sandy loam soil from Japan, was decomposed by autumn sunlight with the respective half-lives of 2, 6, and 18 days [118]. The major product was $CONH_2$-fenvalerate (33), which amounted to 7.9-25.7% of the applied radioactivity after 10 days; it was formed in greatest amounts in sunlight but also formed in the dark. Smaller amounts of decarboxy-fenvalerate (31), the desphenyl analogue of

$CONH_2$-fenvalerate (35), COOH-fenvalerate (34), PBacid, and PBalc were also detected. Of the applied radiocarbon, 3-10% remained unidentified.

4.3 Decomposition in Plants

Fenvalerate (2.4% emulsifiable concentrate (EC)), permethrin (2% EC), and deltamethrin (25 g/litre) were sprayed onto cotton fields in Arizona, USA, at respective rates of 0.11, 0.11, and 0.23 kg/ha, and dislodgeable residues of the insecticides on cotton foliage were examined. Of the original deposits of fenvalerate, 65% remained at the end of 96 h (there were two rains between 24 and 48 h), compared with 47% and 32% for permethrin and deltamethrin, respectively [57].

Fenvalerate deposits on cotton plants (0.8 mg/plant) disappeared rapidly, with only half the material remaining after 8 days of exposure. After 23 days, decarboxy-fenvalerate and ester-cleavage products such as PBacid, PBald, PBalc, and CPIA were detectable, but not quantifiable. Decarboxy-fenvalerate was considerably more stable to UV light than fenvalerate, but it decomposed at a somewhat faster rate than *p,p′*-DDT, yielding mainly the dechlorinated analogue [78].

The metabolism of fenvalerate in kidney bean plants has been studied under laboratory conditions by Ohkawa et al. [136]. Fenvalerate labelled with ^{14}C at the cyano group and the [2S, αRS] isomer labelled separately at the cyano, carboxy, and benzylic carbon atoms were used to treat individual bean leaves of 14-day-old seedlings at a rate of 10 μg per leaf. After 60 days, 85-86% of the applied ^{14}C was recovered from plants treated with the carboxy and benzyl labels, whereas 67% was recovered from plants treated with the cyano label. Only limited translocation was observed and only very low levels of radioactive residues (2-9 μg/kg) were detected in seeds. Fenvalerate and the [2S, αRS] isomer disappeared at a similar rate from the treated leaves with an initial half-life of 14 days.

The metabolism of racemic fenvalerate and of its [2S, αS] isomer was examined in cabbage plants grown under laboratory conditions and treated (20 μg per leaf)

with [^{14}C]-chlorophenyl- and [phenyl-^{14}C]-benzyl-labelled preparations of the two compounds. Both compounds disappeared from the treated leaves with similar half-lives of approximately 12-14 days. They underwent ester cleavage to a significant extent, together with some hydroxylation at the 2- or 4-position of the phenoxy ring and hydrolysis of the nitrile group to amide and carboxyl groups. Most of the carboxylic acids and phenols thus produced occurred as glycoside conjugates. In a separate experiment, the uptake and metabolism of CPIA (17) was examined in the laboratory using abscised leaves of kidney bean, cabbage, cotton, cucumber, and tomato plants. The acid (17) was found to be readily converted, mainly into glucose or 6-O-malonylglucose esters in kidney bean, cabbage, and cucumber, into glucosylxylose, sophorose, and gentiobiose esters in cotton, and into two types of triglucose esters with differing isomerism in tomato. One of the acetyl-derived glucoside conjugates was identical with the authentic deca-acetyl derivative of the [1-6]-triglucose ester [121].

In studies by Ohkawa et al. [136], fenvalerate was metabolized or degraded in bean plants via several routes. A minor route was hydrolysis of the cyano group leading to the formation of the amide (33) and carboxylic acid (34) derivatives of fenvalerate. The 3-phen-oxybenzyl moiety underwent metabolism to yield PBacid, 3-(2′-hydroxyphenoxy)benzoic acid (23) and PBalc, which occurred mainly as sugar conjugates. In addition, glucoside conjugates of α-carboxy-3-phenoxybenzyl alcohol (36) were detected to a lesser extent. The presence of α-cyano-3-phenoxybenzyl alcohol (16) conjugates was inferred since PBald was released upon treatment with beta-glucosidase. A major metabolite of the acid moiety was CPIA (17), which also occurred mainly as glucoside conjugates. The decarboxy derivative (31) of fenvalerate, presumably formed by photochemical reaction on plant foliage as discussed previously, was detected in leaf extracts. When bean plant seedlings were planted and left for 30 days in light clay and sandy loam soils treated with ^{14}C-fenvalerate at 1 mg/kg, the roots retained fairly large amounts of radiocarbon. However, only limited radiocarbon was found in the shoots (0.02 mg/kg), pods and seeds (0.01 mg/kg), and there was no parent compound in the shoots.

Additional studies were carried out to investigate the fate of 3-phenoxybenzoic acid (an important metabolite of fenvalerate and most other pyrethroids) in plants. Using abscised leaves of cabbage, cotton, cucumber, kidney bean and tomato plants, ^{14}C-3-phenoxybenzoic acid was shown to conjugate with a complex range of sugars [120].

4.4 Decomposition in Soils

The degradation of fenvalerate in soils has been studied under various conditions (aerobic or anaerobic conditions, laboratory or field conditions, using radioactive or non-radioactive material).

Samples of ^{14}C-fenvalerate labelled separately in the carboxy and cyano groups were used for soil studies by Ohkawa et al. [133]. When several types of soil were treated at a rate of 1 mg/kg and stored at 25°C under aerobic conditions, the initial half-life of fenvalerate ranged from 15 days to 3 months. As with other pyrethroids, hydrolysis at the ester linkage was a major degradation route, and ring hydroxylation in the 4′-position (25), together with hydrolysis of the cyano group to the amide and carboxyl groups, occurred to smaller extents. The degradation route unique to fenvalerate was ether-bond cleavage yielding α-cyano-3-hydroxybenzyl-1-2-(4-chlorophenyl)-3-methylbutyrate (14), which could be produced through hydroxylation at the 2′-position (13) in the alcohol moiety. No $H^{14}CN$ released during ester-bond cleavage was detected owing to its rapid conversion to $^{14}CO_2$. The amount of $^{14}CO_2$ was greater with the cyano label than the carboxy label. For example, after 30 days in Katano sandy loam soil, 47.5% and 38.2% of the applied radiolabel was evolved as $^{14}CO_2$ from the cyano and carboxyl groups, respectively. In a laboratory soil-leaching study, less than 1% of the applied radiocarbon appeared in the effluent when leaching was started immediately after treatment of the soil. Even after a 30-day incubation, only a trace amount of CPIA (17) was detected in the effluent from soil columns treated with ^{14}C-carbonyl-fenvalerate. In a separate experiment, the degradation of ^{14}C-fenvalerate was studied in a soil-nutrient liquid suspension system. Separate cultures of bacteria and fungi were used for the system. After 2 weeks

of incubation, larger amounts of $^{14}CO_2$ (35-42% of the applied radiolabel) were formed from both culture media when the ^{14}CN-labelled compound was used than when the ^{14}CO-labelled compound was used (1.1-2.3%). In the latter case, the main degradation product was CPIA, which amounted to 34-69% [133].

Studies using ^{14}C-fenvalerate, labelled separately in the chlorophenyl and benzyl groups, confirmed the degradation pathways mentioned above. These studies also showed that the labelled aromatic rings were also readily degraded to $^{14}CO_2$ (up to 66%). In addition, it was found that any "bound residues" formed could be further degraded to $^{14}CO_2$ by admixture with fresh soils [119].

The rate of degradation of the individual isomers of fenvalerate has been investigated. In one soil, the half-lives of the RR, RS, SR, and SS isomers were shown to be 178, 89, 155, and 108 days, respectively [105]. Different rates for the various isomers were similarly obtained in loam and sandy loam soils [160].

Under flooded conditions fenvalerate degrades more slowly than under aerobic conditions. In sterile soil, degradation is minimal, indicating that microbial activity is the major cause of this degradation [102]. Ohkawa et al. [133] reported similar findings.

Studies in which crops were sown in soils containing aged residues of ^{14}C-fenvalerate (aging periods of 30, 120, and 345 days) showed that residues from fenvalerate should not carry over into rotated crops [102].

The persistence of fenvalerate in Lethbridge (Canada) soil has been studied under field and laboratory conditions [74]. Formulated fenvalerate (30% emulsifiable concentrate) was applied once to soil microplots in the field at a dose rate of 600 μg/plot (150 g/ha) or to soil in pots at a dose of 88.7 μg/pot (10 g/ha). The treated pots were maintained at a daily temperature regime of 20°C for 16 h and 10°C for 8 h in the environmental chamber. Fenvalerate was found mainly in the top 2.5 cm of the field soil, and 16 weeks later, 15% of the applied fenvalerate remained. The initial half-lives were 5.9 weeks for the [2S, αR] [2R, αS] enantiomeric pair and 6 weeks for the [2R, αR] [2S, αS] pair. The spring

soil samples, taken 45 weeks after application, contained 11% of the total fenvalerate. Limited degradation occurred during the winter. The degradation of fenvalerate in soil incubated in the environmental chamber was similar to the field results. The [2S, αR] [2R, αS] enantiomeric pair had a half-life of 5 weeks while the [2R, αR] [2S, αS] pair had a half-life of 5.3 weeks. These results were comparable to the average half-life of 7 weeks for fenvalerate incubated in British Columbia soils [198].

In studies by Harris et al. [69], the persistence of fenvalerate in subtropical field soil (average soil temperature, 20-30°C) was investigated after applying 20% emulsifiable concentrate at a rate of 1 kg active ingredient (ai)/ha twice a year (spring and autumn) over a 2.5-year period. Residues in the top 15 cm of soil were monitored for up to one year after the final application. Fenvalerate levels declined rapidly after the spring application and relatively slowly after the autumn application. There was no carry over of the insecticide from year to year, and after 2.5 years of application only 2% of the total fenvalerate remained. The rate of disappearance became slightly slower when fenvalerate application ceased [181]. The degradation of fenvalerate (14.9 mg/kg) in plainfield sand (5% moisture) at 25°C was relatively slow, with an initial half-life of 2 months, as compared with initial half-lives of 0.5, 1, and 2 months for fenpropathrin (7.1 mg/kg), permethrin (8.8 mg/kg), and cypermethrin (7.3 mg/kg), respectively, under laboratory conditions.

A 2-year field study on the relative persistence of permethrin, cypermethrin, fenpropathrin, and fenvalerate in soils was carried out by Chapman & Harris [25]. The pyrethroids were applied as emulsifiable concentrates at a rate of 280 g ai/ha or 140 g ai/ha to duplicate plots in Ontario, Canada, containing either sand or organic soil. For plots treated at the higher rate, the insecticide was immediately raked into the soil, while the plots receiving the lower rate were left undisturbed and the upper 4-5 cm of soil was subjected to gas-liquid chromatography (GLC) analyses. The concentrations of the four pyrethroids incorporated in both soils or remaining on the upper soil layer decreased to less than 50% of the initial values within one month. Again, fenvalerate was slightly more

persistent, with 7% of the initial application remaining in organic soil 28 months after treatment.

Reed et al. [157] demonstrated that when fenvalerate was applied to soil, adsorption prevented significant leaching of the pesticide. Soil metabolites produced either by photolytic or microbial degradation did not accumulate to a significant level or present a problem in subsequent rotation crops (lettuce, beets, and wheat) planted at 30 days, 60 days, 120 days, or 1 year after soil treatment. Although fenvalerate has intrinsically high toxicity to a variety of aquatic organisms, these field studies demonstrated that the toxicant was unavailable to non-target organisms. Therefore, it had little or no impact in this test system following its use at the maximum allowed rate of 2.24 kg/ha per year.

4.5 Decomposition in Water

The hydrolysis of racemic fenvalerate in buffered aqueous solutions at pH 5.0, 7.0, and 9.0 was compared by Katagi et al. [90] with that of the [2S, αS] isomer. Both compounds were fairly stable at pH 5.0 and 7.0 (half-lives of 130-220 days), while at pH 9.0 they underwent hydrolysis (half-lives of 64.6-67.2 days) mainly via ester bond cleavage. The main product was 2-(4-chlorophenyl)-3-methylbutyric acid (17), which amounted to 14.9% of the applied ^{14}C after 28 days. As the [2S, αS] isomer underwent αS/αR epimerization in the alcohol moiety at pH 7.0 and 9.0, its rate of hydrolysis appeared to be rather faster than that of fenvalerate. However, the half-life estimated from the total amounts of [2S, αS] and [2S, αR] epimer was close to that of fenvalerate, which indicates no significant difference in hydrolysis rate.

The persistence of fenvalerate has been evaluated in water and sediment contained in open trenches (3 m x 1 m x 30 cm) lined with alkathene sheet [1]. Insecticide emulsion was sprayed on the surface of the water at the normal rate and at twice the recommended dosage. The dissipation of the insecticide from water was rapid. About 74-80% of the pesticide was lost within 24 h at both application rates. However, residues were found to be adsorbed onto sediment, and these persisted beyond 30 days.

In soil, persistence was moderate, lasting around 30 days.

5. KINETICS AND METABOLISM

Appraisal

The metabolic fate of fenvalerate in rats, mice, and cows has been studied using variously labelled racemic fenvalerate (acid moiety or benzyl or cyano groups labelled).

From oral administration studies, fenvalerate appears to be absorbed rapidly through the gastrointestinal wall.

Following a single oral administration of labelled fenvalerate to rats, the excretion of radiocarbon from the acid or benzyl moieties was fairly rapid. However, the excretion of radiocarbon originating from the cyano group was relatively slow, the rest of the radioactivity being retained in various tissues, particularly in hair and stomach as thiocyanate. The major routes of metabolism were ester cleavage, hydroxylation at the 4′position of the alcohol moiety, and thiocyanate formation from the cyano group. Major metabolites were 2-(4-chlorophenyl)isovaleric acid (Cl-Vacid) and 3-OH-Cl-Vacid (Cl-Vacid hydroxylated at the 3 position) from the acid moiety, and the sulfate conjugate of 3-(4′-hydroxyphenyl)benzoic acid and thiocyanate from the alcohol moiety. A lipophilic metabolite, cholesteryl-[2R]-2-(4-chlorophenyl)isovalerate, which was related to granuloma formation, was detected in the adrenals, liver, and the mesenteric lymph nodes of rats, mice, and some other species. The excretion of fenvalerate in the milk from orally dosed cows was very low (0.44-0.64% of the total dose).

The metabolic fate of fenvalerate in mammals is summarized in Fig. 3.

5.1 Metabolism in Mammals

5.1.1 Rat

Following the single oral administration of fenvalerate, labelled with ^{14}C in the carbonyl of the acid moiety (^{14}CO) and the benzylic carbon ($^{14}C\alpha$), to male rats (7-30 mg/kg body weight), the radiocarbon from the acid and alcohol moieties was rapidly and completely excreted [86, 134]. The tissue residues were generally

very low, except for those in the fat. The total recovery of ^{14}C in urine, faeces, and expired air was 93-99% in 6 days. However, on dosing with ^{14}CN-labelled fenvalerate, the radiocarbon derived from the CN group was excreted relatively slowly into the urine and faeces, and a considerable amount (10%) of the radiocarbon was also excreted as CO_2. Total recovery of ^{14}C in urine, faeces, and expired air was 75-81% in 6 days in this case. The tissue residue levels were generally higher than those from the acid and alcohol moieties. Hair, skin, and stomach contents showed high residue levels, due to retention as ^{14}C-thiocyanate. These excretion and tissue residue patterns for the radiocarbon from the CN group were similar to those with ^{14}C dosed as KCN and KSCN in male rats [134].

It was shown in the same study that fenvalerate underwent oxidation at the 2′and 4′positions of the alcohol moiety, as well as at the 2 and 3 positions of the acid moiety, ester cleavage, and the conjugation of resultant phenols and carboxylic acids with glucuronic acid, sulfuric acid, and glycine. Cleavage of fenvalerate and its ester metabolites appeared to release cyanohydrins, which were, however, unstable under physiological conditions and decomposed easily to cyanide and aldehydes (Fig. 3). The cyanide ion was converted mainly to thiocyanate and CO_2, and 2-iminothiazolidine-4-carboxylic acid, a metabolite detected with other pyrethroids containing a cyanide group, was not positively identified [134]. The major faecal metabolites from ^{14}CO-, ^{14}Cα-, and ^{14}CN-fenvalerate were unchanged fenvalerate (5) and two ester metabolites of 2′-hydroxy-(13) and 4′-hydroxy-fenvalerate (25). The major metabolites in 0- to 2-day pooled urine (50-55% of the dosed radioactivity) from the acid-labelling were 2-(4-chlorophenyl)isovaleric acid (17) (Cl-Vacid), 2-(4-chlorophenyl)-3-hydroxymethylbutyric acid (37) (3-OH-Cl-Vacid), and its lactone (38) (3-OH-Cl-Vacid-lactone). Other minor metabolites were 2-(4-chlorophenyl)-2-hydroxy-3-hydroxymethylbutyric acid (39) (2,3-OH-Cl-Vacid) in the free, the lactone (40) (2,3-OH-Cl-Vacid-lactone), and the conjugated forms, 2-(4-chlorophenyl)-*cis*-2-butenedioic acid anhydride (41) (Cl-BDacid anhydride), and 2-(4-chlorophenyl)-3-methyl-2-butene-4-olide (42) (Cl-B-acid-lactone). On the other hand, the predominant urinary

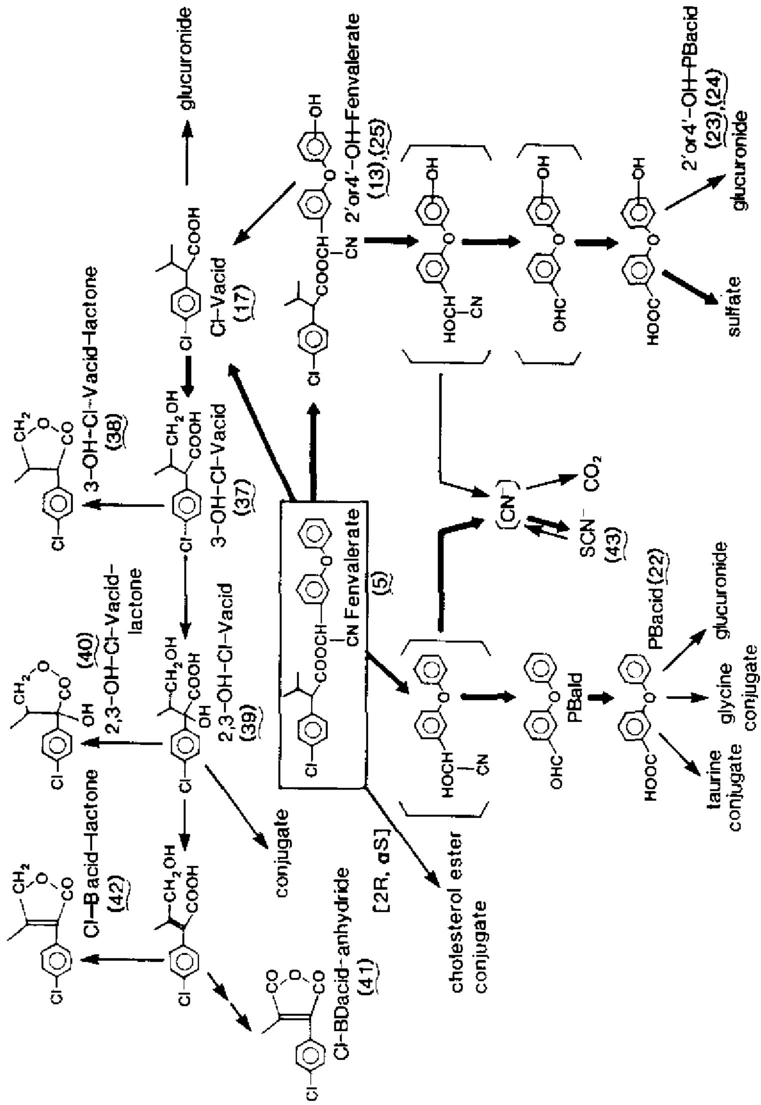

Fig. 3. Metabolic pathways of fenvalerate in mammals.

metabolite from the alcohol moiety was the sulfate conjugate of 3-(4′-hydroxyphenoxy)benzoic acid (23) (4′-OH-PBacid), accounting for approximately 40% of the dose. Other major metabolites were 3-phenoxybenzoic acid (22) (PBacid) in the free (6%), the glucuronide (2%), and the glycine (2%) conjugated forms, 4′-OH-PBacid in the free (5%) and the glucuronide (2%) forms, and the sulfate of 3-(2′-hydroxyphenoxy)benzoic acid (24) (2′-OH-PBacid) (3%). With ^{14}CN-fenvalerate, the major urinary metabolite was thiocyanate (43) [134].

Pydrin insecticide (Y-rich) is an isomerically enriched form of fenvalerate containing an excess ratio of the active diastereomers SS and RR (designated Y) over the less active diastereomers RS and SR (designated X) at a ratio of approximately 85:15. Fenvalerate contains Y:X in a ratio of 45:55. Following a single oral dose of the Y-rich insecticide (8.4 mg/kg) to male and female Sprague-Dawley rats, more than 90% of the administered radioactivity from the acid moiety (chlorophenyl-^{14}C) and the alcohol moiety (phenoxyphenyl-^{14}C) was eliminated within the first 24 h. There was no major difference between the two different fenvalerate preparations in either the elimination rate or the metabolites distribution profile. Cleavage of the ester linkage was the primary metabolic pathway. The acid and alcohol portions of the parent molecule underwent hydroxylation, oxidation, and conjugation. These metabolic reactions were not dependent on the isomeric composition of the test material. Tissue residue data showed that ^{14}C residues were not retained in the various organs [104].

The fate of sugar conjugates, which may be formed as plant metabolites, has been investigated by Mikami et al. [122]. Upon single oral administration to male Sprague-Dawley rats at a concentration of 3.8 mg/kg, the mono-, di-, and tri-glucose conjugates of [^{14}C]-3-phenoxybenzyl alcohol (19) and the mono-glucose conjugate of [^{14}C]-3-phenoxybenzoic acid (22) were rapidly hydrolysed and extensively eliminated in the urine, mostly as the sulfate conjugate of 3-(4-hydroxyphenoxy)benzoic acid (24). Faecal elimination was a minor route, whereas biliary excretion was responsible for about 42% of the dose, and the glucuronide conjugates of (19), (22), and (24) were common major metabolites. The biliary glucuronides were

metabolized in the small intestine to the respective aglycones, which were reabsorbed, metabolized further, and excreted in the urine as the sulfate conjugate of (24). Although small amounts of the mono-, di-, and tri-glucosides were found in the 30-min blood and liver samples following oral administration of the tri-glucoside of (19), they were not detected in the urine, bile, or faeces. Similarly, the sulfate conjugate was one of the major urinary metabolites in germ-free male rats, when dosed with the ^{14}C-glucosides at a rate of 9 μmol/kg via the oral or intraperitoneal route, although certain amounts were excreted unchanged in the urine and faeces. The glucose conjugates were metabolized *in vitro* by intestinal microflora and in various rat tissues including blood, liver, small intestine, and small intestinal mucosa. The tissue enzymes showed a different substrate specificity in hydrolysing the glucosides. However, they were not metabolized in gastric juice, bile, pancreatic juice, or urine.

5.1.2 Mouse

In mice, fenvalerate is metabolized in a similar way to that in rats, but the following significant species differences were found by Kaneko et al. [86]: (a) the taurine conjugate of PBacid was found in mice but not in rats; (b) 4′-OH-PBacid sulfate occurred to a greater extent in rats than in mice; and (c) a greater amount of thiocyanate was excreted in mice than in rats. No significant sex differences were observed in rats and mice. The metabolism of the stereoisomers of fenvalerate, ([2S, αRS] and [2S, αS]) was apparently similar to that of racemic fenvalerate.

Following a single oral administration of the four chiral isomers of [^{14}C-chlorophenyl]-fenvalerate to Sprague-Dawley rats and ddY mice (2.5 mg/kg body weight), the [2R, αS] isomer showed, in both rats and mice, relatively greater residues in the analyzed tissues (except fat), particularly in adrenal glands, compared with the other three isomers. Similarly, this isomer showed higher tissue concentrations than the other isomers when mice were fed a diet containing 500 mg/kg of the [2S, αS], [2R, αS], or [2R, αR] isomers for two

weeks. The greater amount of radioactive residues from the administration of [2R, αS] isomer, as compared with those of other isomers, was explained by the preferential formation of a lipophilic metabolite from the [2R, αS] isomer found in all examined tissues, which was not easily excreted. The amounts of the lipophilic metabolite differed among tissues, being higher in adrenal, liver, and mesenteric lymph nodes. This metabolite was identified as cholesteryl [2R]-2-(4-chlorophenyl)isovalerate. The presence of the same metabolite was also indicated in rat tissues [87].

5.1.3 Domestic animals

Two 3-month-old lambs were fed a diet containing 45 mg/kg fenvalerate for 10 days and then killed to determine the concentrations of fenvalerate in the kidney, liver, leg muscle, and renal fat [210]. Among the analyzed tissues, fat showed the highest fenvalerate level (3.6-4.4 mg/kg dry weight) while other tissues contained less than 0.3 mg/kg. Fenvalerate gave two gas chromatographic peaks and each peak contained a pair of its enantiomers. In all cases, the ratio of the areas of these peaks (peak 1 (RS,SR)/peak 2 (SS,RR)) was 1.08 both for fenvalerate in the diet and for fenvalerate recovered from the fortified control fat. In contrast, the fenvalerate isolated from lamb fat had a peak area ratio of 0.76-0.78. Thus, one or both of the first eluting enantiomers appeared to be metabolized more rapidly than the other enantiomers.

In a study by Wszolek et al. [209], two Holstein cows were fed fenvalerate at 5 and 15 mg/kg diet for 4 days and were then given a clean diet for 6 days. Total excretion of fenvalerate in milk amounted to 0.44 and 0.64% of the total dose for the 5 and 15 mg/kg levels, respectively, whereas about 25% of the dose was eliminated in the faeces.

A lactating Holstein cow was fed grain fortified with 227 mg fenvalerate daily for 4 days and the urine was analysed. Intact fenvalerate was not detected in any samples of the urine excreted by the cow during the 10-day feeding study, nor was the acid metabolite (Cl-Vacid) (17) identified. The *in vitro* study on fenvalerate degradation in

rumen fluid indicated that no significant degradation of fenvalerate was observed during the 6-h incubation [211].

Saleh et al. [161] gave a single oral dose of fenvalerate (10 mg/kg body weight) to chickens and monitored the persistence and distribution of the insecticide over 15 days. A concentration of 4.7 mg/litre in blood after 24 h fell to 0.05 mg/litre after 7 days. Levels in other tissues reached maxima of less than 1.0 mg/kg and fell rapidly. However, brain residues rose to a level of 4.0 mg/kg over 7 days and persisted for the 15 days of the experiment. Concentrations in eggs reached a maximum of 0.3 mg/kg yolk after 4 to 5 days, and a maximum of 0.24 mg/kg egg white. By day 6, levels had returned to the pre-dosing level.

5.2 Enzymatic Systems for Biotransformation

The [2R, αRS] isomer of fenvalerate has been found to be more rapidly hydrolysed by mouse liver esterase than the [2S, αRS] isomer, but less rapidly metabolised than the [2R, αRS] isomer with an oxidase system. A similar correlation was observed with the [2S] and [2R] isomers of S-5439 (3-phenoxybenzyl-2-(4-chlorophenyl)isovalerate) [165].

In an *in vitro* study on the metabolism of the four chiral isomers of fenvalerate using homogenates from various tissues of mice, rats, dogs, and monkeys, only the [2R, αS] isomer yielded cholesteryl-[2R]-2-(4-chlorophenyl)isovalerate (CPIA-cholesterol ester) as a major metabolite. Mouse tissues exhibited a higher rate of CPIA-cholesterol ester formation than those of other animals. Of the mouse tissues tested, the kidney, brain, and spleen showed the greatest ability to form this ester, the relevant enzyme activity being mainly localized in the microsomal fractions. Carboxyesterases for mouse kidney microsomes hydrolyzed the [2R, αS] isomer only of fenvalerate to give CPIA and yielded the corresponding cholesterol ester in the presence of artificial liposomes containing cholesterol. It appears that the CPIA-cholesterol ester resulted from the stereoselective ([2R, αS] only) formation of the CPIA-carboxyesterase complex, which subsequently reacted with cholesterol to yield the CPIA-cholesterol ester [128].

Hydrolysis of the four chiral isomers of fenvalerate by microsomes of various mouse tissues has been investigated by Takamatsu et al. [180]. The kidney, spleen and brain hydrolyzed only the [2R, αS] isomer. Liver hydrolyzed the [2R, αS] and [2R, αR] isomers to a greater extent than the [2S, αR] and [2S, αS] isomers, while plasma hydrolysed the [2S, αR] and [2R, αR] isomers more rapidly than the [2S, αS] and [2R, αS] isomers. The stereoselectivity of hydrolysis of the four isomers by mouse liver microsomes was found to be same as that *in vivo*. Of the four isomers, the [2R, αS] isomer alone was transformed to cholesteryl-[2R]-2-(4-chlorophenyl)isovalerate (CPIA-cholesterol ester) by microsomes of the brain, kidney, spleen, or liver but not by plasma. The rate of CPIA-cholesterol ester formation was lower in the liver than in other tissues. The optimum pH (7.4-9.0) for the formation of this ester was nearly the same as that for hydrolysis of the [2R, αS] isomer to form CPIA in mouse kidney microsomes.

The substrate specificity of microsomal carboxyesterase(s) responsible for the formation of cholesteryl-[2R]-2-(4-chlorophenyl)isovalerate from fenvalerate was investigated by incubating mouse kidney microsomes with ^{14}C-cholesterol and fenvalerate or its analogues. Of the four isomers of fenvalerate, only the [2R, αS] isomer yielded a cholesterol ester. This specificity of cholesterol ester formation was the same as that in the *in vivo* study. Some of the fenvalerate analogues also produced similar cholesterol esters. Steroids other than cholesterol were also investigated as acceptors of the acid moiety of the [2R, αS] isomer by incubating egg lecithin and several steroids with the [2R, αS] isomer in the presence of solubilized carboxyesterase(s). Dehydroisoandrosterone and pregnenolone reacted with the [2R, αS] isomer to give the corresponding ester conjugates [88].

One or more carboxyesterases located in the soluble fraction of mouse brain homogenates hydrolyzed several pyrethroid esters with a substrate specificity different from that of the hepatic esterases. In particular, fenvalerate and fluvalinate were hydrolyzed by brain esterases at rates equal to or greater than that measured for *trans*-permethrin. The results suggest that hydrolysis

in the brain may contribute to the detoxication of some pyrethroids in mammals [64].

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

The acute toxicity data of fenvalerate to aquatic and terrestrial non-target organisms are summarized in Tables 5, 6, and 7.

6.1 Aquatic Organisms

6.1.1 *Toxicity to aquatic invertebrates*

Non-target invertebrates, except molluscs, are more susceptible to the insecticide than fish, the LC_{50} ranging from 0.08 to 2 μg/litre.

Fenvalerate is relatively non-toxic to oysters and algae (LC_{50} >1000 μg/litre) over short exposure periods. Snails *(Heliosoma trivolvis)* exposed for 28 days to 0.79 μg/litre, the highest concentration tested, showed no change in behaviour or survival [4].

Day & Kaushik [32] conducted short-term toxicity tests on three species of cladoceran and one species of calanoid (*Diaptomus oregonensis*). The 48-h LC_{50} values for daphnids were: 2.52 μg/litre for adult *Daphnia magna*, 0.83 μg/litre for *D. magna* aged 48 h (or less); 0.29 μg/litre for adult *Daphnia galeata mendotae;* 0.21 μg/litre for adult *Ceriodaphnia lacustris;* 0.16 μg/litre for *D. galeata mendotae* aged 48 h (or less). *Diaptomus oregonensis* was the most sensitive species with a 48-h LC_{50} of 0.12 μg/litre. No toxicity was found with the emulsifiable concentrate from which fenvalerate was omitted (EC control). Rates of filtration of algae were reduced at sub-lethal concentrations of fenvalerate. *Ceriodaphnia lacustris* was the most sensitive species, with rates of filtration significantly decreased at fenvalerate concentrations of 0.01 μg/litre. Rates of assimilation of algae were decreased at fenvalerate concentrations of 0.05 μg/litre or more.

Day & Kaushik [33] conducted life-cycle studies on the toxicity of fenvalerate to *Daphnia galeata mendotae.* Lifetable methods were used to generate statistical comparisons between treatments. At a concentration of

Table 5. Acute toxicity of fenvalerate to non-target freshwater organisms

Species	Size[a]	Parameter	Toxicity (μg/litre)	Formulation[b]	System[c]	Temperature (° C)	pH	Hardness[d]	Reference
Arthropods									
Gammarus pseudolimnaeus	adult-juv	96-h LC_{50}	0.03	T	F	15	7.6-7.8	46-48	4
Gammarus pseudolimnaeus	1-3 mm, juv	96-h LC_{50}	0.05	T	R	17	7.6-7.8	46-48	4
Waterflea (*Daphnia magna*)	1st instar	96-h LC_{50}	0.032	T	S	17	7.4	44	115
Midge (*Chironomus pulmosus*)	3rd instar	48-h LC_{50}	0.43	T	S	22	7.4	44	115
Mayfly (*Ephemerella* sp.)	larva	9-day LC_{50}	0.08	T	F	15	7.6	46-48	4
Rhagionid fly (*Atherix*)	larva	28-day LC_{50}	0.03	T	F	15	7.6-7.8	46-48	4
Stonefly (*Pteronarcys dorsata*)	naiad	72-h EC_{50}	0.13	T	F	15	7.6-7.8	46-48	4
Stonefly (*Nitocra spinipes*)	3-6 weeks old	96-h LC_{50}	1.9	EC	S	20-22	7.8	7%	107
Fish									
Atlantic salmon (*Salmo salar*)	6.2 cm, 5.3 g	96-h LC_{50}	1.2	T	R	10			110
Rainbow trout (*Salmo gairdneri*)	5-6 cm	48-h LC_{50}	3.0	EC	S	12-25.5			129
Rainbow trout (*Salmo gairdneri*)	6 cm, 3 g	24-h LC_{50}	76	T	S	10	7.5	110	28
Rainbow trout (*Salmo gairdneri*)	6 cm, 3g	24-h LC_{50}	21	EC	S	10	7.5	110	28
Mosquitofish (*Gambusia affinis*)	4-5 cm	48-h LC_{50}	15.0	EC	S	8.8-16			129
Mosquitofish (*Gambusia affinis*)	3-days old	72-h LC_{50}	2.6	T	S	24-27			124

Table 5 (contd).

Species	Size[a]	Parameter	Toxicity (µg/litre)	Formulation[b]	System[c]	Temperature (°C)	pH	Hardness[d]	Reference
Fish (contd)									
Desert pupfish (*Cyprinodon macularis*)	4-5 cm	48-h LC_{50}	25.0	EC	S	11-16.6			129
Tilapia mossambica	5-6 cm	48-h LC_{50}	200.0	EC	S	15-21.4			129
Bluegill sunfish (*Lepomis macrochirus*)	adult	96-h LC_{50}	0.76	T	S	22	7.4	40	115
Fathead minnow (*Pimephales promelas*)	adult	96-h LC_{50}	2.35	T	S	22	7.1	49	115

[a] juv = juvenile.
[b] T = Technical, EC = Emulsifiable concentrate.
[c] R = Renewal, S = Static, F = Flow-through.
[d] expressed as mg $CaCO_3$ per litre

Table 6. Acute toxicity of fenvalerate to non-target estuarine & marine organisms

Species	Size[a]	Parameter	Toxicity (μg/litre)	Formulation[b]	System[c]	Temperature (° C)	pH	Salinity o/oo	Reference
Algae									
Skeletonema costatum		96-h EC_{50}	> 1000	T		20		30	212
Isochrysis galbana		96-h EC_{50}	> 1000	T		20		30	212
Thalassiosira pseudonana		96-h EC_{50}	> 1000	T		20		30	212
Nitzschia angularum		96-h EC_{50}	> 1000	T		20		30	212
Molluscs									
Eastern oyster *(Crassostrea virginica)*	2-h larva	48-h EC_{50}	> 1000	T	S	25		20	212
Arthropods									
Lobster *(Homarus americanus)*	450 g	96-h LC_{50}	0.14	T	R	10		30	110
Shrimp *(Crangon septemspinosa)*	1.3 g	96-h LC_{50}	0.04	T	R	10			110
Shrimp *(Mysidopsis bahia)*	1-day juv	96-h LC_{50}	0.021	T	S	25		20	212
Shrimp *(Mysidopsis bahia)*	newly hatched	96-h LC_{50}	0.008	T	F	25.4		25.3	163
Shrimp *(Penaius duorarum)*	adult	96-h LC_{50}	0.84	T	F	24.8		24.9	163
California grunion *(Leuresthes tenuis)*	3-day larva	96-h LC_{50}	0.29	T	F	26		25	114
California grunion *(Leuresthes tenuis)*	juv	96-h LC_{50}	0.60	T	F	25		22	114
Inland silverside *(Nenidia beryllina)*	26-day larva	96-h LC_{50}	1.00	T	F	24		20	114
Tidewater silverside *(Menidia peninsulae)*	juv	96-h LC_{50}	1.00	T	F	25		20	114

Table 6 contd.

Species	Size[a]	Parameter	Toxicity (µg/litre)	Formulation[b]	System[c]	Temperature (° C)	pH	Salinity ‰	Reference
Fish									
Sheepshead minnow (*Cyprinodon variegatus*)	28-day fry	96-h LC_{50}	121	T	S	25		20	212
Sheepshead minnow (*Cyprinodon variegatus*)	adult	96-h LC_{50}	5	T	F	30		26.5	163
Bleak (*Alburnus alburnus*)	8 cm	96-h LC_{50}	2-3	EC	S	10	7.8	7	107
Atlantic silverside (*Menidia menidia*)	adult	96-h LC_{50}	0.31	T	F	24.1		25	163
Striped mullet (*Mugil cephalus*)	adult	96-h LC_{50}	0.58	T	F	25.9		25.8	163
Gulf toadfish (*Opsanus beta*)	adult	96-h LC_{50}	5.4	T	F	30		24.8	163

[a] juv = juvenile.
[b] T = Technical, EC = Emulsifiable concentrate.
[c] R = Renewal, S = Static, F = Flow-through.

Table 7. Acute toxicity of fenvalerate to non-target terrestrial organisms

Species	Size	Application	Parameter	Toxicity	Temperature (° C)	Reference
Bird						
Broiler chicks	8-12 weeks old, 0.99-2.2 kg	oral	LD_{50}	12 590 (mg/kg)	31-32	155
Hen		oral	LD_{50}	> 1500 (mg/kg)		123
Arthropods						
Insect parasite						
Ichneumoid (*Campoletis sonorensis*)	adult male	film	24-h LC_{50}	1760 (ng/vial)		152
Insect predators						
Lacewing (*Austromicromus tasmaniae*)	adult 2.74 mg	topical	LD_{50}	4.3 (mg/kg)	15	176
	larva 2.52 mg	topical	LD_{50}	67 (mg/kg)	20	176
Lacewing (*Chrysopa carnea*)	3rd instar,	topical	72-h ED_{50}	> 25 (mg/g)	28	164
	larva 9.9-10 mg one generation	topical	ED_{50}	~ 1 (mg/g)	28	164
Lacewing (*Chrysopa carnea*)	larva 5-6 days old	film	LC_{50}	0.073 (mg/vial)	25	151
Beetle (*Coccinella undecimpunctata*)	11.2 mg	topical	LD_{50}	0.38 (mg/kg)	15	164
Earwig (*Labidura riparia*)	mature	soil 0.11 kg ai/ha	mortality	6%		205
		0.22 kg ai/ha	mortality	25%		205
		0.44 kg ai/ha	mortality	50%		205
Honey bee (*Apis mellifera*)	adult	topical	LD_{50}	410 ng/bee	-	5
Predaceous mite species						
Amblyseius fallacis	adult female	slide dip method	LC_{50}	2.6 (mg ai/litre)	27	158
Amblyseius fallacis	adult female	slide dip method	LC_{50}	7.0 (mg ai/litre)	26	199
Typhlodromus pyri	adult female	slide dip method	LC_{50}	8.1 (mg ai/litre)	26	199
Typhlodromus occidentalis	adult female	slide dip method	LC_{50}	2.1 (mg ai/litre)	26	199

0.005 μg/litre, fenvalerate increased the longevity of the daphnids significantly from 37.6 to 51.6 days. However, at the same concentration, production of young was decreased. Higher concentrations of fenvalerate caused reduced survival of the adults. The intrinsic rate of natural increase in the population was reduced at a concentration of 0.5 μg/litre. At 0.01 μg/litre, the net reproductive rate decreased from 126 to 73 offspring per female and the generation time from 20.3 to 17.3 days.

McKenney & Hamaker [109] exposed the estuarine grass shrimp *Palaemonetes pugio* to fenvalerate, in a flow-through system to maintain constant exposure, throughout 20 days of larval development. The study was conducted under optimal salinity conditions (20 ^{o}/oo). A nominal concentration of 3.2 ng/litre significantly reduced the percentage of larvae successfully completing metamorphosis. Exposure to 1.6 ng/litre prolonged larval development. Larvae were also found to be less capable of responding successfully to osmotic stress after exposure to fenvalerate at 0.1 or 0.2 ng/litre.

6.1.2 *Toxicity to fish*

Fenvalerate is toxic to fish, LC_{50} values being 0.29-200 μg/litre (Tables 5 and 6). The LC_{50} value for rainbow trout obtained with an emulsifiable concentrate was 3.6 times lower than that for the technical product [28]. The toxicity of fenvalerate to adult bluegill sunfish *(Lepomis macrochirus)* was unaffected by changes in water hardness and pH [115].

The acute toxicities (96-h LC_{50}) of fenvalerate to juvenile steelhead trout were 172 ng/litre and 88 ng/litre, respectively, under continuous and intermittent exposure (approximate peak concentration: 460 ± 40 ng/litre for 4.5 h). Prolonged intermittent exposure (70 days) of the early life-stage resulted in marked lethality (32%) and reduced terminal weight (50% of control) (mean concentration: 80 ng/litre, peak concentration: 461 ng/litre). However, continuous exposure to 80 ng/litre for 70 days did not effect these parameters [31].

Fenvalerate has narrow safety margins for fish (LC_{50} of fish : LC_{50} of mosquito larvae is in the ratio of 1:24) when the insecticide is used against mosquitoes [129].

Four rainbow trout *(Salmo gairdneri)* died within 11 hours when exposed to 412 µg fenvalerate/litre. Visible signs of poisoning included elevated cough rate, tremors, and seizures. Ventilatory and cardiac activity stopped during the seizures. Histopathological examination of gill tissue showed damage consistent with irritation, and Na^+ and K^+ excretion rates were elevated. Fenvalerate concentrations in brain, liver, and carcass at death were 0.16, 3.62, and 0.25 mg/kg, respectively. The study suggested that, apart from effects on the nervous system, effects on respiratory surfaces and renal ion regulation may be associated with fenvalerate toxicity in fish [15].

When sheepshead minnows *(Cyprinodon variegatus)* were studied during 28 days for early-life-stage toxicity, 3.9 µg fenvalerate/litre significantly reduced the survival of hatched fish and 2.2 µg/litre reduced both length and weight, but no effects were detected at 0.56 µg/litre [68].

6.1.3 Field studies and community effects

Caplan et al. [23] applied fenvalerate at concentrations of 0.2 and 1.0 mg/kg to sediment in a tidal marsh sediment model ecosystem. No adverse effects were seen on the heterotrophic microorganisms in the sediment after a 7-day exposure to either concentration. Plate counts to assess numbers of organisms and measurements of substrate degradation were not different from those of controls. The half-life of fenvalerate was 6.3 days for the treatment at 0.2 mg/kg and 8.9 days at 1.0 mg/kg.

In the field, fenvalerate was applied to ponds at rates of 28-112 g ai/ha as a mosquito larvicide [124]. Populations of plankton, crustaceans, and mayfly nymphs decreased but recovered quickly. Corixids, notonectids, and aquatic beetle populations decreased slightly and the effects remained throughout the study. Chironomid larval populations were suppressed and emergence was inhibited.

However, no deleterious effects were observed on rotifer populations.

When fenvalerate was applied to ponds at rates of 11.2-56 g ai/ha for mosquito control, the insecticide produced complete mortality of mayfly naiads [130]. A single treatment by fenvalerate at 28 g/ha controlled mosquito larvae for more than 7 days, and it also affected populations of mayfly naiads, dragonfly naiads, and diving beetle larva, but not ostracods or damselfly naiads [131].

Studies into the effects of fenvalerate on estuarine benthic communities were conducted in a flow-through system for 8 weeks and 1 week for laboratory- and field-colonized communities, respectively. Technical grade fenvalerate (100%), dissolved in a stock solution consisting of 15% acetone and 85% triethylene glycol, was metered by syringe pump into, and mixed with, the sea water entering the centre of the constant-head box of each apparatus receiving fenvalerate. The same amount of carrier solvent (10 ml/day, 5 mg/litre) was metered into the control apparatus. Nominal concentrations of fenvalerate in sea water were 0.01, 0.1, and 1.0 μg/litre. Samples of water were taken from the constant-head boxes once a week for chemical analyses for fenvalerate concentration. Community structure was altered significantly in both cases by fenvalerate at 0.1 or 1 μg/litre, but not by 0.01 μg/litre. The groups most sensitive to the insecticide were chordates *(Branchiostoma caribaeum)* and amphipods, while annelids and molluscs tolerated concentrations up to 10 μg/litre [177].

Tagatz et al. [178] placed boxes containing sand, either uncontaminated or contaminated (nominal concentration of fenvalerate of 0.1, 1.0, or 10 mg/kg), in an estuary for 8 weeks, and the community structure of benthic organisms colonising the boxes was assessed. The average number of species colonising the sand at the highest treatment level was significantly less than for the controls (35.6 compared to 47.8); lower concentrations had no effect on species diversity. Colonisation by annelids, molluscs, and arthropods was unaffected even at the highest dose. The only organisms deterred by the fenvalerate were chordates (primarily lanceolets).

6.2 Terrestrial Organisms

6.2.1 Toxicity to soil microorganisms

In laboratory trials for effects on soil algae, Megharaj et al. [116] applied fenvalerate to a black cotton soil, taken from a fallow cotton field. Fenvalerate applied once at a dose equivalent to 0.5 or 1.0 kg/ha had no inhibitory effect on soil algae, but two applications of fenvalerate, at concentrations of 0.75 or 5.0 kg/ha, resulted in increased algal populations.

6.2.2 Toxicity to beneficial insects

Fenvalerate is highly toxic to honey bees *(Apis mellifera)* with a topical LD_{50} of 0.41 µg/bee. However, in field tests at a normal application rate of 0.22 kg/ha, the hazard is low because the residue repels bees for about 10 h following application and decreases to non-toxic levels within one day. During the first 5 days after application, fenvalerate caused only light bee mortality. At higher application rates (0.44 kg/ha), however, mortality remained high 8 hours after application [5, 63, 84, 85].

Fenvalerate is toxic to the tobacco budworm *(Heliothis virescens)* and to its predator green lacewing *(Chrysopa carnea)* as well as to the parasite *(Campoletis sonorensis)* of the tobacco budworm. But, it is more toxic to the pest than to either the predator or the parasite. Comparison of the LC_{50} value for the parasite *(C. sonorensis)* with that for the host *(H. virescens)* indicated similar toxicity, the value for the host being 1.5 times that for the parasite [152]. However, in the case of the predator *(C. carnea)*, the insecticide was much less toxic to the predator than to the pest, the selectivity ratio being 0.037 [151].

When third instar larvae of *C. carnea* were topically dosed with 250 µg/insect, they exhibited marked tolerance during a 72-h period. The ED_{50} value (paralysis, failure to pupate, knockdown, and mortality) for fenvalerate through one generation (larva to larva) was approximately 1000 µg/g [164].

Syrett & Penman [176] compared LC_{50} values for fenvalerate when applied topically to lucerne-infesting aphids *(Acyrthosipho kondoi* and *A. pisum)* and to their predators, namely the brown lacewing *(Austromicromus tasmaniae*, adult and larva) and the ladybird *(Coccinella undecimpunctata)*. The values were 0.071, 0.033, 4.3, 67, and 0.38 mg/kg, respectively. From these data, the ladybird was slightly (5-10 times) more tolerant than the aphid species, but lacewing adults were 60-120 times as tolerant as the aphids. Furthermore, the larvae were 15 times more tolerant than the adults. There was a negative temperature coefficient for *A. tasmaniae*, with greater toxicity (approximately 3 times) at 10 °C than at 25 °C [176].

When fenvalerate was applied to loamy sand and then striped earwigs *(Labidura riparia)*, a predator of the cabbage looper *(Trichoplusia ni)*, were added to the soil, fenvalerate was of low toxicity at rates giving good looper control [205].

Laboratory studies of the activity of fenvalerate on spider mites and their predators showed that the spider mite *(Tetranychus urticae)* was considerably more (67-548 times) resistant to fenvalerate than were its predators *(Amblyseius fallacis, Typhlodromus pyri*, and *Typhlodromus occidentalis)* [199]. The LC_{50} value for *T. urticae* was approximately 25 times greater than that for the predator *(A. fallacis)* [158].

In the field, the predatory mite *(T. pyri)* disappeared during the first 4-6 weeks after fenvalerate was sprayed at 25 mg/litre to drip-off, and then small numbers were found 7 weeks after spraying. The insecticide had no appreciable toxicity for spider mites *(Panonychus ulmi)*. The virtual elimination of the predatory mite led to a marked population increase of *P. ulmi* later in the same season [3].

In apple and pear orchards, dramatic increases in the populations of spider mites *(T. urticae, Tetranychus mcdanieli*, or *P. ulmi)* were seen after the application of fenvalerate at rates of 7.5 and 15 mg ai/litre. This was due to a reduction in the numbers of the predatory mite *(Mataseiulus occidentalis)* to zero or near zero [80].

From these results, it was suggested that the recommended application rates for fenvalerate would sometimes be detrimental to integrated mite control programs in orchards, and these would require careful reconsideration.

6.2.3 *Toxicity to birds*

The toxicity of fenvalerate to birds is very low. The acute LD_{50} for the chicken is more than 12 g/kg (Table 7). The toxicity to the bobwhite quail *(Colinus virginianus)* and American kestrel is similarly low.

Bradbury & Coats [13] measured the toxicity of fenvalerate for the bobwhite quail. Acute oral dosing yielded an LC_{50} in excess of 4 g/kg body weight for adult birds and 1.785 g/kg body weight for 5-week-old juveniles. Dietary dosing of 2-week-old chicks for 5 days (with a further 3 days of observation) indicated an LC_{50} of > 15 g/kg diet.

Rattner & Franson [156] dosed American kestrels with fenvalerate (1-4 g/kg body weight) and examined the birds for toxic effects over 10 h after dosing. Some birds were kept at temperatures of 22 °C and others under cold stress at -5 °C. Fenvalerate, at exposures far greater than could be expected in the environment, caused mild intoxication and elevated plasma alanine aminotransferase activity. Cold did not increase the toxicity of the pyrethroid.

6.3 Uptake, Loss, and Bioaccumulation

Fenvalerate is taken up readily by aquatic organisms and rapidly reaches, within the organism, a plateau level related to the water concentration of the pyrethroid. Loss of fenvalerate from organisms is rapid when they are transferred to uncontaminated water. There is no suggestion of biomagnification in food chains.

Under laboratory conditions, the half-life of fenvalerate in sea water containing 100 g sediment per litre sea water was 34 (27-42) days in foil-covered samples and 8 8 days in sunlight-exposed ones. Eastern oysters *(Crassostrea virginica)* kept for 28 days in sea water containing 24 μg fenvalerate/litre gave a steady state bioconcentration factor of 4700. After treatment ceased,

fenvalerate was depurated by the oysters to non-detectable concentrations within a week [163].

Snails exposed for 28 days to fenvalerate (0.79 μg per litre) did not show any changes in behaviour or survival. The bioaccumulation ratios ranged from 356 to 1167 [4].

In a study by Spehar et al. [166], embryonic, larval, and early juvenile stages of fathead minnows *(Pimephales promelas)* were exposed to fenvalerate in a continuous-flow system for 30 days. At 0.33 μg/litre the only effect was a temporary initial impairment of swimming in some larvae. This was more marked at 0.43 μg/litre at which level survival of the larvae was also reduced. The 30-day bio-concentration factor was 3000 ± 1500, but 25 days after transfer to clean water the fenvalerate had again been eliminated.

Rainbow trout *(Salmo gairdneri)* were used to evaluate the gill uptake and toxicokinetics of [^{3}H]-fenvalerate. Fish (weight between 0.64 and 0.97 kg) were exposed in a respirometer-metabolism chamber to technical grade fenvalerate (0.28 or 23 ng/litre) or an emulsifiable-concentrate formulation (16 ng/litre) at 11.0-11.5 °C for 36 to 48 h. No significant effects of emulsifiers or fenvalerate concentration on uptake were observed. The overall mean gill uptake efficiency was 28.6 ± 4.4%. After 8- to 48-h depuration periods, carcass and bile contained 80-90% and 10-20% of the gill-absorbed material, respectively. Urine, faeces, and blood each contained less than 2% of the dose. Significant excretion and blood transport of fenvalerate equivalents were completed within 8-12 h after exposure ceased. Specific tissues from trout exposed to 0.28 ng/litre were analyzed for fenvalerate equivalents. After a 48-h depuration period, bile contained the highest concentration of fenvalerate equivalents (7 ng/g), followed by fat (0.2 ng/g). Remaining tissues contained 0.015-0.045 ng/g. Analysis of biliary metabolites indicated that the glucuronide of 4 -OH-fenvalerate was the only significant degradation product. Results from the present study suggest that efficient gill uptake does not explain the sensitivity of fish to fenvalerate. Instead, a low rate of biotransformation and excretion may play a

significant role in the susceptibility of rainbow trout [14].

When juvenile Atlantic salmon were exposed to static water containing 0.8-9.3 μg fenvalerate/litre for 16-96 h, the concentration of fenvalerate in dead fish ranged from 0.16 to 0.43 mg/kg. The insecticide was not detected (detection limit: 5 μg/kg) either in dead lobster hepatopancreas or in dead shrimps [110].

When carp *(Cyprinus carpio)* was exposed to [^{14}C-CN]-[2S, αRS]-fenvalerate (0.8 μg/litre) under semi-static conditions for 7 days, the radioactivity in fish increased to a level of 922 μg/kg. Once the fish were transferred to fresh water, the levels of radioactivity in the fish decreased with an initial half-life of 5 days [135].

In studies by Ohkawa et al. [135], carp, snails, *Daphnia*, and algae were exposed to fenvalerate in an aquatic model ecosystem where ^{14}C-[2S, αRS] fenvalerate (0.3 mg/kg) was applied to the bottom sandy loam soil. During a 30-day run, concentrations of fenvalerate in the water were 0.35-0.63 μg/litre and 0.14-0.21 μg/litre on days 7 and 30, respectively. The bioconcentration factors for fenvalerate were 122, 617, 683, and 477 on day 7 (162-300, 993-1110, 629-829, and 714-1180 on day 30) in carp, snails, *Daphnia*, and algae, respectively. In carp, large amounts of CP-Vacid (17) and 3-phenoxybenzoic acid (22) were detected, together with small amounts of α-cyano-3-(4′-hydroxyphenoxy)benzyl-2-(4-chlorophenyl)-3-methylbutyrate (4′-OH-Fen) (25). Small amounts of α-carbamoyl-3-phenoxybenzyl-2-(4-chlorophenyl)-3-methylbutyrate ($CONH_2$-Fen) (33), α-carboxy-3-phenoxybenzyl-2-(4-chlorophenyl)-3-methylbutyrate (COOH-Fen) (34), and 4′-OH-Fen (25) were detected in snails. CPIA was specifically present in both Daphnia (prey) and carp (predator). $CONH_2$-Fen (33) and α-carboxy-3-phenoxybenzyl alcohol (36) were common to algae (prey) and carp (predator). Based on the products identified, degradation pathways were proposed for this aquatic model ecosystem (Fig. 4).

In a 28-day early-life stage study (see section 6.1.2), the mean bioconcentration factor in whole fish was 570 [68].

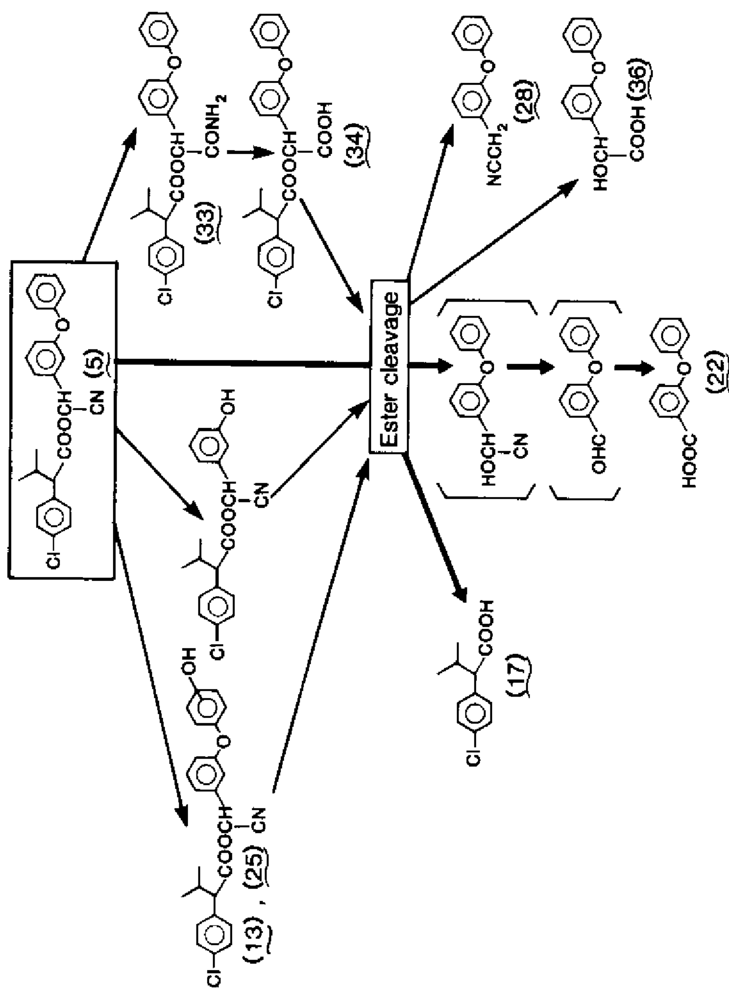

Fig. 4. Proposed degradation pathways for fenvalerate in an aquatic model ecosystem.

7. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

7.1 Single Exposures

Table 8 shows the results of acute toxicity tests with technical grade fenvalerate in various animal species.

The acute toxic signs in rats were restlessness, tremors, piloerection, occasional diarrhoea, and an abnormal gait. Following oral administration, surviving rats recovered rapidly from acute clinical signs of poisoning and were asymptomatic within 3-4 days [20].

Table 9 shows the results of an acute intraperitoneal toxicity study of fenvalerate metabolites in mice [96]. All the compounds were dissolved in corn oil except 3-phenoxybenzoic acid, which was dissolved in DMSO. The acute intraperitoneal toxicity in mice of the proposed decarboxylated photo-products was found to be similar to, or greater than, that of fenvalerate [78].

In a study by Blair and Roderick [12], groups of four male and four female rats were exposed by inhalation (head only) to an aerosol formulation (77-μm particle size) generated from an aqueous suspension containing 3 g/litre. Following a single administration (4 h) of this non-inhalable particulate, acute signs of poisoning were noted for a short period, presumably from oral ingestion of the large particles. There was no mortality and all animals appeared normal within 3 days following exposure.

7.2 Short-Term Exposures

7.2.1 *Oral administration*

Groups of Carworth Farm E rats (12 of each sex per group) were fed fenvalerate in the diet at dose levels of 0, 125, 500, 1000, and 2000 mg/kg for 90 days [72]. Mortality (11/12 male, 9/12 female) was observed at the highest concentration. Body weight gain and food consumption were decreased and blood urea nitrogen concentrations were increased at 1000 and 2000 mg/kg. There were no

Table 8. Acute toxicity of fenvalerate (technical grade) administered to various animal species

Species	Route	Sex	Vehicle[a]	LD_{50} (mg/kg)	Reference
Rat	oral		DMSO	451	195
	oral		PEG:water	> 3200	168
	dermal			5000 (24 h)	140
	inhalation	M, F	water	> 101 mg/m^3 (3 h)	94
	intraperitoneal			340	162
Mouse	oral	M	DMSO	200-300	195
		F		100-200	
	oral		PEG:water	1202	169
	intraperitoneal	M, F	corn oil	85-89	96
	intraperitoneal			132	162
	intravenous		glycerolformol	65	2
	inhalation	M, F	water	> 101 mg/m^3 (3 h)	94
Chinese hamster	oral	M	DMSO	98	195
		F		82	
Rabbit	percutaneous		undiluted	1000-3200	75
Hen	oral			> 1500	123

[a] PEG = polyethylene glycol; DMSO = dimethylsulfoxide.

Table 9. Acute intraperitoneal toxicity of fenvalerate metabolites in mice

Chemical	No.[a]	LD_{50} (mg/kg body weight)	
		Male	Female
Fenvalerate	(5)	88.5	85
2-(4-Chlorophenyl)isovaleric acid	(17)	351	350
3-Phenoxybenzyl alcohol	(19)	371	424
3-(4'-Hydroxyphenoxyl) benzyl alcohol	(21)	750-1000	750-1000
3-(2'-Hydroxyphenoxyl) benzyl alcohol	(20)	876	778
3-Phenoxybenzoic acid	(22)	154	169
3-(4'-Hydroxyphenoxy) benzoic acid	(24)	783	745
3-(2'-Hydroxyphenoxy) benzoic acid	(23)	859	912
3-Phenoxybenzaldehyde	(18)	415	416
NaSCN		604	578

[a] Refers to chemical identification no. in Fig. 3 and in text.

treatment-related changes in any groups of rats in the haematological parameters examined. Increases in liver to body weight ratios and kidney to body weight ratios were observed at 500 mg/kg or more. Gross and microscopic examinations revealed no compound-related changes in any groups. The NOEL was 125 mg/kg diet.

In a study by Parker et al. [150], Fischer 344 rats (30 of each sex per group) were fed decarboxyfenvalerate (one of the major photodegradation products) at concentrations of 0, 30, 100, 300, 3000 or 10 000 mg/kg diet for up to 13 weeks. Body weight was decreased in male rats fed 10 000 mg/kg, but no treatment-related mortality or clinical signs were observed. Absolute and relative liver weight of male and female rats fed 300, 3000, or 10 000 mg/kg were all higher than those of the controls. Significant increases in absolute or relative kidney weights were observed in male and female rats fed 3000 or 10 000 mg/kg. Significant treatment-related microscopic effects were limited to glomerulonephrosis in male and female rats fed 10 000 mg/kg and hepatocellular hypertrophy with pale eosinophilic cytoplasm and hepatocellular focal necrosis in male and female rats fed 3000 or 10 000 mg/kg. A NOEL of 300 mg/kg diet was established in this study.

Groups of young adult beagle dogs (four of each sex per group) were fed fenvalerate in the diet at dose levels of 0, 0.25, 0.5, 1.25, or 12.5 mg/kg body weight for 90 days [70]. There were no treatment-related changes in body weight, food consumption, clinical signs, and clinical laboratory data. Gross and microscopic examinations revealed no effects of the fenvalerate. Thus, daily administration at a level of 12.5 mg/kg body weight for a period of 90 days produced no detectable evidence of toxicological effect.

In a study by Parker et al. [148], male and female beagle dogs (six of each sex per group) were fed diets containing 0, 250, 500, or 1000 mg fenvalerate/kg diet for a period of 6 months. Prominent clinical signs related to treatment were emesis, head shaking, biting of the extremities, and tremors. The mean body weights of female dogs fed fenvalerate at 1000 mg/kg were significantly lower than those of controls. Red blood cell counts and haematocrit and haemoglobin values in both male and female dogs fed the highest dose were significantly lower. Serum cholesterol and alkaline phosphatase levels were also increased, mostly in the group fed 1000 mg/kg. Hepatic multifocal microgranulomas observed during microscopic examination increased in incidence and severity in a dose-dependent way and were considered to be related to treatment. Histiocytic cell infiltrates in the mesenteric lymph nodes of some female dogs fed 500 or 1000 mg/kg and of male dogs fed 1000 mg/kg were the only other treatment-related effects observed microscopically.

7.2.2 Inhalation

Groups of Sprague-Dawley rats and ICR mice (10 of each sex per group) were exposed to fenvalerate by inhalation for 3 h daily for 4 weeks at concentration levels of 0, 2, 7, or 20 mg/m^3 (fully respirable particle size). Although animals showed acute signs of poisoning at the highest dose level, no mortality was observed in any group. There were no treatment-related effects in body weight, haematology, or clinical biochemistry parameters, nor were there any gross or microscopic abnormal findings [82, 95].

7.2.3 Dermal application

In a study by Hine [75], groups of rabbits (7-8 male rabbits per group) were administered fenvalerate dermally at dose levels of 0, 100, or 400 mg/kg daily for 6 h (14 exposures were performed over a 22-day period). Severe weight loss, clinical signs of poisoning, and gross dermal effects were observed at 400 mg/kg, where mortality was also observed.

7.3 Skin and Eye Irritation; Sensitization

7.3.1 Skin and eye irritation

Two formulated products (an emulsifiable concentrate and an ultra-low-volume formulation) were found to be severe eye and skin irritants in rabbits. Dermal irritation was evident for 7 days after a 24-h exposure, and severe conjunctivitis, corneal opacity, and iritis were observed within 30 min of an application of 0.2 ml of the formulation to the conjunctival sac. Irrigation of the eye after treatment reduced the irritation [29, 30]. However, when experiments were carried out using pure (non-formulated) fenvalerate, there was no irritation [138].

7.3.2 Skin sensitization

Skin sensitization by pure fenvalerate (95%) has been evaluated using the Landsteiner-Draize method on guinea-pigs. No sensitization was detected by Okuno et al. [139].

7.4 Long-Term Exposures and Carcinogenicity

7.4.1 Mouse

When groups of ddY mice (35-47 of each sex per group) were administered fenvalerate in the diet for 78 weeks at levels of 0, 100, 300, 1000, or 3000 mg/kg, mortality occurred at the highest dose level. Hyperexcitability was observed at 1000 mg/kg or more, and body weight was depressed at 3000 mg/kg over the 18-month period and at 1000 and 3000 mg/kg over the first 3 months. A variety of

haematological parameters were affected at 3 months, predominantly at the highest dose level, but no haematological changes were observed at the end of the study. Several biochemical changes suggestive of hepatotoxicity were observed at 3 months and at termination of the study in the 300, 1000, and 3000 mg/kg groups. There were gross changes in several organ weights and in organ-to-body weight ratios, predominantly in the liver. Microscopic examination revealed changes in the liver, mesenteric lymph nodes, and kidney. Dose-dependent granulomatous changes were observed in the liver and/or mesenteric lymph nodes in all treatment groups. At the 3-month interim sacrifice, multiple small necrotic foci in the liver and changes in the epithelial cells of the proximal convoluted tubules were noted at the two highest dose levels. There were no indications in this study of tumorigenicity or carcinogenicity as a result of fenvalerate administration [81, 83, 173, 175].

In studies by Okuno et al. [144], male ddY mice were fed diets containing the [2S, αS], [2S, αRS], [2R, αS], and [2R, αR] isomers of fenvalerate at diet-ary dose levels of 0, 500, or 1000 mg/kg, 500, 1000, or 2000 mg/kg, 0, 125, or 1000 mg/kg, and 125, or 1000 mg/kg for 52, 52, 13, and 13 weeks, respectively. Microgranulomatous changes were observed in the mice treated with the [2R, αS] isomer after 1, 2, or 3 months. In contrast, the changes did not occur in mice treated with the [2R, αR] isomer under the same conditions. Neither [2S, αS] nor [2S, αRS] isomers caused microgranulomatous changes at 500 or 1000 mg/kg after 1 year. To clarify the causative agent of granuloma formation, the cholesterol ester of 2-(4-chlorophenyl)isovaleric acid (CPIA), a lipophilic conjugate from the [2R, αS] isomer of fenvalerate, was injected intravenously into ddY mice. Microgranulomatous changes were observed in the liver of mice treated with the [2R]-, [2S]-, or [2RS]-CPIA-cholesterol esters 1 week after a single treatment of 1, 10, or 100 mg/kg body weight, as well as in the liver of mice treated with a single dose of 10 or 30 mg/kg body weight of the [2R]-CPIA-cholesterol ester and kept up to 26 weeks afterwards. Histochemical examination and microscopic autoradiography of the liver demonstrated the presence of tritium, derived from ^{3}H-labelled [2R]-CPIA and cholesterol in giant cells and

Kuppfer cells. Another histochemical examination showed the presence of cholesterol ester in the liver of mice treated with the [2R, αS] isomer. These results support the hypothesis that the CPIA-cholesterol ester is the causative agent of the microgranulomatous changes induced by fenvalerate.

In further studies by Okuno et al. [145], male and female ddY mice were fed diets containing technical fenvalerate (either 0, 10, 30, 100, or 300 mg/kg diet for 20 months or 0, 100, 300, 1000, or 3000 for 17-18 months). Microgranulomatous changes were observed in the lymph nodes, liver, and spleen, the NOEL for such changes being 30 mg/kg. To examine the reversibility of these changes, ddY mice (male and female) were fed a diet containing technical fenvalerate at dose levels of 1000 and 3000 mg/kg for 6 weeks, followed by a control diet for up to 12 months. The size and number of the microgranulomatous changes were reduced with time. These changes were typical of foreign body granulomas and did not have the appearance of granulomas formed in response to an immunological stimulus.

When $B6C3F_1$ mice (50 of each sex per group) were fed fenvalerate at dietary concentrations of 0, 10, 50, 250, or 1250 mg/kg for 2 years, mortality was increased and body weight significantly decreased in male and female mice fed 1250 mg/kg. The mean body weight of female mice fed 250 mg/kg was also generally lower than that of controls after the 60th week of feeding. The only treatment-related non-neoplastic pathological effect observed in the study was multifocal microgranulomata in the lymph nodes, liver, and spleen of male mice fed 1250 mg/kg and of female mice fed 250 or 1250 mg/kg. No statistically significant differences were observed in either the number or type of neoplasms in mice fed fenvalerate (compared to concurrent controls). Thus, fenvalerate was found not to be carcinogenic in $B6C3F_1$ mice under the conditions of the test [146].

7.4.2 Rat

When groups of Wistar rats (15 of each sex per group) were fed fenvalerate at concentrations of 0, 50, 150, 500, or 1500 mg/kg diet for 15 months, there was no mortality

attributable to fenvalerate. The hyperexcitability observed during the early stages of the study disappeared within 3 months. Body weight was significantly depressed in both sexes at the highest dose level. No compound-related changes were detected in the urine or in the eyes, but the haemoglobin concentration was depressed in males at the highest dose level and the females at 150 mg/kg or more. Several blood biochemistry parameters were significantly altered at the highest dose level (blood urea nitrogen was increased in both sexes; protein content and plasma cholinesterase were decreased in females). Gross and microscopic examination revealed no dose-related effects [174].

In a study by Gordon & Weir [66], groups of Sprague-Dawley rats (93 males and 93 females per treated group; 183 of each sex used as the control group) were fed fenvalerate in the diet at dose levels of 0, 1, 5, 25, 250, or 500 mg/kg. There was no compound-related mortality, although body weight was reduced at the highest dose level. The group fed 500 mg/kg and a separate control group were sacrificed at 26 weeks while the other animals were maintained for 2 years. There were no significant effects on food consumption, growth, behavior, haematology, blood biochemical composition or urine consumption. At the conclusion of the study, organ weight and organ-to-body weight ratios were normal. Gross and microscopic findings in the treated groups did not differ significantly from those of the controls. A specific pathology examination of the sciatic nerve of animals fed 250 mg/kg revealed no treatment-related changes. Thus, the no-observed-effect level in this study was 250 mg/kg diet.

Parker et al. [147] fed Sprague-Dawley rats (93 of each sex per group) diets containing 0.1, 5, 25, or 250 mg fenvalerate/kg for up to 2 years. The control group consisted of 183 males and 183 females. Ten treated and 20 control rats of each sex from each group were killed at intervals of 3, 6, 12, and 18 months. When body weight, organ weight, food consumption, haematology, and clinical chemical analysis measurements did not reveal any effect resulting from the treatment, two additional groups of rats (50 of each sex per group) were fed 0 or 1000 mg fenvalerate/kg diet for 2 years. Body weight was decreased and organ-to-body weight ratios were increased in brain,

liver, spleen, testes, kidneys (females only), and heart (females only), in the treated animals. Mammary and pituitary tumours were commonly observed, along with a variety of other tumours that occurred randomly among all control and treatment groups. No statistically significant differences in the number and type of neoplasms were observed, except for mammary tumours in females in the main study. These effects were judged not to be toxicologically significant, since mammary tumour incidences did not exceed expected incidences in aged female Sprague-Dawley rats. In addition, the time taken for tumours to appear was unchanged, and no change in the ratio of benign to malignant tumours occurred. Sarcomas identified in the subcutis and dermis in 5 out of 51 males fed 1000 mg/kg were also identified in 2% (1/50), 2% (2/102), and 0-6% of concurrent, original, and historical controls, respectively. The no-observed-effect level was 250 mg/kg.

When male and female Wistar rates were fed a diet containing technical fenvalerate at 0, 50, 150, 500, or 1500 mg/diet for 24-28 months, microgranulomatous changes were observed in lymph nodes, liver, spleen, and adrenal glands. The no-observed-effect level for these microgranulomatous changes was 150 mg/kg [145].

7.5 Mutagenicity

7.5.1 Microorganism and insects

The DNA-damaging capacity of fenvalerate has been examined in a Rec-assay with *Bacillus subtilis* M45 *rec*⁻ and H17 wild type strains at concentrations up to 10 mg/disk per plate. Fenvalerate had no inhibitory effect on the growth of indicator strains, and was judged to be non-mutagenic [170].

Fenvalerate has also been examined for its mutagenic potency with the Ames test in Salmonella typhimurium (TA 1535, TA 1538, TA 98, and TA 100), using dose levels of up to 1 mg/plate both with and without a metabolic enzyme system. Fenvalerate was non-mutagenic in these tests [170]. It was also tested using hepatic metabolic enzyme systems prepared from various PCB-treated animals (three strains of rats, six strains of mice and the Syrian

golden hamster). At dose levels of up to 1 mg/plate, Fenvalerate was non-mutagenic [171, 172].

In further studies by Suzuki & Miyamoto [170], fenvalerate was given orally at doses of 60 and 125 mg/kg to groups of mice, and indicator cells (S. typhimurium G46) were injected intraperitoneally. Fenvalerate did not induce any significant level of mutation among the indicator cells recovered from the abdominal cavity. On the other hand, the positive control, dimethylnitrosamine, significantly increased the mutation frequency of the indicator organism.

Another host-mediated assay of fenvalerate in mice was conducted using *Saccharomyces cerevisiae* as indicator microorganism. Groups of mice were administered fenvalerate orally at doses of 25 and 50 mg/kg, and were injected with a suspension of indicator cells intraperitoneally. No mutagenic effect on the indicator cells was detected [17].

Fenvalerate was not found to be mutagenic in S. typhimurium strains TA 100 or TA 98 in the presence or absence of a rat liver activation system by fluctuation tests at a concentration of up to 10 μg/ml or in V79 Chinese hamster cells in the presence or absence of hepatocytes at a concentration of up to 40 μg/ml [153].

Fenvalerate did not induce sex-linked recessive lethals, sex-chromosome losses, or non-disjunction in *Drosophila melanogaster* when it was given to adults (up to 20 mg/litre in the diet) or larvae (up to 50 mg/litre in the diet), or was injected into adults (at 20 μg/ml) [7].

7.5.2 Rat

In a study by Chatterjee et al. [26], groups of rats (21 per group) were administered fenvalerate orally at doses of 50, 75, or 100 mg/kg per day for 3 weeks. The rats were killed 24 h after the last treatment and bone marrow cells were examined for chromosomal aberrations. Although an increase in the frequency of chromosomal aberrations was observed in fenvalerate-treated animals, it was not possible to draw any definite conclusion because it was not dose related and may have been non-specific.

Fenvalerate has also been studied for the enhancement of gamma-glutamyl transpeptidase-positive enzyme-altered focus incidence in partially hepatectomized, nitrosodiethylamine-initiated male Sprague-Dawley rats. Fenvalerate administered peritoneally (75 mg/kg body weight per day, 5 days a week for 10 weeks) induced significantly more foci per cm^3 and a larger percentage of liver tissue occupied by focus tissue, compared with a vehicle-control group. Analysis of the size distribution of foci in fenvalerate- and vehicle-treated rats showed elevated focus incidences in fenvalerate-treated rats at all focus sizes. Fenvalerate induced no hepatotoxic effects, as judged by serum transaminase activities and histopathological analysis [58].

7.5.3 *Mouse*

In a dominant lethal assay, groups of male mice (10-11 per group) were administered fenvalerate orally at doses of 25, 50, or 100 mg/kg body weight. Each male was mated with three virgin females for 7 days. The procedure was repeated weekly as a standard dominant lethal test. The females were sacrificed and examined for dominant lethality at the 13th day of gestation. Fetal implants in females, mated to males that had been treated with 100 mg/kg for 2 weeks, showed a significant reduction in viability. A significant increase in early fetal death was observed in females mated with males that had been treated for 4 weeks with the highest dose [34].

The significance of the above data was further studied as follows:

(1) By using a two-way analysis of variance, it was judged that the reduction in fetal implants in females mated to males the second week after dosing at 100 mg/kg and the increase in early fetal deaths in the 4th week were statistically significant. But these increases or decreases appeared to be random and were not considered to be biologically significant.

(2) Using a t-test and the Mann-Whitney U-test, no significance was shown in any mean proportions for the above parameters.

From these findings, it was concluded that fenvalerate did not cause dominant lethal effects in mice[a].

7.5.4 Hamster

In a study by Dean & Senner [35], fenvalerate was administered orally to groups of hamsters (six males and six females per group) at two successive daily doses of 12.5 and 25 mg/kg. The chromosomal preparations were made 8 or 24 h after administration. Fenvalerate did not induce any chromosomal damage in the bone marrow cells from treated animals, whereas the positive control, methyl methanesulfonate (50 mg/kg), had induced a substantial number of chromatid gaps within 8 h of dosing.

Fenvalerate, and the fenvalerate metabolite 2-(4-chlorophenyl)isovaleric acid, were investigated for the inhibition of gap-junctional intercellular communication *in vitro* in the Chinese hamster lung fibroblast (V79) metabolic cooperation assay [58]. This study showed that both fenvalerate and 2-(4-chlorophenyl)isovaleric acid were inhibitors of intercellular communication at non-cytotoxic concentrations.

7.6 Teratogenicity and Reproduction Studies

7.6.1 Teratogenicity

In studies by Kohda et al. [93], groups of pregnant ICR mice (32-33 per group) were orally administered fenvalerate at dose levels of 0, 5, 15, or 50 mg/kg per day on days 6 to 15 of gestation. Groups of 20 mice were sacrificed on day 18, and the fetuses were removed and examined for visceral and skeletal abnormalities. The remaining dams were allowed to deliver naturally and the young were maintained until weaning to evaluate postnatal

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[a] *Personal communication, J. Miyamoto, 1981, Comments on "Further work information" required by 1979 JMPR on fenvalerate, Laboratory of Biochemistry and Toxicology (Unpublished report submitted to WHO by Sumitomo Chemical Co. Ltd).*

deficits. Additionally two male and two female weanlings from each dam were maintained for 8 weeks and mated to investigate their reproductive potential. Although toxic signs were noted in the dams at the highest dose level, there was no significant mortality. Examination of the fetuses revealed no external, visceral, or skeletal abnormalities. Treatment of the dams with fenvalerate did not affect the reproductive performance of the offspring.

Van Der Pauw et al. [187] dosed groups of pregnant Dutch rabbits (20 to 31 per group) orally with fenvalerate (0, 12.5, 25, or 50 mg/kg body weight per day) from day 6 to day 18 of gestation. The dams were sacrificed on day 28 and standard teratogenic assessments made. The body weights of the dams given the highest dose were reduced. There were no significant differences from controls in any of the other parameters examined. Fenvalerate was not found to be teratogenic in this study.

7.6.2 Reproduction studies

In studies by Stein [167] and Beliles et al. [10], groups of Sprague-Dawley rats (11 males and 22 females per group) were fed fenvalerate in the diet at levels of 0, 1, 5, 25, or 250 mg/kg. The animals were dosed for 9 weeks prior to mating and the initiation of a standard three-generation (two litters per generation) reproduction study. Fertility, viability, gestation, and lactation indices were calculated for each group of rats and were compared to control values. Ten of the female weanlings and all of the males from the F_{3b} litters were examined histologically at the conclusion of the study. The mean body weight of the F_{2b} adults was decreased at 250 mg/kg, but no pathological changes were noted to account for this weight loss. No effects on reproductive parameters in any of the three generations were observed. Histological examination revealed no treatment-related changes in any group.

Groups of pregnant ICR mice (32-33 mice per group) were orally administered fenvalerate at dose levels of 0, 5, 15, or 50 mg/kg body weight per day on days 6 to 15 of gestation in a standard teratogenicity bioassay. Two male and two female weanlings from each dam were maintained for

8 weeks and mated to investigate their reproductive potential. Toxic signs were noted in maternal mice at the highest dose level. There was no significant mortality over the course of the study, and no effects were noted on any of the other animals as a result of continuous administration of fenvalerate. The animals maintained in the abbreviated reproduction study showed no differences from the control value in their ability to reproduce. There were no changes in the reproduction indices with any animals examined [93].

7.7 Neurotoxicity

In a study by Butterworth & Carter [20], histopathological examination was performed on the sciatic nerve and posterior tibial nerve of rats that had been exposed to acutely toxic levels of fenvalerate. After poisoning, and for 9 days during the course of recovery, axonal breaks, swelling, and vacuolisation, accompanied by phagocytosis of myelin, were seen. The degree to which myelin was disrupted was dose dependent and was closely associated with the acute signs of toxicity.

Acute oral administration of fenvalerate, cypermethrin, resmethrin, permethrin, and natural pyrethrum to rats at very high dose levels resulted in severe clinical signs of poisoning and mortality within 24 h. Histopathological lesions were observed in the sciatic nerve with all compounds tested. Fenvalerate did not cause the clinical signs or histopathological lesions at a lower dose level (200 mg/kg), nor did the other compounds [141, 142].

When groups of six male and six female rats were fed fenvalerate in the diet at a concentration of 2000 mg/kg for 8 to 10 days, all the animals showed typical signs of acute intoxication, such as ataxia, tremors, and hyperexcitability. Histopathological examinations did not reveal any adverse effects of fenvalerate on the sciatic nerve [73].

In order to evaluate the reversibility of the lesions induced in the sciatic nerve, rats were administered fenvalerate in the diet at dose levels of 0 or 3000 mg/kg diet for 10 days. This was followed by a control diet for

12 weeks. During the treatment period, mortality was 60% in the animals treated with fenvalerate. Rats on the recovery control diets, sacrificed at 3 weeks, continued to show swelling and disintegration of axons of the sciatic nerves. However, there were no histopathological lesions after 6, 9, or 12 weeks of the recovery period. These results showed the reversibility of the sciatic nerve lesions caused by fenvalerate [143].

In studies by Butterworth & Hend [21], fenvalerate was administered orally to Wistar or Carworth Farm E (CFE) rats either as single doses or in the diet. When given in large quantities by a single dose of 250, 500, 800, or 1000 mg/kg body weight, which were sufficient to kill some of the treated animals, fenvalerate produced sporadic Wallerian degeneration in the sciatic nerve. The neuropathy was never severe and was not seen in animals given the compound in sub-lethal doses. In feeding studies (for 5 weeks at 1000 mg/kg diet and for 3 months at 2000 mg/kg diet), no lesions were seen in the peripheral nerve, brain, or spinal cord, and there was no evidence of cumulative neurotoxicity.

$B6C3F_1$ mice and Sprague-Dawley rats showed the characteristic signs of intoxication following single oral doses of fenvalerate ranging from 56 to 320 and 133 to 1000 mg/kg body weight, respectively. Neurological signs, such as splayed gait, tremors, ataxia, and hind limb incoordination, were observed at doses of 100 mg/kg or more (mice) and 133 mg/kg or more (rats) within 1-8 h after dosing. These signs had disappeared in most animals within 72 h. Slight peripheral nerve fibre damage was detected in surviving mice and rats sacrificed 10 days after dosing. The incidence and severity were dose related at doses $\geq$ 56 and $\geq$ 180 mg/kg; however, even at lethal doses, there was no evidence of nerve lesions in some animals. Thus, two distinct neurological effects were observed, i.e., (a) a reversible ataxia and (b) incoordination plus a neuropathological effect manifested as sparse axonal damage in peripheral nerves [149].

In a study by Milner & Butterworth [123], groups of six hens were administered fenvalerate orally at dose levels of 0 or 1000 mg/kg per day for 5 days. A positive control of tri-*ortho*-cresyl phosphate (0.5 ml/kg) (TOCP)

was also included in the study. The fenvalerate-treated birds were retreated, using the same dose regimen, after 3 weeks. The TOCP-treated hens showed signs of delayed neurotoxicity and histopathological lesions in their sciatic nerve and spinal cord. As would be expected for a non-organophosphorus insecticide, there were no typical clinical signs and histopathological lesions related to fenvalerate.

7.8 Behavioural Studies

Guinea-pigs responded to dermal applications of fenvalerate by scratching the treated sites of the skin. This characteristic response was essentially over within 3-4 h. When the powerful skin irritant oil of mustard was applied to fenvalerate-treated sites of skin 4-72 h after the fenvalerate treatment, the behavioural skin sensory response was re-stimulated. Oil of mustard alone did not produce skin sensory stimulation. These results indicate that pyrethroid treatment causes a transient sensitivity to stimulation produced by chemical irritants [111].

To develop an animal model for studying skin sensory stimulation, Duncan-Hartley guinea-pigs were treated with pyrethroid solutions on one side and control substances on the other side of their shaved back. The animals responded by licking, scratching, or biting the test sites, and activity was quantified by counting the number of times the animals responded. This behavioural activity reached a maximum 1-4 h after treatment. A chemical irritant (oil of mustard) was able to restimulate the behavioural activity when applied within 24 h after pyrethroid application. Skin sensory stimulation produced by cyano-containing pyrethroids, including fenvalerate, was significantly greater than that produced by non-cyano-containing pyrethroids. This behavioural model provides a quantitative means of evaluating pyrethroid non-erythematous skin sensory stimulation [22].

'.9 Miscellaneous Studies

In an antidotal study, phenobarbital, pentobarbital, and diphenylhydantoin were found to be effective in relieving the acute signs of intoxication in the rat.

Intraperitoneal injection of phenobarbital (50 mg/kg) prevented tremor, diphenylhydantoin (100 mg/kg) by the same route reduced the toxic reaction, and pentobarbital (35 mg/kg intraperitoneally) removed the tremor reaction completely within 30 min. The combination of diphenylhydantoin with either of the barbiturates was effective in reducing the onset and severity of tremors whereas various other agents d-tubocurarine, atropine, meprobamate, diazepam, biperiden, and trimethadione) were ineffective [113].

The therapeutic potency of intraperitoneally administered methocarbamol was examined as an antidote against the acute oral intoxication of rats by a lethal dose of fenvalerate. Methocarbamol was initially administered at a dose of 400 mg/kg body weight, followed by repeated doses of 200 mg/kg body weight when tremors or hyperexcitability to sound were observed. Methocarbamol markedly decreased the mortality from 80%, which would be caused by an administration of 850 mg fenvalerate/kg, to 0%, and was effective in alleviating motor symptoms such as fibrillation, tremors, hyperexcitability, clonic seizures, and choreoathetotic movements. A subcutaneous administration of atropine sulfate (25 mg/kg body weight) was also effective in reducing the salivation produced by fenvalerate [76].

Effective treatments against fenvalerate-mediated effects have been investigated by quantifying behavioural skin sensory responses such as licking, scratching, or biting of the treated sites by fenvalerate-treated guinea-pigs. Preparations containing vitamin E, corn oil, or the local anesthetic benzocaine were most effective [111].

Intraperitoneal administration of *O*-ethyl-*O*-(4-nitrophenyl)phenylphosphonothioate (EPN) or *S,S,S*-tributylphosphorotrithioate (DEF) to mice at 25 mg/kg increased the intraperitoneal toxicity of fenvalerate (administered 1 h later) by more than 25-fold; the LD_{50} decreased from > 1000 mg/kg to 37 or 42 mg/kg. This suggests that mammalian esterases highly sensitive to inhibition by certain organophosphorus compounds may play a critical role in fenvalerate detoxication. This kind of synergism among pesticides would be detrimental in increasing the toxicity of certain pyrethroids to mammals [62].

Fenvalerate, administered to dogs at a dose sufficient to induce toxic signs, showed no consistent cardiovascular effects. Respiratory stimulation was noted at high levels, and this was not reduced by anaesthetic supplements (urethane, chloralose, and pentobarbital) [91].

7.10 Mechanism of Toxicity - Mode of Action

The intravenous toxicity of fenvalerate (50-100 mg/kg) to rats was examined by Verschoyle & Aldridge [189]. [2S, αS]-Fenvalerate induced choreoathetosis with salivation (CS-syndrome), and was classified as a Type II pyrethroid. For the mode of action of pyrethroids in general see Appendix 1.

The intracerebral injection of [2S, αS]-fenvalerate (0.01 mg/kg) to mice produced the Type II syndrome, consisting of choreoathetosis, convulsion, and salivation [98]. The Type II syndrome is produced characteristically by pyrethroids with an α-cyano group and the site of action in mammals is considered to be the central nervous system.

In intact locusts and neuromuscular preparations of locusts, fenvalerate caused (a) prolonged firing in the crural nerve without associated muscle contractions; (b) sustained muscle contractions; and (c) a block of neurally evoked muscle contractions at low concentration (10^{-8} to 10^{-5} mol/litre). However, fenvalerate did not cause repetitive firing and after-discharges with associated muscle contractions [27]. The fenvalerate stereoisomers with an (S) configuration in the alcohol moiety are more active pharmacologically and toxicologically than those with the (R) configuration or the racemate (R,S). It is also apparent that stereoisomers with the (S) configuration in the acid moiety are more active than those with the (R) configuration or the racemate (R,S) [27].

[S,S]-Fenvalerate does not induce repetitive firing in the cockroach cercal sensory nerves either *in vivo* or *in vitro*. It does, however, cause different signs, including bursts of spikes in the cercal motor nerve [60].

There are no clear-cut links between electrophysiological findings in insects and toxicity to mammals.

8. EFFECTS ON HUMANS

8.1 Occupational Exposure

Appraisal

Fenvalerate has been found to induce skin sensations in some of the workers who handle this insecticide. Clinical studies showed that the skin sensations develop with a latent period of approximately 30 min, peak by 8 h and deteriorate after 24 h. Numbness, itching, tingling, and burning are symptoms frequently reported. Alpha-tocopheryl acetate has been found to inhibit the occurrence of these skin sensations.

In a study by Kolmodin-Hedman et al. [97], personnel (52 people) at various plant nurseries who had handled conifer seedlings treated with fenvalerate were examined. The symptoms were mainly irritative, such as itching, paraesthesia and burning of the skin, and itching and irritation of the eyes. The frequency (% of people who reported these signs) was about 10%. Increased nasal secretion was reported by 19% of the personnel.

No clinical case of pyrethroid poisoning had been reported until outbreaks of acute deltamethrin and fenvalerate poisoning occurred among cotton growers in China in 1982. Having been told (in error) that pyrethroids were non-toxic, the farmers handled the pyrethroid insecticides without taking any precautions. After repeated spraying in the cotton fields, the mild cases presented severe headaches, dizziness, fatigue, nausea, and anorexia, with transient changes in the electroencephalogram (EEG), while a severe case developed muscular fasciculation, repetitive discharges in the electromyogram (EMG), and frequent convulsions. However, all were found by follow-up studies to

have completely recovered and the prognosis of acute pyrethroid poisoning proved to be correct [71][a].

Among 23 workers exposed to synthetic pyrethroids, including fenvalerate, 19 experienced one or more episodes of abnormal facial sensation, developing between 30 min and 3 h after exposure and persisting for 30 min to 8 h [106]. However, there were no abnormal neurological signs, and electrophysiological studies showed normal responses in the arms and legs. The symptoms were most likely due to transient lowering of the threshold of sensory nerve fibres or sensory nerve endings following exposure of the facial skin to pyrethroids.

In a study by Tucker & Flannigan [182], selected individuals who had worked extensively with fenvalerate in the delta region of the Mississippi and Alabama, USA, were interviewed and examined. They had, on some occasions, noted paraesthesia associated with exposure to this insecticide. The cutaneous sensation was described as a stinging or burning, which progressed to numbness in approximately one-third of the exposed workers. The sensation typically began a number of hours after contact, peaked in the evening, and rarely was present the following morning. The intensity of the sensation varied according to the type and extent of exposure. Clinical signs of inflammation such as oedema or vesiculation were not apparent. Erythema was present in a few individuals but this was difficult to distinguish from sunburn. Several environmental factors were found to affect the cutaneous sensation associated with fenvalerate exposure.

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[a] *More recently, the same author reviewed 573 cases of acute pyrethroid poisoning reported in the Chinese medical literature during 1983-1988 [213]. Among these there were 196 cases of acute fenvalerate poisoning, 63 of which were occupational, due to inappropriate handling and 133 accidental, mostly due to ingestion. Two died of convulsions. All others recovered with symptomatic and supportive treatment within 1-6 days. A comprehensive review of clinical manifestations is included.*

8.2 Clinical Studies

A double-blind study with 29 male volunteers was performed to test the skin reaction to formulated fenvalerate. The emulsifiable concentrate formulation was diluted with water and applied to one side of the face, on the cheek, with a control formulation on the opposite cheek. There were no signs of dermatitis 24 h after application, nor did the fenvalerate formulation produce any abnormal skin sensations. There were no indications that any of the symptoms such as tingling, itching, or burning were associated with fenvalerate [18].

A double-blind study was performed to compare human discrimination of technical fenvalerate, the heavy-ends fraction of distilled fenvalerate, and ethyl alcohol (vehicle) applied to the lower edge of each earlobe of 36 adult (both male and female) volunteers on three separate occasions. Both forms of fenvalerate caused a statistically significant increase in paraesthesia, compared with the vehicle alone. The onset of the cutaneous sensations occurred 1 h after application, peaked at 3-6 h, and lasted approximately 24 h. Numbness, itching, burning, tingling, and warmth were the most frequently reported sensations. The difference between the effects of the two fractions of fenvalerate was not statistically significant [92].

Flannigan & Tucker [55], Flannigan et al. [56, 57], and Malley et al. [112] studied the difference in the degree of paraesthesia induced by a number of pyrethroids. Applications of 0.05 ml fenvalerate formulated to field strength (0.13 mg/cm^2) were made to a 4 cm^2 area of earlobe on five occasions, the opposite earlobe receiving distilled water. Participant evaluation after each application continued for 48 h and involved description of the cutaneous sensations. Each participant was treated after each application with one of the remaining compounds. Fenvalerate (like the other pyrethroids) induced skin sensations. The paraesthesia developed with a latent period of approximately 30 min, peaked by 8 h, and deteriorated as early as 24 h. The local application of dl-alpha tocopheryl acetate markedly inhibited the occurrence of skin sensations.

9. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) has discussed and evaluated fenvalerate at its meetings in 1979, 1981, 1982, 1984, 1986, and 1987 [40-47, 49, 50, 52-4].

Since 1986, an acceptable daily intake (ADI) of 0-0.02 mg/kg body weight has been established.

In the WHO Recommended Classification of Pesticides by Hazard, technical fenvalerate is classified as "moderately hazardous" (Class II) [197].

REFERENCES

1. AGNIHOTRI, N.P., JAIN, H.K., & GAJBHIYE, V.T. (1986) Persistence of some synthetic pyrethroid insecticides in soil, water and sediment - Part I. *J. entomol. Res.*, **10**(2): 147-151.

2. ALBERT, J.R. & SUMMITT, L.M. (1976) *Intravenous toxicity of WL 43775 (6-1-0-0) in the mouse* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

3. ALINIAZEE, M.T. & CRANHAM, J.E. (1980) Effect of four synthetic pyrethroids on a predatory mite, *Typhlodromus pyri* and its prey, *Panonychus ulmi* on apples in southeast England. *Environ. Entomol.*, **9**: 436-439.

4. ANDERSON, R.L. (1982) Toxicity of fenvalerate and permethrin to several non-target aquatic invertebrates. *Environ. Entomol.*, **11**: 1251-1257.

5. ATKINS, E.L., KELLUM, D., & ATKINS, K.W. (1981) *Reducing pesticide hazards to honey bees: mortality prediction techniques and integrated management strategies*, Berkeley, California, University of California, Division of Agricultural Sciences (Leaflet No. 2883).

6. 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.

7. BATISTE-ALENTORN, M., XAMENA, N., VELAZQUEZ, A., CREUS, A., & MARCOS, R. (1987) Non-mutagenicity of fenvalerate in Drosophilia. *Mutagenesis*, **2**: 7-10.

8. BATTELLE (1982) *Pesticide programme of research and market planning. Part I. Insecticides*, Geneva, Battelle Research Centre.

9. BATTELLE (1986) *World pesticide programme: Insecticide II*, Geneva, Battelle Research Centre.

10. BELILES R.P., MARIS, S.L., & WEIR, R.J. (1978) *Three-generation reproduction study in rats*, Kensington, Maryland, Litton Bionetics Inc. (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

11. BIRDIE, N.S., BANERJI, R.K., & CHAUHAN, A.K. (1986) Gas liquid chromatographic separation of pyrethrins from some synthetic pyrethroids in formulations. *Pyrethrum Post*, **16**(3): 77-80.

12. BLAIR, D. & RODERICK, H. (1975) *Toxicity studies on the pyrethroid insecticide WL 43775, emulsifiable concentrate FX 3368: Acute inhalation exposure to an aqueous spray* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

13. BRADBURY, S.P. & COATS, J.R. (1982) Toxicity of fenvalerate to bob-white quail (*Colinus virginianus*) including brain and liver residues associated with mortality. *J. Toxicol. environ. Health*, **10**: 307-319.

14. BRADBURY, S.P., COATS, J.R., & MCKIM, J.M. (1986) Toxicokinetics of fenvalerate in rainbow trout *(Salmo gairdneri). Environ. Toxicol. Chem.*, **5**: 567-576.

15. BRADBURY, S.P., MCKIM, J.M., & COATS, J.R. (1987) Physiological response of rainbow trout *(Salmo gairdneri)* to acute fenvalerate intoxication. *Pestic. Biochem. Physiol.*, **27**: 275-288.

16. BRAUN, H.E. & STANEK, J. (1982) Application of the AOAC multi-residue method to determination of synthetic pyrethroid residues in celery and animal products. *J. Assoc. Off. Anal. Chem.*, **65**: 685-689.

17. BROOKS, T.M. (1976) *Toxicity studies with WL 43775: Mutagenicity studies with WL43775 in the host-mediated assay* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

18. BROWN, L.J. & SLOMKA, M.B. (1979) *Skin reaction potential of use dilution (1.33%) PYDRIN EC* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

19. BRUCE, M.L. & CARUSO, J.A. (1985) The laminar flow torch for gas chromatographic He microwave plasma detection of pyrethroids and dioxins. *Appl. Spectrosc.*, **39**(6): 942-949.

20. BUTTERWORTH, S.T.G. & CARTER, B.I. (1976) *Toxicity studies on the insecticide WL 43775: Acute oral toxicity and neuropathological effects in rats* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

21. BUTTERWORTH, S.T.G. & HEND, R.W. (in press) Peripheral nerve lesions induced by large doses of pyrethroid. *Neuropathol. appl. Neurobiol.*

22. CAGEN, S.Z., MALLEY, L.A., PARKER, C.M., GARDINER, T.H., VAN GELDER, G.A., & JUD, V.A. (1984) Pyrethroid-mediated skin sensory stimulation characterized by a new behavioural paradigm. *Toxicol. appl. Pharmacol.*, **76**: 270-279.

23. CAPLAN, J.R., ISENSEE, A.R., & NELSON, J.O. (1984) Fate and effect of [^{14}C]fenvalerate in a tidal marsh sediment ecosystem model. *J. agric. food Chem.*, **32**: 166-171.

24. CAYLEY, G.R. & SIMPSON, B.W. (1986) Separation of pyrethroid enantiomers by chiral high-performance liquid chromatography. *J. Chromatogr.*, **356**: 123-134.

25. CHAPMAN, R.A. & HARRIS, C.R. (1981) Persistence of four pyrethroid insecticide in a mineral and organic soil. *J. environ. Sci. Health*, **B16**: 605-615.

26. CHATTERJEE, K.K., TALUKDER, G., & SHARMA, A. (1982) Effects of synthetic pyrethroids on mammalian chromosomes I. Sumicidin. *Mutat. Res.*, **105**: 101-106.

27. CLEMENTS, A.N. & MAY, T.E. (1977) The actions of pyrethroids upon the peripheral nervous system and associated organs in the locust. *Pestic. Sci.*, **8**: 661-680.

28. COATS, J.R. & O'DONNELL-JEFFREY, N.L. (1979) Toxicity of four synthetic pyrethroid insecticides to rainbow trout. *Bull. environ. Contam. Toxicol.*, **23**: 250-255.

29. COOMBS, A.D. & CARTER, B.I. (1975) *Toxicity studies on insecticide WL 43775: Acute toxicity, skin irritancy potential of the emulsifiable concentrate FX 3368* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

30. COOMBS, A.D. & CARTER, B.I. (1976) *Toxicity studies on the insecticide WL43775: Toxicity and skin and eye irritancy potential of the ULV formulation FX4353* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

31. CURTIS, L.R., SEIM, W.K., & CHAPMAN, G.A. (1985) Toxicity of fenvalerate to developing steelhead trout following continuous or intermittent exposure. *J. Toxicol. environ. Health*, **15**: 445-457.

32. DAY, K. & KAUSHIK, N.K. (1987a) Short-term exposure of zooplankton to the synthetic pyrethroid, fenvalerate, and its effects on rates of filtration and assimilation of the alga *Chlamydomonas reinhardii*. *Arch. environ. Contam. Toxicol.*, **16**: 423-432.

33. DAY, K. & KAUSHIK, N.K. (1987b) An assessment of the chronic toxicity of the synthetic pyrethroid, fenvalerate, to *Daphnia galeata mendotae*, using life tables. *Environ. Pollut.*, **44**: 13-26.

34. DEAN, B.J. (1975) *Toxicity studies with WL 43775: Dominant lethal assays in male mice after single oral doses of WL 43775* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

35. DEAN, B.J. & SENNER, R.K. (1975) *Toxicity studies with WL 43775: Chromosome studies on bone marrow cells of Chinese hamster after two daily oral doses of WL 43775* (Unpublished report to WHO submitted by Shell Development Co., Ltd).

36. ELLIOTT, M. (1977) *Synthetic pyrethroids*, Washington, DC, American Chemical Society, p. 229 (ACS Symposium Series No. 42).

37. ESTESEN, B.J., BUCK, N.A., & WARE, G.W. (1979) Dislodgable insecticide residue on cotton foliage: permethrin, curacron, fenvalerate, sulprofos, decis, and endosulfan. *Bull. environ. Contam. Toxicol.*, 22: 245-248.

38. EVANS, M.H. (1976) End-plate potentials in frog muscle exposed to a synthetic pyrethroid *Pestic. Biochem. Physiol.*, **6**: 547-550.

39. FAO (1982) *Report of the Second Government Consultation on International Harmonization of Pesticide Registration Requirements, Rome, 11-15 October, 1982*, Rome, Food and Agriculture Organization of the United Nations.

40. FAO/WHO (1980a) *Pesticide residues in food. Report of the 1979 Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues*, Rome, Food and Agriculture Organization of the United Nations, pp. 46-49 (FAO Plant Production and Protection Paper 20).

41. FAO/WHO (1980b) *1979 Evaluations of some pesticide residues in food*, Rome, Food and Agriculture Organization of the United Nations, pp. 299-353 (FAO Plant Production and Protection Paper 20 Sup.).

42. FAO/WHO (1982a) *Pesticide residues in food. Report of the 1981 Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues*, Rome, Food and Agriculture Organization of the United Nations, pp. 26-28 (FAO Plant Production and Protection Paper 37).

43. FAO/WHO (1982b) *1982 Evaluations of some pesticide residues in food*, Rome, Food and Agriculture Organization of the United Nations, pp. 209-256 (FAO Plant Production and Protection Paper 42).

44. FAO/WHO (1983a) *Pesticide residues in food. Report of the 1982 Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues*, Rome, Food and Agriculture Organization of the United Nations, p. 28 (FAO Plant Production and Protection Paper 46).

45. FAO/WHO (1983b) *1982 Evaluations of some pesticide residues in food*, Rome, Food and Agriculture Organization of the United Nations, p. 420 (FAO Plant Production and Protection Paper 49).

46. FAO/WHO (1985a) *Pesticide residues in food. Report of the 1984 Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues*, Rome, Food and Agriculture Organization of the United Nations, pp. 46-49, 83, 90-93 (FAO Plant Production and Protection Paper 62).

47. FAO/WHO (1985b) *1984 Evaluations of some pesticide residues in food*, Rome, Food and Agriculture Organization of the United Nations, pp. 343-353 (FAO Plant Production and Protection Paper 67).

48. FAO/WHO (1985c) *Guide to Codex recommendations concerning pesticide residues. Part 8: Recommendations for methods of analysis of pesticide residues*, 3rd ed., Rome, Codex Committee on Pesticide Residues, Food and Agriculture Organization of the United Nations.

49. FAO/WHO (1986a) *Pesticide residues in food. Report of the 1986 Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues*, Rome, Food and Agriculture Organization of the United Nations, pp. 28-29, 61 (FAO Plant Production and Protection Paper 77).

50. FAO/WHO (1986b) *1986 Evaluations of some pesticide residues in food. Part I - Residues*, Rome, Food and Agriculture Organization of the United Nations, pp. 189-193, 355 (FAO Plant Production and Protection Paper 78/1).

51. FAO/WHO (1986c) *Codex maximum limits for pesticide residues*, 2nd ed., Rome, Codex Alimentarius Commission, Food and Agriculture Organization of the United Nations (CAC XIII).

52. FAO/WHO (1987a) *1986 Evaluations of some pesticide residues in food. Part II - Toxicology*, Rome, Food and Agriculture Organization of the United Nations, p. 219 (FAO Plant Production and Protection Paper 78/2).

53. FAO/WHO (1987b) *Pesticide residues in food. Report of the 1987 Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues*, Rome, Food and Agriculture Organization of the United Nations, p. 27 (FAO Plant Production and Protection Paper 84).

54. FAO/WHO (1988) *1987 Evaluations of some pesticide residues in food. Part I - Residues*, Rome, Food and Agriculture Organization of the United Nations, pp. 57-59 (FAO Plant Production and Protection Paper 86/1).

55. FLANNIGAN, S.A. & TUCKER, S.B. (1985) Variation in cutaneous sensation between synthetic pyrethroid insecticides. *Contact Dermatitis*, **13**: 140-147.

56. FLANNIGAN, S.A., TUCKER, S.B., KEY, M.M., ROSS, C.E., FAIRCHILD, E.J., GRIMES, B.A., & HARRIST, R.B. (1985a) Primary irritant contact dermatitis from synthetic pyrethroid insecticide exposure. *Arch. Toxicol.*, **56**: 288-294.

57. FLANNIGAN, S.A., TUCKER, S.B., KEY, M.M., ROSS, C.E., FAIRCHILD, E.J., GRIMES, B.A., & HARRIST, R.B. (1985b) Synthetic pyrethroid insecticides: a dermatological evaluation. *Brit. J. ind. Med.*, **42**: 363-372.

58. FLODSTROM, S., WARNGARD, 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.

59. GAMMON, D.W. & CASIDA, J.E. (1983) Pyrethroids of the most potent class antagonize GABA action at the crayfish neuromuscular junction. *Neurosci. Lett.*, **40**: 163-168.

60. GAMMON, D.W., BROWN, M.A., & CASIDA, J.E. (1981) Two classes of pyrethroid action in the cockroach. *Pestic. Biochem. Physiol.*, **15**: 181-191.

61. GAMMON, D.W., LAWRENCE, L.J., & CASIDA, J.E. (1982) Pyrethroid toxicology: Protective effects of Diazepam and phenobarbital in the mouse and the cockroach. *Toxicol. appl. Pharmacol.*, **66**: 290-296.

62. GAUGHAN, L.C., ENGEL, J.I., & CASIDA, J.E. (1980) Pesticide interactions: effects on organophosphorus pesticides on the metabolism, toxicity and persistence of selected pyrethroid insecticides. *Pestic. Biochem. Physiol.*, **14**: 81-85.

63. GERIG, L. (1985) Testing the toxicity of synthetic pyrethroid insecticides to bees. *Pestic. Sci.*, **16**: 206-207.

64. GHIASUDDIN, S.M. & SODERLUND, D.M. (1984) Hydrolysis of pyrethroid insecticides by soluble mouse brain esterases. *Toxicol. appl. Pharmacol.*, **74**: 390-396.

65. GLICKMAN, A.H. & CASIDA, J.E. (1982) Species and structural variations affecting pyrethroid neurotoxicity. *Neurobehav. Toxicol. Teratol.*, **4**:(6) 793-799.

66. GORDON, E.B. & WEIR, R.J. (1978) *Lifetime feeding study in rats, SD-43775 Technical*, Kensington, Maryland, Litton Bionetics, Inc. (Project No. 2054, Report AT-81-0181) (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

67. GREENBERG, R.S. (1981) Determination of fenvalerate, a synthetic pyrethroid, in grapes, peppers, apples, and cotton seeds by gas-liquid chromatography. *J. agric. food Chem.*, 29: 856-860.

68. HANSEN, D.J., GOODMAN, L.R., MOORE, J.C., & HIGDON, P.K. (1983) Effects of the synthetic pyrethroids AC 222, 705, permethrin and fenvalerate on sheepshead minnows in early life stage toxicity tests. *Environ. Toxicol. Chem.*, **2**(2): 251-8

69. HARRIS, C.R., CHAPMAN, R.A., & HARRIS, C. (1981) Laboratory studies on the persistence and behavior in soil of four pyrethroid insecticides. *Can. Entomol.*, **113**: 685-694.

70. HART, E.R. (1975) *90-day subacute toxicity study in dogs, SD 43775 Technical (sumicidin)*, Kensington, Maryland, Litton Bionetics, Inc. (Technical Report No. AT-51-0013) (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

71. HE, FENSHENG (1987) *Occupational neurotoxicology: Current problems and trends*. Presented at the XXII International Congress on Occupational Health, Sydney, Australia, 27 September-2 October, 1987.

72. HEND, R.W. & BUTTERWORTH, S.T.G. (1975) *Toxicity studies of the insecticide WL 43775: A three-month feeding study in rats* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

73. HEND, R.W. & BUTTERWORTH, S.T.G. (1976) *Toxicity studies of the insecticide WL 43775: A short-term feeding study in rats* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

74. HILL, B.D. (1981) Persistence and distribution of fenvalerate residues in soil under field and laboratory conditions. *J. agric. food Chem.*, **29**: 107-110.

75. HINE, C. (1975) *SD-43775 Toxicity: Acute and repeated (14-day) dermal toxicity in the rabbit*, San Francisco, Hine Inc. (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

76. HIROMORI, T., NAKANISHI, T., KAWAGUCHI, S., SAKO, H., SUZUKI, T., & MIYAMOTO, J. (1986) Therapeutic effects of methocarbamol on acute intoxication by pyrethroids in rats. *J. Pestic. Sci.*, **11**: 9-14.

77. HOLMSTEAD, R.L. & FULLMER, D.G. (1977) Photodecarboxylation of cyanohydrine esters. Models for pyrethroid photodecomposition. *J. agric. food Chem.*, **25**: 56-58.

78. HOLMSTEAD, R.L., FULLMER, D.G., & RUZO, L.O. (1978) Pyrethroid photodecomposition: Pydrin. *J. agric. food Chem.*, **26**: 954-959.

79. 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.

80. HOYT, S.C., WESTIGARD, P.H., & BURTS, E.C. (1978) Effects of two synthetic pyrethroids on the codling moth, pear psylla, and various mite species in northwest apple and pear orchards. *J. econ. Entomol.*, **71**: 431-434.

81. ITO, N. (1976a) *Histopathological findings of mice treated with S5602 for three months* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

82. ITO, N. (1976b) *Histopathological findings of mice and rats exposed to mist of S5602 for four weeks* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

83. ITO, N. (1978) *Histopathological findings in mice treated with S5602*, Nagoya, Nagoya City University Medical School (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

84. JOHANSEN, C., MAYER, D., MADSEN, R., & ROBINSON, W. (1975) *Bee research investigations, 1975*, Pullman, Washington, Washington State University, Department of Entomology (Unpublished report).

85. JOHANSEN, C., KIOUS, C., SCHULTZ, G., GUPTA, R., & STANFORD, A. (1978) *Bee research investigations, 1978*, Pullman, Washington, Washington State University, Department of Entomology (Unpublished report).

86. KANEKO, H., OHKAWA, H., & MIYAMOTO, J. (1981) Comparative metabolism of fenvalerate and the [2S, S]-isomer in rats and mice. *J. Pestic. Sci.*, **6**: 317-326.

87. 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.

88. KANEKO, H., TAKAMATSU, Y., OKUNO, Y., ABIKO, J., YOSHITAKE, A., & MIYAMOTO, J. (1988) Substrate specificity for formation of cholesterol ester conjugates from fenvalerate analogues and for granuloma formation. *Xenobiotica*, **18**(1): 11-19.

89. KATAGI, T., MIKAMI, N., MATSUDA., T., & MIYAMOTO, J. (1985a) *Photodegradation of fenvalerate and esfenvalerate on soils* (Unpublished Report No. LLM-50-0005 submitted to WHO by Sumitomo Chemical Co., Ltd).

90. KATAGI, T., MIKAMI, N., MATSUDA, T., & MIYAMOTO, J. (1985b) *Hydrolysis of fenvalerate and esfenvalerate in buffered aqueous solutions* (Unpublished Report No. LLM-50-0006 submitted to WHO by Sumitomo Chemical Co., Ltd).

91. KIRKLAND, V.L. & ALBERT, J.R. (1977) *Preliminary pharmacodynamic investigation of SD 43775 (6-10-0) administered intravenously to the anesthetized dog. I. Effects on the cardiovascular system and respiration. II. Electrocardiographic (ECG) findings* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

92. KNOX, J.M., II, TUCKER, S.B., & FLANNIGAN, S.A. (1984) Paraesthesia from cutaneous exposure to a synthetic pyrethroid insecticide. *Arch. Dermatol.*, **120**: 744-746.

93. KOHDA, H., KADOTA, T., & MIYAMOTO, J. (1976a) *Teratogenic study on S5602 in mice* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

94. KOHDA, H., KADOTA, T., & MIYAMOTO, J. (1976b) *Acute inhalation toxicity of S3206 and S5602 in mice and rats* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

95. KOHDA, H., KADOTA, T., & MIYAMOTO, J. (1976c) *Subacute inhalation toxicity study of S5602 in mice and rats* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

96. KOHDA, H., KANEKO, H., OHKAWA, H., KADOTA, T., & MIYAMOTO, J. (1979) *Acute intraperitoneal toxicity of fenvalerate metabolites in mice* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

97. KOLMODIN-HEDMAN, B., SWENSSON, A., & AKERBLOM, M. (1982) Occupational exposure to some synthetic pyrethroids (permethrin and fenvalerate). *Arch. Toxicol.*, **50**: 27-33.

98. LAWRENCE, L.J. & CASIDA, J.E. (1982) Pyrethroid toxicology: mouse intracerebral structure-toxicity relationship. *Pestic. Biochem. Physiol.*, **18**: 9-14.

99. LAWRENCE, L.J. & CASIDA, J.E. (1983) Stereospecific action of pyrethroid insecticides on the gamma-aminobutyric acid receptor-ionophore complex. *Science*, 221: 1399-1401.

100. LAWRENCE, L.J., GEE, K.W., & YAMAMURA, H.I. (1985) Interactions of pyrethroid insecticides with chloride ionophore-associated binding sites. *Neurotoxicology*, **6**: 87-98.

101. LEAHEY, J.P. (1985) *The pyrethroid insecticides*, London, Taylor & Francis Ltd, p. 440.

102. LEE, P.W. (1985) Fate of fenvalerate (Pydrin insecticide) in the soil environment. *J. agric. food Chem.*, **33**: 993-998.

103. LEE, P.W., WESTCOTT, N.D., & REICHLE, R.A. (1978) Gas-liquid chromatographic determination of Pydrin, a synthetic pyrethroid, in cabbage and lettuce. *J. Assoc. Off. Anal. Chem.*, **61**: 869-871.

104. LEE, P.W., STEARNS, S.M., & POWELL, W.R. (1985) Rat metabolism of fenvalerate (Pydrin insecticide). *J. agric. food Chem.*, **33**: 988-993.

105. LEE, P.W., POWELL, W.R., STEARNS, S.M. & MCCONNEL, O.J. (1987) Comparative aerobic soil metabolism of fenvalerate isomers. *J. agric. food Chem.*, **35**: 384-387.

106. 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.

107. LINDEN, E., BENGTSSON, B.E., SVANBERG, O., & SUNDSTROM, G. (1979) The acute toxicity of 78 chemicals and pesticide formulations against two brackish water organisms, the bleak *(Alburnus alburnus)* and the harpacticoid *Nitocra spinipes*. *Chemosphere*, **11/12**: 843-851.

108. LUND, A.E. & NARAHASHI, T. (1983) Kinetics of sodium channel modification as the basis for the variation in the nerve membrane effects of pyrethroids and DDT analogs. *Pestic. Biochem. Physiol.*, **20**: 203-216.

109. MCKENNEY, C.L., Jr & HAMAKER, D.B. (1984) Effects of fenvalerate on larval development of *Palaemonetes pugio* (Holthuis) and on larval metabolism during osmotic stress. *Aquat. Toxicol.*, **5**: 343-355.

110. MCLEESE, D.W., METCALFE, C.D., & ZITKO, V. (1980) Lethality of permethrin, cypermethrin and fenvalerate to salmon, lobster and shrimp. *Bull. environ. Contam. Toxicol.*, **25**: 950-955.

111. MALLEY, L.A., CAGEN, S.Z., GARDINER, T.H., & VAN GELDER, G.A. (1984) Characterization of fenvalerate mediated skin sensory stimulation. *Neurotoxicology*, **5**: 71-72.

112. MALLEY, L.A., CAGEN, S.Z., PARKER, C.M., GARDINER, T.H., VAN GELDER, G.A., & ROSE, G.P. (1985) Effect of vitamin E and other amelioratory agents on the fenvalerate-mediated skin sensation. *Toxicol. Lett.*, **29**: 51-58.

113. MATSUBARA, R.A., SUZUKI, T., KADOTA, T., & MIYAMOTO, J. (1977) *Antidotes against poisoning by S5602 in rats* (Unpublished report submitted by Sumitomo Chemical Co., Ltd).

114. MAYER, F.L., Jr (1987) *Acute toxicity handbook of chemicals to estuarine organisms*. Washington, DC, US Environmental Protection Agency, p. 115 (EPA-600/8-87/017).

115. MAYER, F.L., Jr & ELLERSIECK, M.R. (1986) *Manual of acute toxicity: Interpretation and data base for 410 chemicals and 66 species of freshwater animals*, Washington, DC, US Department of the Interior, Fish and Wildlife Service, pp. 235-236.

116. MEGHARAJ, M., VENKATESWARLU, K., & RAO, A.S. (1986) Influence of cypermethrin and fenvalerate on natural soil algal populations. *Ecotoxicol. environ. Saf.*, 12: 141-145.

117. MEISTER, R.T., BERG, G.L., SINE, C., MEISTER, S., & POPLYK, J. (1983) *Farm chemicals handbook. Section C. Pesticide dictionary*, Willoughby, Ohio, Meister Publishing Co., pp. C104-C105.

118. MIKAMI, N., TAKAHASHI, N., HAYASHI, K., & MIYAMOTO, J. (1980) Photodegradation of fenvalerate (Sumicidin) in water and on soil surface. *J. Pestic. Sci.*, 5: 225-236.

119. MIKAMI, N., SAKATA, S., YAMADA, H., & MIYAMOTO, J. (1984a) Further studies on degradation of the pyrethroid insecticide fenvalerate in soils. *J. Pestic. Sci.*, 9: 697-702.

120. MIKAMI, N., WAKABAYASHI, N., YAMADA, H., & MIYAMOTO, J. (1984b) New conjugated metabolites of 3-phenoxybenzoic acid in plants. *Pestic. Sci.*, 15: 531-542.

121. MIKAMI, N., WAKABAYASHI, N., YAMADA, H., & MIYAMOTO, J. (1985a) The metabolism of fenvalerate in plants: The conjugation of the acid moiety. *Pestic Sci.*, 16: 46-58.

122. MIKAMI, N., YOSHIMURA, J., KANEKO, H., YAMADA, H., & MIYAMOTO, J. (1985b) Metabolism in rats of 3-phenoxybenzyl alcohol and 3-phenoxybenzoic acid glucoside conjugates formed in plants. *Pestic. Sci.*, 16: 33-45.

123. MILNER, C.K. & BUTTERWORTH, S.T.G. (1977) *Toxicity of pyrethroid insecticide. Investigation of neurotoxic potential of WL 43775* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

124. MIURA, T. & TAKAHASHI, R.M. (1976) Effects of a synthetic pyrethroid, SD43775, on nontarget organisms when utilized as a mosquito larvicide. *Mosq. News*, 36: 322-326.

125. MIYAMOTO, J. (1976) Degradation, metabolism and toxicity of synthetic pyrethroids. *Environ. Health Perspect.*, 14: 15-28.

126. MIYAMOTO, J. (1981) The chemistry, metabolism and residue analysis of synthetic pyrethroids. *Pure appl. Chem.*, 53: 1967-2022.

127. MIYAMOTO, J. & KEARNEY, P.C. (1983) *Pesticide chemistry-human welfare and the environment. Proceedings of the Fifth International Congress of Pesticide Chemistry, Kyoto, Japan, 29 August-4 September, 1982*, Oxford, Pergamon Press, Vol. 1-4.

128. 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**(2): 79-94.

129. MULLA, M.S., NAVVAB-GOJRATI, H.A., & DARWAZEH, H.A. (1978a) Toxicity of mosquito larvicidal pyrethroids to four species of freshwater fishes. *Environ. Entomol.*, **7**: 428-430.

130. MULLA, M.S., NAVVAB-GOJRATI, H.A., & DARWAZEH, H.A. (1978b) Biological activity and longevity of new synthetic pyrethroids against mosquitoes and some nontarget insects. *Mosq. News*, **38**: 90-96.

131. MULLA, M.S., DARWAZEH, H.A., & DHILLON, M.S. (1980) New pyrethroids as mosquito larvicides and their effects on nontarget organisms. *Mosq. News*, **40**: 6-12.

132. NOBLE, P.J. (1976) *AF1117 residue data in animal tissues, milk and cream* (Unpublished data submitted to WHO by Shell Chemical (Australia), Ltd).

133. OHKAWA, H., NAMBU, K., INUI, H., & MIYAMOTO, J. (1978) Metabolic fate of fenvalerate (Sumicidin) in soil and by microorganisms. *J. Pestic. Sci.*, **3**: 129-141.

134. OHKAWA, H., KANEKO, H., TSUJI, H., & MIYAMOTO, J. (1979) Metabolism of fenvalerate (Sumicidin) in rats. *J. Pestic. Sci.*, **4**: 143-155.

135. OHKAWA, H., KIKUCHI, R., & MIYAMOTO, J. (1980a) Bioaccumulation and biodegradation of the [S]-acid isomer of fenvalerate (Sumicidin) in an aquatic model ecosystem. *J. Pestic. Sci.*, **5**: 11-12.

136. OHKAWA, H., NAMBU, K., & MIYAMOTO, J. (1980b) Metabolic fate of fenvalerate (Sumicidin) in bean plants. *J. Pestic. Sci.*, **5**: 215-223.

137. OHNO, N., FUJIMOTO, K., OKUNO, Y., MIZUTANI, T., HIRANO, M., ITAYA, N., HONDA, T., & YOSHIOKA, H. (1976) 2-Arylalkanoates, a new group of synthetic pyrethroid esters not containing cyclopropanecarboxylates. *Pestic. Sci.*, **7**: 241-246.

138. OKUNO, Y., KADOTA, T., & MIYAMOTO, J. (1975a) *Eye and skin irritation of S-3206 and S-5602 in rabbits* (Technical Report No. AT-50-0214) (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

139. OKUNO, Y., KADOTA, T., & MIYAMOTO, J. (1975b) *Skin sensitization study of S-5602 in guinea pigs* (Technical Report No. AT-50-0214) (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

140. OKUNO, Y., KADOTA, T., & MIYAMOTO, J. (1976) *Neurotoxic effects of some synthetic pyrethroids and natural pyrethrins by dermal applications in rats* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

141. OKUNO, Y., KADOTA, T., & MIYAMOTO, J. (1977a) *Neurotoxic effects of some synthetic pyrethroids and natural pyrethrins by oral administration in rats* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

142. OKUNO, Y., KADOTA, T., & MIYAMOTO, J. (1977b) *Neurotoxic effects of S5602 and natural pyrethrins by oral administration in rats* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

143. OKUNO, Y., KADOTA, T., & MIYAMOTO, J. (1977c) *Recovery of histopathological lesions in rats caused by short-term feeding of S5602* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

144. 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 lipophilic conjugate from fenvalerate. *Toxicol. appl. Pharmacol.*, **83**: 157-169.

145. 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.

146. PARKER, C.M., MCCULLOUGH, C.B., GELLATLY, J.B.M., & JOHNSTON, C.D. (1983) Toxicologic and carcinogenic evaluation of fenvalerate in the B6C3F1 mouse. *Fundam. appl. Toxicol.*, 3: 114-120.

147. PARKER, C.M., PATTERSON, D.R., VAN GELDER, G.A., GORDON, E.B., VALERIO, M.G., & HALL, W.C. (1984a) Chronic toxicity and carcinogenicity evaluation of fenvalerate in rats. *J. Toxicol. environ. Health*, **13**: 83-97.

148. PARKER, C.M., PICCIRILLO, V.J., KURTZ, S.L., GARNER, F.M., GARDINER, T.H., & VAN GELDER, G.A. (1984b) Six-month feeding study of fenvalerate in dogs. *Fundam. appl. Toxicol.*, 4: 577-586.

149. 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.

150. PARKER, C.M., WIMBERLY, 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.

151. PLAPP, F.W., Jr & BULL, D.L. (1978) Toxicity and selectivity of some insecticides to *Chrysopa carnea*, a predator of the tobacco budworm. *Environ. Entomol.*, 7: 431-434.

152. PLAPP, F.W., Jr & VINSON, S.B. (1977) Comparative toxicities of some insecticides to the tobacco budworm and its ichneumonid parasite, *Campoletis sonorensis*. *Environ. Entomol.*, 6: 381-384.

153. 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.

154. POTTER, J.C. (1976) *(a) Tissues of rats fed SD43775-C-14; (b) and (c) milk and tissues of cows; (d) eggs and tissues from laying hens; (e) cream from the milk of cows fed SD 43775* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

155. RANGACHAR, T.R.S., SURESH, T.P., & THINMMAIAH, K. (1981) Acute oral toxicity of Sumicidin 20E in poultry. *Indian vet. J.*, **58**: 941-942.

156. RATTNER, B.A. & FRANSON, J.C. (1983) Methyl parathion and fenvalerate toxicity in American kestrels: acute physiological responses and effects of cold. *Can. J. Physiol. Pharmacol.*, **62**: 787-792.

157. REED, W.T., EHMAN, A., LEE, P., BARBER, G., & BISHOP, J. (1983) Pydrin insecticide (fenvalerate) on non-target systems following field applications. In: Miyamoto, J. & Kearney, P.C., ed. *Pesticide chemistry: Human welfare and the environment*, Oxford, Pergamon Press, Vol. 2, pp. 213-221.

158. ROCK, G.C. (1979) Relative toxicity of two synthetic pyrethroids to a predator *Amblyseius fallacis* and its prey *Tetranychus urticae*. *J. econ. Entomol.*, **72**: 293-294.

159. RUIGT, G.S.F. & VAN DEN BERCKEN, J. (1986) Action of pyrethroids on a nerve - muscle preparation of the clawed frog, *Xenopus laevis*. *Pestic. Biochem. Physiol.*, **25**: 176-187.

160. SAKATA, S., MIKAMI, N., MATSUDA, T., & MIYAMOTO, J. (1985) *Degradation of esfenvalerate and its isomers in soils* (Unpublished Report No. LLM-30-0003 submitted to WHO by Sumitomo Chemical Co., Ltd).

161. SALEH, M.A., IBRAHIM, N.A., SOLIMAN, N.Z., & EL SHEIMY, M.K. (1986) Persistence and distribution of cypermethrin, deltamethrin and fenvalerate in laying chickens. *J. agric. food Chem.*, **34**: 895-898.

162. SASINOVICH, L.M. & PANSHINA, T.N. (1987) [Substantiation of hygiene rules for synthetic pyrethroid content in the work zone air.] *Gig. tr. prof. Zabol.*, **8**: 48-50 (in Russian).

163. SCHIMMEL, S.C., GARNAS, R.L., PATRICK, J.M., & MOORE, J.C. (1983) Acute toxicity, bioconcentration, and persistence of AC 222,705, benthiocarb, chlorpyrifos, fenvalerate, methyl parathion, and permethrin in the estuarine environment, *J. agric. food Chem.*, **31**: 104-113.

164. SHOUR, M.H. & CROWDER, L.A. (1980) Effects of pyrethroid insecticides on the common green lacewing. *J. econ. Entomol.*, **73**: 306-309.

165. SODERLUND, D.M. & CASIDA, J.E. (1977) Effect of pyrethroid structure on rates of hydrolysis and oxidation by mouse liver microsomal enzymes. *Pestic. Biochem. Physiol.*, **7**: 391-401.

166. SPEHAR, R.L., TANNER, D.K., & GIBSON, J.H. (1982) *Effects of Kelthane and Pydrin on early life stages of Fathead Minnows (Pimephales promelas) and Amphipods (Hyalella azteca),* Philadelphia, American Society for Testing and Materials (Special Technical Publication No. 766).

167. STEIN, A.A. (1977) *Histopathology evaluation of animals from 3-generation reproduction study.* Albany, New York, Biological Research, Ltd (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

168. SUMMIT, L.M. & ALBERT, J.R. (1977a) *Oral lethality of WL 43775 (6-1-0-0) in the rat* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

169. SUMMIT, L.M. & ALBERT, J.R. (1977b) *Determination of the acute oral lethality of WL 43775 (6-1-0-0) in the male and female mouse* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

170. SUZUKI, H. & MIYAMOTO, J. (1976) *Studies on mutagenicity of S 5602 with bacteria systems* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

171. SUZUKI, H. & MIYAMOTO, J. (1977) *Studies on mutagenicity of some pyrethroids on salmonella strains in the presence of mouse hepatic S9 fractions* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

172. SUZUKI, H., KISHIDA, F., & MIYAMOTO, J. (1979) *Studies on mutagenicity of S5602 in Ames test in the presence of hepatic S9 fractions* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

173. SUZUKI, T., KADATA, T., & MIYAMOTO, J. (1976) *One-year chronic toxicity study of S5602 in mice (three month interim report)* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

174. SUZUKI, T., OKUNO, Y., HIROMORI, T., ITO, S., KADOTA, T., & MIYAMOTO, J. (1977a) *Fifteen-month chronic toxicity study of S5602 in rats* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

175. SUZUKI, T., OKUNO, Y., HIROMORI, T., KADOTA, T., & MIYAMOTO, J. (1977b) *Eighteen-month chronic toxicity study of S5602 in mice* (Unpublished report submitted to WHO by Sumitomo Chemical Co., Ltd).

176. SYRETT, P. & PENMAN, D.R. (1980) Studies of insecticide toxicity to lucerne aphids and their predators. *N.Z. J. agric. Res.*, 23: 575-580.

177. TAGATZ, M.E. & IVEY, J.M. (1981) Effects of fenvalerate on field- and laboratory-developed estuarine benthic communities. *Bull. environ. Contam. Toxicol.*, 27: 256-267.

178. TAGATZ, M.E., STANLEY, R.S., PLAIA, G.R., & DEANS, C.H. (1987) Responses of estuarine macrofauna colonizing sediments contaminated with fenvalerate. *Environ. Toxicol. Chem.*, 6: 21-25.

179. TAKAHASHI, N., MIKAMI, N., MATSUDA, T., & MIYAMOTO, J. (1985) *Photodegradation of the [2S, αS] isomer of fenvalerate in distilled water* (Unpublished Report No. LLM-50-0001 submitted to WHO by Sumitomo Chemical Co., Ltd).

180. 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.

181. TALEKER, N.S., CHEN, J.S., & KAO, H.T. (1983) Persistence of fenvalerate in subtropical soil. *J. econ. Entomol.*, **76**: 223-226.

182. TUCKER, S.B. & FLANNIGAN, S.A. (1983) Cutaneous effects from occupational exposure to fenvalerate. *Arch. Toxicol.*, **54**: 195-202.

183. VAN DEN BERCKEN, J. (1977) The action of allethrin on the peripheral nervous system of the frog. *Pestic. Sci.*, **8**: 692-699.

184. VAN DEN BERCKEN, J. & VIJVERBERG, H.P.M. (1980) Voltage clamp studies on the effects of allethrin and DDT on the sodium channels in frog myelinated nerve membrane. In: *Insect: Neurobiology and pesticide action*, London, Society of Chemical Industry, pp. 79-85.

185. VAN DEN BERCKEN, J., AKKERMANS, L.M.A., & VAN DER ZALM, J.M., (1973) DDT-like action of allethrin in the sensory nervous system of *Xenopus laevis*. *Eur. J. Phamacol.*, **21**: 95-106.

186. VAN DEN BERCKEN, J., KROESE, A.B.A., & AKKERMANS, L.M.A. (1979) Effect of insecticides on the sensory nervous system. In: Narahashi, T., ed. *Neurotoxicology of insecticides and pheromones*, New York, London, Plenum Press, pp. 183-210.

187. VAN DER PAUW, C.L., DIX, K.M., BLANCHARD, K., & MCCARTHY, W.V. (1975) *Teratological studies in rabbits given WL 43775 orally* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

188. VAKENTI, J.M. (1986) *Persistence of fenvalerate in orchard soils, Okanagan Valley, British Columbia* (Unpublished report of cooperative study of Agriculture Canada and Ciba-Geigy Canada, Ltd).

189. VERSCHOYLE, R.D. & ALDRIDGE, W.N. (1980) Structure-activity relationship of some pyrethroids in rats. *Arch. Toxicol.*, **45**: 325-329.

190. VIJVERBERG, H.P.M. & VAN DEN BERCKEN, J. (1979) Frequency dependent effects of the pyrethroid insecticide decamethrin in frog myelinated nerve fibres. *Eur. J. Phamacol.*, **58**: 501-504.

191. VIJVERBERG, H.P.M. & VAN DEN BERCKEN, J. (1982) Action of pyrethroid insecticides on the vertebrate nervous system. *Neuropathol. appl. Neurobiol.*, **8**: 421-440.

192. VIJVERBERG, H.P.M., RUIGT, G.S.F., & VAN DEN BERCKEN, J. (1982a) Structure-related effects of pyrethroid insecticides on the lateral-line sense organ and on peripheral nerves of the clawed frog, *Xenopus laevis*. *Pestic. Biochem. Physiol.*, **18**: 315-324.

193. VIJVERBERG, H.P.M., VAN DER ZALM, J.M., & VAN DEN BERCKEN, J. (1982b) Similar mode of action of pyrethroids and DDT on sodium channel gating in mylinated nerves. *Nature (Lond.)*, **295**: 601-603.

194. VIJVERBERG, H.P.M., VAN DER ZALM, J.M., VAN KLEEF, R.G.D.M., & VAN DEN BERCKEN, J. (1983) Temperature and structure-dependent interaction of pyrethroids with the sodium channels in frog node of Ranvier. *Biochim. Biophys. Acta*, **728**: 73-82.

195. WALKER, B.J., HEND, R.W., & LINNETT, S. (1975) *Toxicity studies on the insecticide WL 43775: Summary of results of preliminary experiments* (Unpublished report submitted to WHO by Shell Development Co., Ltd).

196. WHO (1979) WHO Technical Report Series No. 634 *(Safe use of pesticides. Third Report of the WHO Expert Committee on Vector Biology and Control)*, pp.18-23.

197. WHO (1988) *The WHO recommended classification of pesticides by hazard. Guidelines to classification 1988-89*, Geneva, World Health Organization (Unpublished report VBC/88.953).

198. WILLIAMS, I.H. & BROWN, M.J. (1979) Persistence of permethrin and WL 43775 in soil. *J. agric. food Chem.*, **27**: 130-132.

199. WONG, S.W. & CHAPMAN, R.B. (1979) Toxicity of synthetic pyrethroid insecticides to predaceous phytoseiid mites and their prey. *Aust. J. agric. Res.*, **30**: 497-501.

200. WOOD MACKENZIE (1980) Pyrethroids. *Agrochem. Monit.*, **9**: 3-14.

201. WOOD MACKENZIE (1981) Pyrethroids. *Agrochem. Monit.*, **15**: 3-27.

202. WOOD MACKENZIE (1982) Pyrethroids. *Agrochem. Monit.*, **21**: 3-17.

203. WOOD MACKENZIE (1983) Pyrethroids. *Agrochem. Monit.*, **27**: 3-12.

204. WOOD MACKENZIE (1984) Pyrethroids. *Agrochem. Monit.*, **33**: 2-12.

205. WORKMAN, R.B. (1977) Pesticides toxic to striped earwig, an important insect predator. *Proc. Florida. State Hortic. Soc.*, **90**: 401-402.

206. WORTHING, C.R. (1979) *The pesticide manual*, 6th ed., Croydon, British Crop Protection Council, p. 270.

207. WORTHING, C.R. & WALKER, S.B. (1987) Fenvalerate In: *The pesticide manual*, 8th ed., Croydon, British Crop Protection Council, pp. 395-396.

208. WOUTERS, W. & VAN DEN BERCKEN, J. (1978) Action of pyrethroids. *Gen. Pharmacol.*, **9**: 387-398.

209. WSZOLEK, P.C., LEIN, D.H., & LISK, D.J. (1980) Excretion of fenvalerate insecticide in the milk of dairy cows. *Bull. environ. Contam. Toxicol.*, **24**: 296-298.

210. WSZOLEK, P.C., HOGUE, D.E., & LISK, D.J. (1981a) Accumulation of fenvalerate insecticide in lamb tissues. *Bull. environ. Contam. Toxicol.*, **27**: 869-871.

211. WSZOLEK, P.C., LAFAUNCE, N.A., WACHS, T., & LISK, D.J. (1981b) Studies of possible bovine urinary excretion and rumen decomposition of fenvalerate insecticide and a metabolite. *Bull. environ. Contam. Toxicol.*, **26**: 262-266.

212. BORTHWICK, P.W. & WALSH, G.E. (1981) *Initial toxicological assessment of Ambush, Bolero, Bux, Dursban, Fentrifanil, Larvin, and Pydrin: static acute toxicity tests with selected estuarine algae, invertebrates, and fish.* Gulf Breeze, Florida, US Environmental Protection Agency (EPA-600/4-81-076).

213. 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.

APPENDIX 1

On the basis of electrophysiological studies with peripheral nerve preparations of frogs *(Xenopus laevis; Rana temporaria*, and *Rana esculenta)*, it is possible to distinguish between 2 classes of pyrethroid insecticides: (Type I and Type II). A similar distinction between these 2 classes of pyrethroids has been made on the basis of the symptoms of toxicity in mammals and insects [65, 98, 186, 189, 196]. The same distinction was found in studies on cockroaches [60].

Based on the binding assay on the gamma-aminobutyric acid (GABA) receptor-ionophore complex, synthetic pyrethroids can also be classified into two types: the α-cyano-3-phenoxybenzyl pyrethroids and the non-cyano pyrethroids [59, 61, 99, 100].

Pyrethroids that do not contain an α-cyano group (allethrin, d-phenothrin, permethrin, tetramethrin, cismethrin, and bioresmethrin) (Type I: T-syndrome)

The pyrethroids that do not contain an α-cyano group give rise to pronounced repetitive activity in sense organs and in sensory nerve fibres [185]. At room temperature, this repetitive activity usually consists of trains of 3-10 impulses and occasionally up to 25 impulses. Train duration is between 10 and 5 milliseconds.

These compounds also induce pronounced repetitive firing of the presynaptic motor nerve terminal in the neuromuscular junction [183]. There was no significant effect of the insecticide on neurotransmitter release or on the sensitivity of the subsynaptic membrane, nor on the muscle fibre membrane. Presynaptic repetitive firing was also observed in the sympathetic ganglion treated with these pyrethroids.

In the lateral-line sense organ and in the motor nerve terminal, but not in the cutaneous touch receptor or in sensory nerve fibres, the pyrethroid-induced repetitive activity increases dramatically as the temperature is lowered, and a decrease of 5 °C in temperature may cause a

more than 3-fold increase in the number of repetitive impulses per train. This effect is easily reversed by raising the temperature. The origin of this "negative temperature coefficient" is not clear [194].

Synthetic pyrethroids act directly on the axon through interference with the sodium channel gating mechanism that underlies the generation and conduction of each nerve impulse. The transitional state of the sodium channel is controlled by 2 separately acting gating mechanisms, referred to as the activation gate and the inactivation gate. Since pyrethroids only appear to affect the sodium current during depolarization, the rapid opening of the activation gate and the slow closing of the inactivation gate proceed normally. However, once the sodium channel is open, the activation gate is restrained in the open position by the pyrethroid molecule. While all pyrethroids have essentially the same basic mechanism of action, however, the rate of relaxation differs substantially for the various pyrethroids [55].

In the isolated node of Ranvier, allethrin causes prolongation of the transient increase in sodium permeability of the nerve membrane during excitation [184]. Evidence so far available indicates that allethrin selectively slows down the closing of the activation gate of a fraction of the sodium channels that open during depolarization of the membrane. The time constant of closing of the activation gate in the allethrin-affected channels is about 100 milliseconds compared with less than 100 microseconds in the normal sodium channel, i.e., it is slowed down by a factor of more than 100. This results in a marked prolongation of the sodium current across the nerve membrane during excitation, and this prolonged sodium current is directly responsible for the repetitive activity induced by allethrin [194].

The effects of cismethrin on synaptic transmission in the frog neuromuscular junction, as reported by Evans [38], are almost identical to those of allethrin, i.e., presynaptic repetitive firing, and no significant effects on transmitter release or on the subsynaptic membrane.

Interestingly, the action of these pyrethroids closely resembles that of the insecticide DDT in the peripheral nervous system of the frog. DDT also causes pronounced

repetitive activity in sense organs, in sensory nerve fibres, and in motor nerve terminals, due to a prolongation of the transient increase in sodium permeability of the nerve membrane during excitation. Recently, it was demonstrated that allethrin and DDT have essentially the same effect on sodium channels in frog myelinated nerve membrane. Both compounds slow down the rate of closing of a fraction of the sodium channels that open on depolarization of the membrane [185, 186, 193].

In the electrophysiological experiments using giant axons of crayfish, the type I pyrethroids and DDT analogues retain sodium channels in a modified open state only intermittently, cause large depolarizing after-potentials, and evoke repetitive firing with minimal effect on the resting potential [108].

These results strongly suggest that permethrin and cismethrin, like allethrin, primarily affect the sodium channels in the nerve membrane and cause a prolongation of the transient increase in sodium permeability of the membrane during excitation.

The effects of pyrethroids on end-plate and muscle action potentials were studied in the pectoralis nerve-muscle preparation of the clawed frog *(Xenopus laevis)*. Type I pyrethroids (allethrin, cismethrin, bioresmethrin, and 1R, *cis*-phenothrin) caused moderate presynaptic repetitive activity, resulting in the occurrence of multiple end-plate potentials [159].

Pyrethroids with an α-cyano group on the 3-phenoxybenzyl alcohol (deltamethrin, cypermethrin, fenvalerate, and fenpropanate) (Type II: CS-syndrome)

The pyrethroids with an α-cyano group cause an intense repetitive activity in the lateral line organ in the form of long-lasting trains of impulses [192]. Such a train may last for up to 1 min and contains thousands of impulses. The duration of the trains and the number of impulses per train increase markedly on lowering the temperature. Cypermethrin does not cause repetitive activity in myelinated nerve fibres. Instead, this pyrethroid causes a frequency-dependent depression of the nervous impulse, brought about by a progressive depolarization of

the nerve membrane as a result of the summation of depolarizing after-potentials during train stimulation [190, 194].

In the isolated node of Ranvier, cypermethrin, like allethrin, specifically affects the sodium channels of the nerve membrane and causes a long-lasting prolongation of the transient increase in sodium permeability during excitation, presumably by slowing down the closing of the activation gate of the sodium channel [190, 194]. The time constant of closing of the activation gate in the cypermethrin-affected channels is prolonged to more than 100 milliseconds. Apparently, the amplitude of the prolonged sodium current after cypermethrin is too small to induce repetitive activity in nerve fibres, but is sufficient to cause the long-lasting repetitive firing in the lateral-line sense organ.

These results suggest that α-cyano pyrethroids primarily affect the sodium channels in the nerve membrane and cause a long-lasting prolongation of the transient increase in sodium permeability of the membrane during excitation.

In the electrophysiological experiments using giant axons of crayfish, the Type II pyrethroids retain sodium channels in a modified continuous open state persistently, depolarize the membrane, and block the action potential without causing repetitive firing [108].

Diazepam, which facilitates GABA reaction, delayed the onset of action of deltamethrin and fenvalerate, but not permethrin and allethrin, in both the mouse and cockroach. Possible mechanisms of the Type II pyrethroid syndrome include action at the GABA receptor complex or a closely linked class of neuroreceptor [61].

The Type II syndrome of intracerebrally administered pyrethroids closely approximates that of the convulsant picrotoxin (PTX). Deltamethrin inhibits the binding of [^{3}H]-dihydropicrotoxin to rat brain synaptic membranes, whereas the non-toxic R epimer of deltamethrin is inactive. These findings suggest a possible relation between the Type II pyrethroid action and the GABA receptor complex. The stereospecific correlation between the toxicity of Type II pyrethroids and their potency to inhibit

the [^{35}S]-TBPS binding was established using a radioligand, [^{35}S]-*t*-butyl-bicyclophosphoro-thionate [^{35}S]-TBPS. Studies with 37 pyrethroids revealed an absolute correlation, without any false positive or negative, between mouse intracerebral toxicity and *in vitro* inhibition: all toxic cyano compounds including deltamethrin, 1R,*cis*-cypermethrin, 1R,*trans*-cypermethrin, and [2S, αS]-fenvalerate were inhibitors, but their non-toxic stereoisomers were not; non-cyano pyrethroids were much less potent or were inactive [99].

In the [^{35}S]-TBPS and [^{3}H]-Ro 5-4864 (a convulsant benzodiazepine radioligand) binding assay, the inhibitory potencies of pyrethroids were closely related to their mammalian toxicities. The most toxic pyrethroids of Type II were the most potent inhibitors of [^{3}H]-Ro 5-4864 specific binding to rat brain membranes. The [^{3}H]-dihydropicrotoxin and [^{35}S]-TBPS binding studies with pyrethroids strongly indicated that Type II effects of pyrethroids are mediated, at least in part, through an interaction with a GABA-regulated chloride ionophore-associated binding site. Moreover, studies with [^{3}H]-Ro 5-4864 support this hypothesis and, in addition, indicate that the pyrethroid-binding site may be very closely related to the convulsant benzodiazepine site of action [100].

The Type II pyrethroids (deltamethrin, 1R, *cis*-cypermethrin and [2S, αS]-fenvalerate) increased the input resistance of crayfish claw opener muscle fibres bathed in GABA. In contrast, two non-insecticidal stereoisomers and Type I pyrethroids (permethrin, resmethrin, allethrin) were inactive. Therefore, cyanophenoxybenzyl pyrethroids appear to act on the GABA receptor-ionophore complex [59].

The effects of pyrethroids on end-plate and muscle action potentials were studied in the pectoralis nerve-muscle preparation of the clawed frog *(Xenopus laevis).* Type II pyrethroids (cypermethrin and deltamethrin) induced trains of repetitive muscle action potentials without presynaptic repetitive activity. However, an intermediate group of pyrethroids (1R-permethrin, cyphenothrin, and fenvalerate) caused both types of effect. Thus, in muscle or nerve membrane the pyrethroid induced repetitive activities due to a prolongation of the sodium current.

But no clear distinction was observed between non-cyano and α-cyano pyrethroids [159].

Appraisal

In summary, the results strongly suggest that the primary target site of pyrethroid insecticides in the vertebrate nervous system is the sodium channel in the nerve membrane. Pyrethroids without an α-cyano group (allethrin, d-phenothrin, permethrin, and cismethrin) cause a moderate prolongation of the transient increase in sodium permeability of the nerve membrane during excitation. This results in relatively short trains of repetitive nerve impulses in sense organs, sensory (afferent) nerve fibres, and, in effect, nerve terminals. On the other hand, the α-cyano pyrethroids cause a long-lasting prolongation of the transient increase in sodium permeability of the nerve membrane during excitation. This results in long-lasting trains of repetitive impulses in sense organs and a frequency-dependent depression of the nerve impulse in nerve fibres. The difference in effects between permethrin and cypermethrin, which have identical molecular structures except for the presence of an α-cyano group on the phenoxybenzyl alcohol, indicates that it is this α-cyano group that is responsible for the long-lasting prolongation of the sodium permeability.

Since the mechanisms responsible for nerve impulse generation and conduction are basically the same throughout the entire nervous system, pyrethroids may also induce repetitive activity in various parts of the brain. The difference in symptoms of poisoning by α-cyano pyrethroids, compared with the classical pyrethroids, is not necessarily due to an exclusive central site of action. It may be related to the long-lasting repetitive activity in sense organs and possibly in other parts of the nervous system, which, in a more advance state of poisoning, may be accompanied by a frequency-dependent depression of the nervous impulse.

Pyrethroids also cause pronounced repetitive activity and a prolongation of the transient increase in sodium permeability of the nerve membrane in insects and other invertebrates. Available information indicates that the sodium channel in the nerve membrane is also the most

important target site of pyrethroids in the invertebrate nervous system [196, 208].

Because of the universal character of the processes underlying nerve excitability, the action of pyrethroids should not be considered restricted to particular animal species, or to a certain region of the nervous system. Although it has been established that sense organs and nerve endings are the most vulnerable to the action of pyrethroids, the ultimate lesion that causes death will depend on the animal species, environmental conditions, and on the chemical structure and physical characteristics of the pyrethroid molecule [191].

RESUME, EVALUATION, CONCLUSIONS ET RECOMMANDATIONS

1. Résumé et évaluation

1.1 *Identité, propriétés physiques et chimiques, méthodes d'analyse*

La fenvalérate est un insecticide puissant utilisé depuis 1976. C'est un ester de l'acide (chloro-4 phényle)-2 méthyl-3 butyrique et de l'alcool α-cyano-phénoxy-benzylique. Malgré l'absence du cycle cyclopropane, ses propriétés insecticides le rattachent au groupe des pyréthroïdes. Il s'agit d'un mélange racémique de quatre isomères optiques dont les configurations sont [2S, αS], [2S, αR], [2R, αS] et [2R, αR]. L'isomère [2S, αS] est le plus actif biologiquement; vient ensuite l'isomère [2S, αR].

Le fenvalérate de qualité technique se présente sous la forme d'un liquide visqueux jaune ou brun dont la densité est de 1,175 à 25 °C. Il est relativement non volatil, sa tension de vapeur étant de 0,037 mPa à 25 °C. Pratiquement insoluble dans l'eau (environ 2 µg/litre), il est soluble dans les solvants organiques comme l'acétone, le xylène et le kérosène. Il est stable à la lumière, à la chaleur et à l'humidité, mais instable en milieu alcalin par suite de l'hydrolyse du groupement ester.

Le dosage des résidus et les analyses écotoxicologiques peuvent s'effectuer par chromatographie en phase gazeuse avec détection par capture d'électrons, la concentration minimale décelable étant de 0,005 mg/kg. Pour l'analyse des produits techniques on utilise la même méthode mais avec un détecteur à ionisation de flamme.

1.2 *Production et usage*

On utilise dans le monde environ 1000 tonnes de fenvalérate par an (chiffres de 1979-1983), essentiellement en agriculture mais également pour la désinsectisation des habitations et des jardins et le déparasitage

des bestiaux, soit seul, soit en association avec d'autres insecticides. Il est présenté sous forme de concentré émulsionnable, de concentré pour épandage à très bas volume, de poudre pour poudrage et de poudre mouillable.

1.3 Exposition humaine

C'est essentiellement du fait de la présence de résidus dans les aliments que la population dans son ensemble est exposée à cet insecticide. Le respect des règles de bonne pratique permet en général de maintenir les résidus dans les récoltes à un faible niveau. L'exposition qui en découle pour la population générale devrait a priori être très faible mais on ne dispose pas de données tirées d'études de la ration totale.

L'analyse des résidus présents dans les céréales ensilées a montré que plus de 70% de la dose appliquée subsistent sur le blé au bout de dix mois à 25 °C. Après mouture et panification, la teneur en résidus du pain blanc et de la farine de froment est à peu près la même (environ 0,06-0,1 mg/kg).

Les informations relatives à l'exposition professionnelle au fenvalérate sont très fragmentaires.

1.4 Destinée dans l'environnement

Dans le sol, il y a dégradation par coupure de la liaison ester et du groupement diphényl-éther, hydroxylation du cycle benzénique, hydratation du nitrile en amide, l'oxydation des fragments se poursuivant jusqu'à l'obtention d'anhydride carbonique qui constitue le principal produit final. L'étude du potentiel de lixiviation du fenvalérate et de ses produits de dégradation a montré qu'il n'y avait guère de pénétration au niveau du sol.

Dans l'eau et à la surface du sol, la fenvalérate subit une photodégradation par la lumière solaire. On a montré qu'il se produisait une coupure du groupement ester, une hydrolyse du groupement cyano, une décarboxylation conduisant au (phénoxy-3)-2 (chloro-4 phényle)-3 méthyl-4 pentane-nitrile (décarboxy-fenvalérate), ainsi que d'autres réactions à initiation radicalaire.

Sur les végétaux, la fenvalérate a une demi-vie d'environ 14 jours. La principale réaction consiste dans la rupture de la liaison ester suivie d'une oxydation et/ou d'une conjugaison des fragments. Il se produit également une décarboxylation en décarboxy-fenvalérate.

En général, la dégradation dans l'environnement conduit à des produits moins toxiques.

Dans l'environnement, le fenvalérate est assez rapidement dégradé. La demi-vie est de 4 à 15 jours dans les rivières, 8 à 14 jours sur les végétaux, 1 à 18 jours par photodégradation à la surface du sol et 15 jours à 3 mois dans le sol.

Il n'y a pratiquement aucune lixiviation du fenvalérate présent dans le sol. Il est donc improbable que ce composé puisse s'accumuler de façon importante dans le milieu aquatique.

1.5 Cinétique et métabolisme

On a étudié la destinée du fenvalérate chez le rat et la souris au moyen de fenvalérate radio-marqué au niveau du groupement carboxylate, ou des groupements benzyle ou cyano. Sauf dans le cas des composés marqués au niveau du groupement cyano, la radioactivité administrée est rapidement excrétée (jusqu'à 99% en six jours). Les principales réactions métaboliques consistent en une rupture du groupement ester et une hydroxylation en position 4. On a également observé diverses réactions d'oxydation et de conjugaison conduisant à un mélange complexe. Lorsque le fenvalérate est radio-marqué au niveau du groupement cyano, la dose radioactive s'élimine moins rapidement (jusqu'à 81% en six jours). La radioactivité restante est principalement confinée dans la peau, les poils et l'estomac sous forme de thiocyanate. Il existe aussi une voie métabolique secondaire, quoique très importante, qui consiste dans la formation d'un conjugué lipophile de (chloro-4 phényle)-2-[2R] isovalérate. Ce conjugué qui intervient dans la formation de granulomes a été décelé dans les surrénales, le foie et les ganglions mésentériques des rats, des souris et de certaines autres espèces.

1.6 *Effets sur les êtres vivant dans leur milieu naturel*

Au laboratoire, le fenvalérate se révèle extrêment toxique pour les organismes aquatiques. La CL_{50} varie de 0,008 µg/litre pour des mysidacées nouvellement écloses à 2 µg/litre pour une espèce d'éphéméroptère. Les épreuves portant sur le cycle évolutif de *Daphnia galeata mendotae* ont révélé que la dose sans effet observable était de 0,005 µg/litre. Le fenvalérate est également extrêment toxique pour les poissons. Les valeurs de la CL_{50} à 96 heures vont de 0,03 µg/litre pour la larve de *Leuresthes tenuis* à 200 µg/litre pour le *Tilapia* adulte. La dose sans effet observable sur 28 jours s'établit à 0,56 µg/litre pour les premiers stades de certains vairons. Le fenvalérate est moins toxique pour les algues et les mollusques aquatiques, la CL_{50} à 96 heures étant supérieure à 1000 µg/litre.

La forte toxicité potentielle du fenvalérate pour les organismes aquatiques ne se manifeste pas dans les essais sur le terrain ni dans les conditions d'utilisation pratique. Certains invertébrés aquatiques sont détruits par un épandage à la surface des eaux mais l'effet sur les populations est temporaire. On n'a pas signalé de mortalité chez les poissons. La toxicité moindre observée lors des épandages de plein champ s'explique par une forte adsorption du composé par les sédiments.

Le fenvalérate est très toxique pour l'abeille. En applications topiques la DL_{50} est de 0,41 µg/abeille, toutefois l'effet répulsif intense qu'exerce le fenvalérate sur ces insectes en réduit l'action dans la pratique. Rien n'indique qu'il y ait eu des destructions importantes d'abeilles dans les conditions normales d'utilisation. Le fenvalérate est plus toxique pour les acariens prédateurs que pour les espèces cibles de ravageurs.

Administré par voie orale ou mêlé à la nourriture, le fenvalérate est très peu toxique pour les oiseaux. La DL_{50} est supérieure à 1500 mg/kg de poids corporel en administration orale directe et dépasse 15 000 mg/kg de nourriture en administration dans la ration alimentaire pour le colin de Virginie.

Les organismes aquatiques fixent rapidement le fenvalérate. Le facteur de bioconcentration varie de 120 à 4700 selon l'organisme en cause (algues, mollusques, daphnies et poissons) selon les études effectuées sur des modèles d'écosystèmes. Toutefois, ce fenvalérate s'élimine rapidement lorsque les organismes sont replacés en eau propre. On peut donc considérer qu'en pratique, ce composé ne présente aucune tendance à la bioaccumulation.

1.7 Effets sur les animaux d'expérience et les systèmes d'épreuve *in vitro*

La toxicité aiguë par voie orale du fenvalérate est modérée à faible. Toutefois, les valeurs de la DL_{50} peuvent varier considérablement (de 82 à plus de 3200 mg/kg) selon l'espèce animale en cause et le véhicule d'administration. Les signes cliniques d'intoxication aiguë apparaissent rapidement mais les survivants redeviennent asymptomatiques au bout de trois à quatre jours. Parmi les signes d'intoxication produits par le mélange racémique, ainsi que par l'isomère [2S, αS], on note de l'agitation, des tremblements, une horripilation, de la diarrhée, une démarche anormale, une choréo-athétose et une salivation (syndrome CS); il est classé comme pyréthroïde du type II. Du point de vue électrophysiologique, il produit des bouffées de pointes au niveau des nerfs moteurs des cerques de la blatte. Toutefois, il n'y a pas de relation bien définie entre les effets électrophysiologiques chez l'insecte et la toxicité pour les mammifères.

Des rats ayant reçu du fenvalérate pendant 8 à 10 jours à raison de 2000 mg/kg de nourriture ont présenté des signes typiques d'intoxication aiguë. A la dose de 3000 mg/kg de nourriture, on observait des modifications morphologiques réversibles au niveau du nerf sciatique. On a également observé des modifications histopathologiques au niveau du même nerf chez des rats et des souris ayant reçu en une seule fois du fenvalérate par voie orale à des doses létales ou sublétales.

Des poulets ayant reçu par voie orale du fenvalérate pendant cinq jours à raison de 1000 mg/kg par jour n'ont pas présenté de signes cliniques ou morphologiques de neurotoxicité retardée.

Chez la souris, la toxicité aiguë par voie intrapéritonéale des métabolites du fenvalérate n'est pas supérieure à celle du fenvalérate lui-même.

Lors d'études de toxicité subaiguë et subchronique, des souris, des rats, des chiens et des lapins ont reçu pendant trois semaines à six mois, du fenvalérate par voie orale, percutanée et respiratoire. Chez le rat et la souris, des études d'inhalation de quatre semaines ont permis de fixer la dose sans effet observable à 7 mg/m^3. Chez le rat, lors d'une étude de 90 jours, elle s'établissait à 125 mg/kg de nourriture, et sur deux ans à 250 mg/kg de nourriture (soit 12,5 mg/kg de poids corporel). Dans une étude de 24 à 28 mois, elle s'est établie à 150 mg/kg de nourriture, soit 7,5 mg/kg de poids corporel. Une étude de deux ans sur la souris a permis de fixer la dose à 50 mg/kg de nourriture, soit 6 mg/kg de poids corporel et une étude de 20 mois, à 30 mg/kg de nourriture, soit 3,5 mg/kg de poids corporel. Chez le chien cette dose a été établie à 12,5 mg/kg de poids corporel, lors d'une étude de 90 jours. Certaines formulations de fenvalérate ont provoqué une irritation cutanée et oculaire. Toutefois, le fenvalérate technique n'est pas irritant et n'a pas d'effet sensibilisateur.

Lors d'études de toxicité à long terme, on a noté l'apparition de microgranulomes chez des souris qui avaient été traitées avec l'isomère [2R, αS] (125 mg/kg de nourriture) sur une période de un à trois mois. Ces anomalies disparaissaient lorsqu'on supprimait le fenvalérate. L'agent causal en était l'ester cholestérique de l'acide (chloro-4 phényl)-2 isovalérique, un métabolite lipophile de l'isomère [2R, αS] du fenvalérate. La dose sans effet observable relative à la formation de microgranulomes chez la souris s'établit à 30 mg de fenvalérate par kg de nourriture.

Lors d'une autre étude de toxicité à long terme, on a également observé ces anomalies microgranulomateuses chez des rats à la dose de 500 mg/kg de nourriture, la dose sans effet observable étant dans ce cas de 150 mg par kg de nourriture.

Administré à des souris dans leur nourriture pendant 78 semaines en doses allant jusqu'à 3000 mg/kg ou pendant deux ans à raison de 1250 mg/kg, le fenvalérate ne s'est

pas révélé cancérogène. Il ne l'a pas été non plus chez des rats qui avaient reçu pendant deux ans une alimentation contenant jusqu'à 1000 mg d'insecticide par kg.

Le fenvalérate n'est ni mutagène, ni délétère pour les chromosomes ainsi qu'il ressort d'un certain nombre d'épreuves *in vitro* et *in vivo*.

Il n'est pas non plus tératogène pour la souris et le lapin à des doses quotidiennes allant jusqu'à 50 mg par kg de poids corporel et, lors d'une étude de reproduction portant sur trois générations de rats où les animaux recevaient des doses allant jusqu'à 250 mg/kg de nourriture, il n'a affecté aucun des paramètres de la fonction de reproduction.

1.8 Effets sur l'être humain

Le fenvalérate peut provoquer des sensations d'engourdissement, de démangeaison, de picotement et de brûlure chez les travailleurs exposés; les symptômes apparaissent après une période de latence d'environ 30 minutes, atteignent leur acmé au bout de 8 heures et disparaissent dans les 24 heures suivantes. Certains cas d'intoxication se sont produits à la suite d'une exposition professionnelle due au non respect des mesures de sécurité.

Rien n'indique que le fenvalérate soit nocif pour l'être humain dans la mesure où il est utilisé conformément aux recommandations.

2. Conclusions

2.1 *Population générale*

L'exposition de la population générale au fenvalérate est probablement très faible. Il n'y a sans doute aucun risque si on l'emploie conformément aux recommandations.

2.2 *Exposition professionnelle*

Utilisé de manière raisonnable, et moyennant certaines mesures d'hygiène et de sécurité, le fenvalérate ne devrait pas être dangereux pour les personnes qui lui sont exposées de par leur profession.

2.3 *Environnement*

Il est improbable que le fenvalérate ou ses produits de dégradation puissent s'accumuler dans l'environnement en quantité suffisante pour créer des problèmes, dans la mesure où l'on respecte les doses d'emploi recommandées. Au laboratoire, le fenvalérate se révèle extrêmement toxique pour les poissons, les arthropodes aquatiques et les abeilles. Toutefois, il ne semble pas que des effets nocifs durables puissent se produire sur le terrain si l'insecticide est utilisé conformément aux recommandations.

3. Recommandations

Les concentrations alimentaires qui résultent d'une utilisation conforme aux recommandations sont considérées comme très faibles; toutefois il conviendrait de confirmer ce point de vue en étendant les études de surveillance au fenvalérate.

Le fenvalérate est utilisé depuis de nombreuses années et seuls quelques effets temporaires ont été observés ça et là à la suite d'expositions professionnelles. Néanmoins, il serait bon de poursuivre les observations sur l'exposition humaine.

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