IPCS International Programme on Chemical Safety

Environmental Health Criteria 82

Cypermethrin

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization

WORLD HEALTH ORGANIZATION GENEVA 1989

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43. Chlordecone
44. Mirex

(continued on p. ...)

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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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CONTENTS

Page

Page

Page

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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. 988400 - 985850).

* * *

NOTE:

The proprietary information contained in this document cannot be used in place of the documentation required 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 paragraphs 82-84 and recommendations paragraph 90 of the 2nd FAO Government Consultation (1982).

ENVIRONMENTAL HEALTH CRITERIA FOR CYPERMETHRIN

A WHO Task Group on Environmental Health Criteria for Cypermethrin met in Geneva from 1 to 5 December 1986. Dr M. Mercier, Manager, IPCS, opened the meeting and welcomed the participants on behalf of the heads of the three IPCS co-sponsoring organizations (UNEP/ILO/WHO). The group reviewed and revised the draft criteria document and made an evaluation of the risks for human health and the environment from exposure to cypermethrin.

The first draft of the criteria document was prepared by Dr G.J. van Esch of the Netherlands on the basis of two data sources:

1. A draft document based on published literature prepared by Dr J. Miyamoto and Dr M. Matsuo of Sumitomo Chemical Co., Ltd. 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 in the finalization of this draft.
2. A review of all studies on Cypermethrin, including the proprietary information, made available to the IPCS by Shell International Chemical Company Limited, London, United Kingdom.

The second draft of the criteria document was prepared by Dr van Esch, incorporating comments received following the circulation of the first draft to the IPCS contact points for Environmental Health Criteria documents.

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

* * *

Partial financial support for the publication of this criteria document was kindly provided by the United States Department of Health and Human Services, through a contract from the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA - a WHO Collaborating Centre for Environmental Health Effects. The United Kingdom Department of Health and Social Security generously supported the cost of printing.

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 (1R/1S 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 Elliot (1977), Miyamoto (1981), Miyamoto & Kearney (1983), and Leahey (1985).

1. SUMMARY

1.1 General

Cypermethrin was initially synthesized in 1974 and first marketed in 1977 as a highly active synthetic pyrethroid insecticide, effective against a wide range of pests in agriculture, public health, and animal husbandry. In agriculture, its main use is against foliage pests and certain surface soil pests, such as cutworms, but because of its rapid breakdown in soil, it is not recommended for use against soil-borne pests below the surface.

In 1980, 92.5% of all the cypermethrin produced in the world was used on cotton; in 1982, world production was 340 tonnes of the active material. It is mainly used in the form of an emulsifiable concentrate, but ultra low volume concentrates, wettable powders, and combined formulations with other pesticides are also available.

Chemically, cypermethrin is the alpha-cyano-3-phenoxybenzyl ester of the dichloro analogue of chrysanthemic acid, 2,2-dimethyl-3-(2,2-dichlorovinyl) cyclopropanecarboxylic acid. The molecule embodies three chiral centres, two in the cyclopropane ring and one on the alpha cyano carbon. These isomers are commonly grouped into four cis- and four trans-isomers, the cis-group being the more powerful insecticide. The ratio of cis- to trans-isomers varies from 50:50 to 40:60. Cypermethrin is the racemic mixture of all eight isomers and, in this appraisal, cypermethrin refers exclusively to the racemic mixture (ratio 50:50) unless otherwise stated.

Most technical grades of cypermethrin contain more than 90% of the active material. The material varies in physical form from a brown-yellow viscous liquid to a semi-solid.

Cypermethrin has a very low vapour pressure and solubility in water, but it is highly soluble in a wide range of organic solvents. Analytical methods are available for the determination of cypermethrin in commercially available preparations. In addition, methods for the determination of residues of cypermethrin in foods and in the environment are well established. In most substrates, the practical limit of determination is 0.01 mg/kg.

1.2 Environmental Transport, Distribution, and Transformation

Unlike the natural pyrethrins, cypermethrin is relatively stable to sunlight and, though it is probable that photodegradation plays a significant role in the degradation of the product on leaf surfaces and in surface waters, its effects in soils are limited. The most important photodegradation

products, 2,2-dimethyl-3-(2,2-dichlorovinyl) cyclopropane-carboxylic acid (CPA), 3-phenoxybenzoic acid (PBA) and, to some extent, the amide of the intact ester, do not differ greatly from those resulting from biological degradation.

Degradation in the soil occurs primarily through cleavage of the ester linkage to give CPA, PBA, and carbon dioxide. Some of the carbon dioxide is formed through the cleavage of both the cyclopropyl and phenyl rings under oxidative conditions. The half-life of cypermethrin in a typical fertile soil is between 2 and 4 weeks.

Cypermethrin is adsorbed very strongly on soil particles, especially in soils containing large amounts of clay or organic matter. Movement in the soil is therefore extremely limited and downward leaching of the parent molecule through the soil does not occur to an appreciable extent under normal conditions of use. The two principal degradation products show, on the scale of Helling, "intermediate mobility".

Cypermethrin is also relatively immobile in surface waters and, when applied to the surface of a body of water at rates typical of those used in agriculture applications, it is largely confined to the surface film and does not reach deeper levels or the sediment in appreciable concentrations. Cypermethrin also degrades readily in natural waters with a typical half-life of about 2 weeks. It is probable that both photochemical and biological processes play a part. It has been shown that spray drift reaching surface waters adjacent to sprayed fields does not result in long-term residues in such waters.

Accumulation studies have shown that cypermethrin is rapidly taken up by fish (accumulation factor approximately 1000); the half-life of residues in rainbow trout was 8 days. In view of the low concentrations of cypermethrin that are likely to arise in water bodies and their rapid decline, it has been concluded that, under practical conditions, residues in fish will not reach measurable levels.

The results of field studies have shown that, when applied at recommended rates, the levels of cypermethrin and its degradation products in soil and surface waters are very low. Thus, it is unlikely that the recommended use of cypermethrin will have any effects on the environment.

1.3 Environmental Levels and Human Exposure

Cypermethrin is used in a wide range of crops. In general, the maximum residue limits are low, ranging from 0.05 to 2.0 mg/kg in the different food commodities. The residues will be further reduced during food processing. In food of animal origin, residues may range between 0.01 and 0.2 mg/kg product. Residues in non-food commodities are generally

higher, ranging up to 20 mg/kg product.

Total dietary intake values for man are not available, but it can be expected that the oral exposure of the general population is low to negligible.

1.4 Kinetics and Metabolism

Absorption of cypermethrin from the gastrointestinal tract and its elimination are quite rapid. The major metabolic reaction is cleavage of the ester bond. Elimination of the cyclopropane moiety in the rat, over a 7-day period, ranged from 40 to 60% in the urine and from 30 to 50% in the faeces; elimination of the phenoxybenzyl moiety was about 30% in the urine and 55 to 60% in the faeces. Biliary excretion is a minor route of elimination for the cyclopropane moiety and small amounts are exhaled as carbon dioxide. In principle, these absorption and elimination rates and metabolic pathways hold for all animal species studied, including domestic animals. In cows fed 100 mg cypermethrin/day, the highest level found in milk was 0.03 mg/litre; levels of up to 0.1 mg/kg tissue were found in subcutaneous fat. Under practical conditions, the oral intake of cypermethrin with feed will be much lower. Cypermethrin used as a spray or dip to combat parasites, may give rise to maximum residues of 0.05 mg/kg tissue and 0.01 mg/litre milk.

Laying hens exposed orally to 10 mg cypermethrin/kg diet for 2 weeks, showed cypermethrin levels of up to 0.1 mg/kg in the fat, and up to 0.09 mg/kg in the eggs (predominantly in the yolk).

Consistent with the lipophilic nature of cypermethrin, the highest mean tissue concentrations are found in body fat, skin, liver, kidneys, adrenals, and ovaries. Only negligible concentrations are found in the brain. The half-life of cis-cypermethrin in the fat of the rat ranges from 12 to 19 days and that of the trans-isomer, from 3 to 4 days. In mice, these half-lives are 13 days and 1 day, respectively.

Overall, the metabolic transformation has been similar in the different animals studied, including man. Differences that occur have been related to the rate of formation rather than to the nature of the metabolites formed and to conjugation reactions. Cypermethrin (both the cis- and trans-isomers) is metabolized via the cleavage of the ester bond to phenoxybenzoic acid and cyclopropane carbolic acid. The fact that thiocyanate has been identified in in vivo studies, indicates that the cyanide moiety is further metabolized. The 3-phenoxybenzoic acid is mainly excreted as a conjugate. The type of conjugate differs in a number of animal species. Phenoxybenzoic acid is further metabolized to a hydroxy derivative and conjugated with glucuronic acid or sulfate.

The cyclopropyl moiety is mainly excreted as a glucuronide conjugate, hydroxylation of the methyl group only occurring to a limited extent.

Ester cleavage is much slower in certain fish species than in other animal species, the main metabolic pathway being hydroxylation of the phenoxybenzoic and the cyclopropyl moieties.

Ester cleavage also takes place in plants. The phenoxybenzyl and cyclopropyl moieties are readily converted into glucoside conjugates. In mammals, these conjugates are hydrolysed into the original acids and metabolized.

1.5 Effects on Organisms in the Environment

High doses of cypermethrin may exert transient minor effects on microflora activity in the soil. However, no influence on ammonification and nitrification has been found.

Cypermethrin is very toxic for fish (in laboratory tests 96-h LC_{50}s were generally within the range of 0.4-2.8 µg/litre), and aquatic invertebrates (LC_{50}s in the range of 0.01-> 5 µg/litre). The presence of suspended solids decreases the toxicity by at least a factor of 2, because of adsorption of cypermethrin to the solids.

Cypermethrin is not very toxic for birds. Signs of cypermethrin intoxication were seen at dose levels of 3000 mg/kg body weight or more. Administration of 1000 mg cypermethrin/kg body weight to laying hens over a 5-day period did not cause signs of intoxication. However, cypermethrin was highly toxic for honey bees in laboratory tests, the oral LD_{50} ranging from 0.03 to 0.12 µg/bee. Under field conditions, the hazard is considerably lower, because of the repellent effect of cypermethrin on worker honey bees, which lasts for at least 6 h after spraying.

Earthworms are not sensitive to cypermethrin. No deaths occurred in worms exposed to levels of 100 mg/kg soil for 14 days.

In studies involving deliberate overspraying of experimental ponds under field conditions, peak concentrations of 2.6 µg cypermethrin/litre were measured in the water. Fish were not affected, but populations of crustaceae, mites, and surface-breathing insects were severely reduced. Most of these populations returned to normal levels after 15 weeks. Free-swimming dipterous larvae and bottom-dwelling invertebrates, snails, flatworms, etc., were not affected. Under normal agricultural conditions (during which drifts may reach adjacent ditches or streams), the only effects seen in surface-breathing or -dwelling insects were hyperactivity or immobilization.

The relative toxicity of cypermethrin for pests and their parasites and predators is such that the balance between host/prey and parasites/predator may not be adversely affected in the field. However, care should be taken where predatory mites are important in pest management.

1.6 Effects on Experimental Animals and In Vitro Test Systems

The acute oral toxicity of cypermethrin is moderate. While LD_{50} values differed considerably among animal species depending on the vehicle used and the cis-/trans-isomeric ratios, the toxic responses in all species were found to be very similar. The acute toxicity of the trans-isomer in the rat (LD_{50} > 2000 mg/kg body weight) was lower than that of the cis-isomer (LD_{50}, 160-300 mg/kg body weight). The onset of toxic signs of poisoning was rapid and they disappeared within several days in survivors. The toxic signs are characterized by salivation, tremors, increased startle response, sinuous writhing of the whole body (choreoathetosis), and clonic seizures. Myelin and axon degeneration were noted in the sciatic nerve at near lethal dose levels.

Cypermethrin was moderately to severely irritating, when applied to the skin or the eye of the rabbit. The severity was partly dependent on the vehicle used. In guinea-pigs, a mild skin sensitizing potential was found using the maximization test.

No toxic effects were observed in rats, fed cypermethrin at 100 mg/kg diet for 3 months. Furthermore, prolonged feeding of cypermethrin (2 years) to dogs at a level of 300 mg/kg feed did not produce any toxicological effects. A level of 600 mg/kg diet resulted in reduced body weight gain, but no gross pathological or histopathological effects were seen.

Two long-term studies on rats and one on mice were carried out. The dose levels in the rat studies ranged up to 1500 mg/kg diet, equivalent to 75 mg/kg body weight. No effects were seen at 150 mg/kg diet. At the highest dose level, reduced body weight gain, increased liver weights (accompanied by increased smooth endoplasmatic reticulum), and some haematological and biochemical changes were observed. No increase in tumour incidence was noted. The same type of effects were seen in the mouse study at 1600 mg cypermethrin/kg diet. No effects were seen in the 400 mg/kg diet group.

The effect of cypermethrin on the immune system was studied in rats. The results showed the possibility of immunesuppression by pyrethroids. More attention should be paid to this aspect, but, at present, no opinion can be given about its relevance in the extrapolation of these data for man.

Repeated oral administration of cypermethrin to rats and other animal species at levels sufficiently high to produce significant mortality in one group of animals, produced biochemical changes in the peripheral nerves, consistent with sparse axonal degeneration. Histopathological changes (swelling and/or disintegration of axons of the sciatic nerve) were observed. There was no cumulative effect. The magnitude of the change was substantially less than that encountered with established neurotoxic agents. The neurotoxic effects seem to be reversible; presumably the clinical signs are not related to the induction of neuro-pathological lesions.

Further evidence to support the minor nature of the nerve lesions has been afforded by electrophysiological studies on rats. Measurements of the maximal motor conduction velocities of the sciatic and tail nerves of rats were made before, and at intervals of up to 5 weeks after, exposure to a single dose or repeated high doses of cypermethrin. It was concluded from the results that, even at near-lethal doses, cypermethrin did not cause any effects on maximal motor conduction velocities and conduction velocities of the slower motor fibres in rat peripheral nerves. No delayed neurotoxicity was observed in domestic hens.

The ability of the major metabolite of cypermethrin, 3-phenoxybenzoic acid, to produce axonal changes has been investigated and found to be negative.

In a multigeneration reproduction study on rats, dose levels up to 500 mg/kg feed were tested. The parent animals at the highest dose level showed decreased food intake and reduction in body weight gain. No influence on reproductive performance or on survival of the offspring was found. However, at the highest dose level, reductions in litter size and total litter weights were seen. The pooled body weights of weaning pups of the 500 mg/kg group were decreased over 3 generations. No effect was found with 100 mg cypermethrin/kg diet.

Embryotoxic and teratogenic effects were not found in rats administered dose levels of up to 70 mg/kg body weight and clear teratogenic effects were not observed in rabbits given dose levels of up to 30 mg/kg body weight during days 6-18 of gestation.

Cypermethrin did not show any mutagenic activity in bacteria or in yeast, with or without metabolic activation, or in V_{79} Chinese hamster cells. Furthermore, cypermethrin gave negative results in an *in vivo* chromosomal aberration test with Chinese hamsters and in dominant lethal studies on mice. In a host-mediated assay with mice, no increase in the rate of mitotic gene conversion in *Saccharomyces cerevisae* was found. In a chromosome study using the bone marrow cells of Chinese hamsters, cypermethrin did not increase the number of

chromosome abnormalities. However, in a micronucleus test with mouse bone marrow cells, an increase in the frequency of polychromatic erythrocytes with micronuclei was found after oral and dermal applications of cypermethrin. Intraperitoneal application gave a negative result. A sister chromatid exchange study using bone marrow cells of mice showed a dose-response related increase in sister chromatid exchanges of dividing cells.

In long-term/carcinogenicity studies, oral administration of cypermethrin to rats did not induce an increase in the incidence of tumours. In a mouse study, dose levels of up to 1600 mg cypermethrin/kg diet did not produce any increase in tumours of types not commonly associated with the mouse strain employed. The incidence of tumours was similar in all groups with the exception of a slight increase in the incidence of benign alveolar lung tumours in the females in the 1600 mg/kg diet group. However, the increased incidence, when compared with concurrent and historical control incidence, was not sufficient to warrant concern. There was no suggestion of increased malignancy and no evidence of a decrease in the latency of the tumours. Furthermore, there was no evidence of a carcinogenic response in the male mice in this study and, as the results of mutagenicity studies on cypermethrin have been mainly negative, it is concluded that there is no evidence for the carcinogenic potential of cypermethrin.

1.7 Mechanism of Toxicity

Extensive studies have been carried out to explain the mechanism of toxicity of cypermethrin, especially with regard to the effects on the nervous system. The results strongly suggest that the primary target site of cypermethrin (and of pyrethroid insecticides in general) in the vertebrate nervous system is the sodium channel in the nerve membrane. The α-cyano pyrethroids, such as cypermethrin, cause a long-lasting prolongation of the normally transient increase in sodium permeability of the nerve membrane during excitation, resulting in long-lasting trains of repetitive impulses in sense organs and a frequency-dependent depression of the nerve impulse in nerve fibres. Since the mechanisms responsible for nerve impulse generation and conduction are basically the same throughout the entire nervous system, pyrethroids may well act in a similar way in various parts of the central nervous system. It is suggested that the facial skin sensations that may be experienced by people handling cypermethrin are brought about by repetitive firing of sensory nerve terminals in the skin, and may be considered as an early warning signal that exposure has occurred.

1.8 Effects on Man

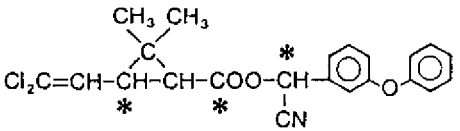
No cases of accidental poisoning have been reported as a result of occupational exposure.

Skin sensations, reported by a number of authors to have occurred during field studies, generally lasted only a few hours and did not persist for more than one day after exposure. Neurological signs were not observed. General medical and extensive clinical blood-chemistry studies, and electrophysiological studies on selected motor and sensory nerves in the legs and arms did not show any abnormalities.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Chemical formula



IUPAC chemical name	(RS)-alpha-cyano-3-phenoxybenzyl(1RS)-cis-, trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate
CAS chemical name	(RS)-cyano(3-phenoxyphenyl)methyl(1RS)-cis-trans-3-(2,2-dichloroethenyl)-2.2-dimethylcyclopropane carboxylate
CAS registry number	52315-07-8 (formerly 69865-47-0)
RTECS registry number	GZ1250000
Common synonyms	NRDC 149, WL43467, PP 383, CG-A 55186
Common trade names	Ammo, Avicade, Barricade, CCN 52, Cymbush, Folcord, Imperator, Kafil Super, Polytrin, Ripcord, Stockade

The asymetric centres are marked with an asterisk and give rise to the 8 isomers shown in Fig. 1. Conventionally, the 4 isomers where the dichlorovinyl group is trans in relation to the phenoxybenzyl group are referred to as trans-isomers, and the other 4 as cis-isomers.

Cypermethrin is the ISO name for the pure racemic compound. The technical products commonly available contain more than 90% cypermethrin and the ratio of cis- to trans-isomers varies from 50:50 to 40:60. The data presented in this document refer to products within this range of composition, unless otherwise stated.

2.2 Physical and Chemical Properties

Some physical and chemical properties of cypermethrin are given in Table 1.

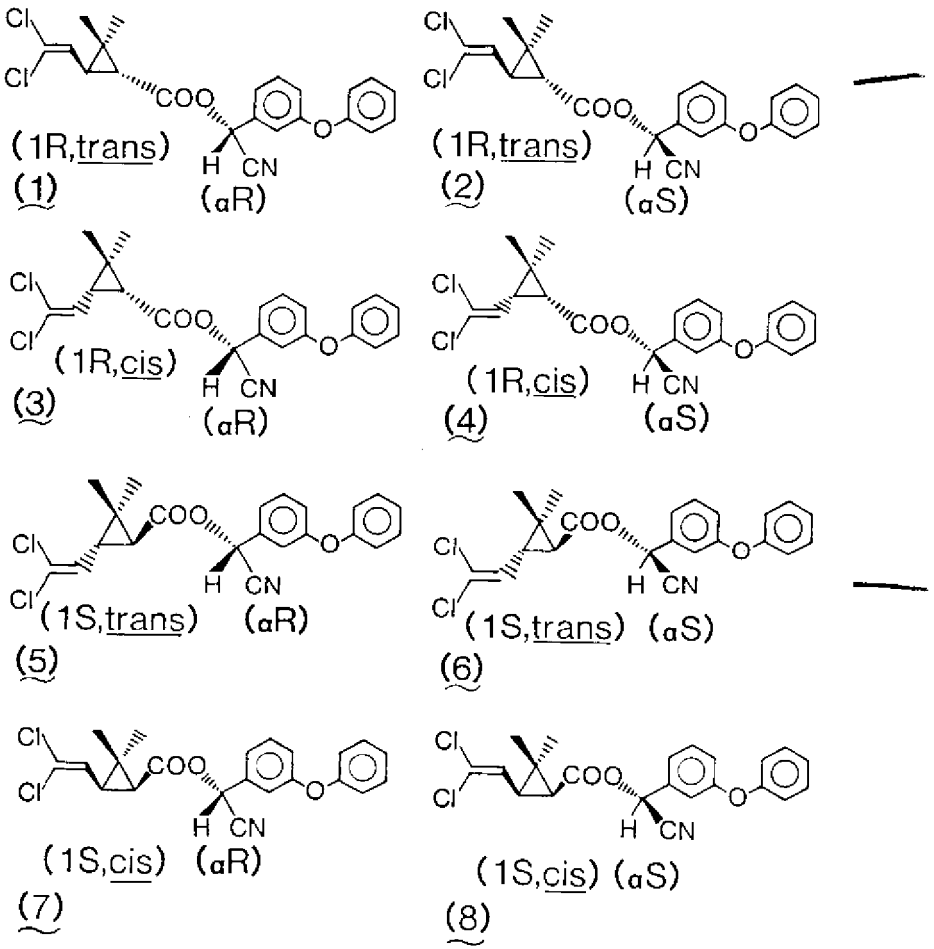


Fig. 1. Configuration of the 8 isomers that constitute cypermethrin.

Table 1. Some physical and chemical properties of cypermethrin [a]

Physical state	varies from a viscous yellow liquid to a semi-solid crystalline mass at ambient temperatures
Relative molecular mass	416.3
Melting point	up to 80 °C depending on purity and *cis*: *trans* ratio
Boiling point	decomposes at 220 °C
Density (22 °C)	1.12 g/ml
Solubility in water (20 °C)	0.009 mg/litre
Solubility in organic solvents:	
hexane	103 g/litre
xylene	> 450 g/litre
	also comparable solubility in cyclohexanone, ethanol, acetone, and chloroform
Vapour pressure (20 °C)	1.9×10^{-7} Pa (1.4×10^{-9} mmHg)
n-octanol/water partition coefficient	2×10^{6} ($\log P_{ow}$ 6.3)

[a] From: FAO/WHO (1980b); Grayson et al (1982); Working & Walker (1983).

Cypermethrin is highly stable to light and at temperatures below 220 °C. It is more resistant to acidic than to alkaline media, with an optimum stability at pH 4. Cypermethrin is hydrolysed under alkaline conditions in the same way as simple aliphatic esters: the rate-determining step is the nucleophilic attack by a hydroxyl group (Camilleri, 1984). Dilute aqueous solutions are subject to photolysis, which occurs at a moderate rate (Martin & Worthing 1977; FAO/WHO, 1980b; Meister et al., 1983; Worthing & Walker, 1983).

2.3 Analytical Methods

The most widely adopted procedures for the determination of cypermethrin residues in crops, soil, animal tissues and products, and environmental samples are based on extraction of the residue with organic solvent, clean-up of the extract, as necessary, by means of solvent-solvent partition and adsorption column chromatography, followed by determination of the residue using gas chromatography with electron capture detector (GC/ECD). The identity of residues can be confirmed

by GC with mass selective detection (GC-MSD) or by thin-layer chromatography (TLC) followed by GC/ECD.

Methods using these procedures have been applied for the determination of cypermethrin residues in the presence of other synthetic pyrethroids or other classes of pesticides, including organochlorine insecticides.

Alternative procedures, based on high-performance liquid chromatography with UV detection (HPLC/UV) and TLC with a colorimetric end point, have been described, but have not been widely adopted, because of the simplicity and sensitivity of the GC/ECD methods. This is also true for more elaborate procedures based on hydrolysis and derivatization.

Procedures have also been developed for the determination of the more important cypermethrin metabolites, 3-phenoxybenzoic acid (PBA), the cyclopropane carboxylic acid (CPA), and the amide. Following extraction and clean-up, these materials are determined by HPLC/UV or by GC procedures, after derivatization in the case of the two acids.

The Codex Committee on Pesticide Residues lists recommended methods for the determination of cypermethrin residues (FAO/WHO 1986).

The methods for residue, environmental, and product analysis for cypermethrin are summarized in Table 2.

Table 2. Published analytical methods for cypermethrin

Sample	Sample preparation			Method of determination	LD[b] (mg/kg)	Reference
	Extraction solvent	Partition	Clean-up Column/elution	GLC or HPLC condition[a]		
Residue analysis						
Apple Pear Cabbage Potato	n-hexane:acetone (1:1)	extraction solvent:H_2O	silica gel/ CH_2Cl_2	electron capture detection-gas chromatography	0.01 0.01 0.01 0.01	Baker & Bottomley (1982)
Apple Pear Cabbage Potato	n-hexane:acetone (1:1)	extraction solvent:H_2O	silica gel/ CH_2Cl_2	high-performance liquid chromatography	0.2 0.2 0.2 0.2	Baker & Bottomley (1982)
Onion Carrot	$CH_3CN:H_2O$ (2:1)	CH_2Cl_2	Florisil/ether:n-hexane	electron capture detection-gas chromatography		Frank et al. (1982)
Celery	CH_3CN	n-hexane:2% NaCl	Florisil/ CH_3CN/CH_2Cl_2: n-hexane	electron capture detection-gas chromatography	0.005	Braun & Stanek (1982)
Wheat grain flour bran middling	n-hexane:acetone (1:1)	2% NaCl:extraction solvent	Florisil/benzene	electron capture detection-gas chromatography	0.02	Joia et al. (1981, 1985a)
Beef muscle	$CH_3CN:H_2O$ (85:15)	n-hexane:2% NaCl solution	Florisil/ CH_3CN/CH_2Cl_2: n-hexane	electron capture detection-gas chromatography	0.005	Braun & Stanek (1982)

Table 2 (contd).

Sample	Sample preparation			Method of determination	LD[b] (mg/kg)	Reference
	Extraction solvent	Partition	Clean-up Column/elution	GLC or HPLC condition[a]		
Egg yolk	$CH_3CN:H_2O$ (85:15)	n-hexane:2% NaCl solution	Florisil/ CH_3CN/CH_2Cl_2: n-hexane	electron capture detection-gas chromatography	0.005	Braun & Stanek (1982)
Milk	CH_3CN	n-hexane:2% NaCl solution	Florisil/ CH_3CN/CH_2Cl_2: n-hexane	electron capture detection-gas chromatography	0.005	Braun & Stanek (1982)
Cotton foliage (dislodgable residue)	n-hexane		Florisil/n-hexane: EtOAc	electron capture detection-gas chromatography		Estesen et al. (1982)
Environmental analysis						
Fish Shrimp	n-hexane:acetone (1:1)		alumina/n-hexane: benzene	electron capture detection-gas chromatography		McLeese et al. (1980)
Water Seawater	XAD-2 resin: acetone	extraction solvent:n-hexane		electron capture detection-gas chromatography		McLeese et al. (1980)
Soil	acetone	sat. Na_2SO_4: n-hexane		electron capture detection-gas chromatography		Harris et al. (1981)
Soil	$CH_3CN:H_2O$ (2:1)	CH_2Cl_2	Florisil/ether: n-hexane	electron capture detection-gas chromatography		Frank et al. (1982)

Table 2 (contd).

Product analysis			
Technical grade	n-hexane	flame ionization detection-gas chromatography	Chapman & Simmons (1977)
Technical and formulated material	methylene chloride (containing as internal standard dicyclohexylphthalate)	flame ionization detection-capillary gas chromatography	Bland (1985)

a GLC = gas-liquid chromatography.
HPLC = high-performance liquid chromatography.

b LD = limit of determination. (The lower practical limit of determination for most of the analytical methods based on GLC is usually 0.01 mg/kg. The actual level achievable, however, depends to some extent on the substrate and to a great extent on the intensity of the clean-up steps in the procedure).

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Industrial Production

Cypermethrin was synthesized by Elliott et al. in 1974. It was prepared by the esterification of a chloro analogue of chrysanthemic acid (1R, 1S or 1RS, 3R, 3S, or cis-, trans-)-2,2-dimethyl-3-(2,2-dichloroviny1)cyclopropanecarboxylic acid with (αR, αS, or αRS)-α-cyano-3-phenoxybenzyl alcohol. Today there are many other methods of preparation.

Cypermethrin has been marketed since 1977. Recent global production figures are given in Table 3.

Table 3. Global production of cypermethrin

Year	Production (tonnes)	Reference
1979	200	Wood, Mackenzie, & Co. (1980)
1980	380	Wood, Mackenzie, & Co. (1981)
1981	375	Wood, Mackenzie, & Co. (1982)
1982	340	Wood, Mackenzie, & Co. (1983)

3.2 Use Patterns

Cypermethrin is a highly active synthetic pyrethroid insecticide, effective against a wide range of pests in many crops. According to Battelle (1982), global consumption of cypermethrin amounted to 159 tonnes in 1980. Fifty-eight tonnes were consumed in Africa and 9 tonnes in western Europe. Global production in 1982 was 340 tonnes. Cypermethrin was mainly (92.5%) used on cotton, the major consumer areas being Turkey (47 tonnes), Central America (44 tonnes), and Egypt (25 tonnes) (Battelle, 1982). Other agricultural uses included the treatment of hop, vegetables, and maize. Cypermethrin is also used for the control of veterinary and public health insects, such as flies, lice, and mites and, in the United Kingdom, it is used as a wood preservative.

Cypermethrin is formulated as emulsifiable concentrates (100 and 250 g/litre), ultra-low-volume concentrate (10-50 g/litre), wettable powder (125 g/kg), and animal dip concentrate (5-15%).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSPORTATION

4.1 Transport and Distribution between Media

Because of its physical and chemical characteristics, cypermethrin is comparatively immobile in the outdoor environment and transport between media is restricted. It has a very low vapour pressure and water solubility and is strongly adsorbed from aqueous solutions by solid surfaces. This drastically restricts its movement in air and water, and particularly in soils.

4.1.1 Transport from soil to water

Kaufman et al. (1981), working in the laboratory with radio-labelled cypermethrin in soil columns, down which a volume of water equivalent to their moisture equivalent was allowed to percolate, reported virtually no movement of radioactivity below the top 2.5 cm. Using the procedure introduced by Helling & Turner (1968), where the mobility was studied using thin layer chromatographic (TLC) plates, very little movement of cypermethrin occurred in soils. However, radio-labelled PBA leached down the soil columns to a level of about 8 cm and CPA reached a maximum concentration at this level. On the basis of the Helling nomenclature for soil TLC, CPA and PBA were of "intermediate mobility" to "mobile". While the mobilities of CPA and PBA were relatively little affected by the organic matter content of the soil, pH appeared to be a most important factor, mobility being greatest in soils of highest pH, presumably because of increased dissociation.

Stevens & Hill (1980) studied the leaching of cypermethrin in the laboratory in 4 different soil types, a clay loam, a loamy sand, a coarse sand, and a fen peat. The compound was incubated for three weeks with each soil under aerobic conditions. The soils were then packed into glass columns and leached with 67.5 cm water over a 10-week period. At the end of the period of incubation, a substantial proportion of the cypermethrin had been lost as $^{14}CO_2$ (up to a third in one case), and only minor amounts of degradation products had been formed. It was found that, after the leaching period, more than 99% of the ^{14}C residue remained within the top 5 cm in all the soils. Radioactivity in the leachate was below the limit of determination in all cases.

In laboratory studies using labelled cypermethrin and soil columns, Jackson (1977) found little penetration of cypermethrin below the top 2-cm layer, even after the percolation of 1.35 metres of water.

In a further study on the percolation of distilled water through sandy loam soils containing ^{14}C-benzyl cypermethrin from spent sheep-dip baths, Standen (1977) reported that up to 0.3% of the applied radioactivity was leached out. However, most of the radioactivity was associated with fine soil particles in the leachate and could not be extracted with organic solvents. The water contained small amounts of unchanged cypermethrin and PBA. Most (89%) of the radioactivity was contained in the top 14 cm of the columns, mainly as cypermethrin itself.

Sakata et al. (1986) studied the leaching with distilled water of radio-labelled cypermethrin through columns of 4 different types of soil in the laboratory. The water flow was at a rate of 3 ml/h and was continued for 3 weeks at 25 °C, so that the total flow through the column was equivalent to about 3 metres. Cypermethrin was relatively resistent to leaching but radioactivity was found in the leachate, especially in one sandy soil where, after 30 days of incubation, about 30% of the cyclopropyl label first added was collected in the leachate. The major products associated with radioactivity in the leachates were either CPA or PBA, depending on the position of the label. Unchanged cypermethrin was present only in trace amounts in sand containing less than 0.1% organic matter.

4.1.2 Transport within water bodies

Cypermethrin moves slowly in water bodies. In the experimental overspraying of ponds carried out by Crossland (1982) and described in detail in section 4.4.2, it was calculated that 48 h after treatment with 100 g cypermethrin/ha, only about 8-16% of the amount applied could be found underneath the surface film of 0.05 mm depth. In all of Crossland's studies, the levels of cypermethrin residues in the sediment at the bottom of the ponds were below 7 µg/kg.

With spray levels applied according to normal agricultural practice, Crossland et al. (1982) found that water bodies adjacent to sprayed arable fields in the United Kingdom received only four-five orders of magnitude less cypermethrin per m^2 than the land itself and that the initial concentration in the surface film of water was between 6 and 20 µg/litre. Residues in the water below the surface film did not reach more than 0.1 µg/litre and within 24 h the levels had nearly all fallen to below the limit of determination of 0.01 µg/litre. A similar study in French vineyards showed comparable results, though the initial concentrations reached in the surface films were higher, probably because conditions in the area were more favourable for spray drift than those in the British study.

Shires & Bennett (1985) reported similar results concerning water in drainage ditches adjacent to cereal fields in the United Kingdom treated with an aerial spray application of 25 g cypermethrin/ha.

From the available studies, it can be concluded that contamination of water bodies by overspray is likely to be very superficial and of comparatively short duration.

4.2 Abiotic Degradation

4.2.1 Photodegradation

4.2.1.1 Basic studies

According to Ruzo et al. (1977), cypermethrin is one of the more light-stable pyrethroids. Thus, when exposed in the solid phase to sunlight for 30 h, no loss of cypermethrin was detected. When exposed in methanol solution to light of wavelength > 290 nm for about 2 days, 55% of cypermethrin was recovered, but no data on the photodecomposition products formed were reported. According to Ruzo & Casida (1980), the reaction quantum yield at 300 nm in methanol was low, at 0.022. Ruzo (1983) further demonstrated the comparative resistance of cypermethrin to irradiation in his studies on the involvement of oxygen in the photodegradation of pyrethroids.

Cypermethrin is more susceptible to radiation of lower wavelengths; Lauren & Henzel (1977) reported that under ultraviolet radiation, 90% of cypermethrin on a glass petri dish was decomposed after 3 days, but only 45% was decomposed after 3 days when the cypermethrin was deposited on grass and placed under an UV-lamp.

4.2.1.2 Photodegradation

(a) Water

Day & Leahey (1980) studied the effects of sunlight on dilute aqueous solutions of cypermethrin. In their studies, ^{14}C-labelled *cis*- or *trans*- isomers were used with the label in either the cyclopropyl or the benzyl ring. They were dissolved in sterile aqueous acetonitrile at a concentration of 1 mg/litre, irradiated in sunlight for 32 days and the irradiated solutions compared with controls stored for the same length of time in the dark. The degree of photodegradation was very limited. At the end of the study, 89.4% of the cypermethrin remained in the case of the irradiated benzyl label, compared with 97.4% in the dark control. Corresponding figures for the cyclopropyl label were 92.3 and 96.8%. Six of

the 8 photodegradation products separated by chromatography were positively identified; cis- and trans-CPA, phenoxybenzyl alcohol, aldehyde and acid, and alpha-cyano-3-phenoxybenzyl alcohol.

The effects of natural sunlight on aqueous solutions of the (1R, cis-, alpha RS) and (1R, trans-, alpha RS) isomers were studied by Takahashi et al. (1985a,b). The products were labelled with ^{14}C in either the cyclopropyl ring, the benzyl ring, or the cyano carbon. The aqueous solutions were made from distilled water, 2% acetone, aqueous humic acid, sea water, or natural river water (both of which had been filtered). The isomers were added to the water in the form of a stabilized suspension using Tween 20 to give 50 µg/litre test suspension. The rates of degradation of the isomers were very rapid compared with those reported by other authors, however, a large part of the changes involved transformation to other isomers. The degradation was more rapid in river or sea water (half-life of cis-isomer, 0.6-0.7 days) than in distilled water or humic acid (half-life of cis-isomers, 2.3-2.6 days), but the most rapid change of all occurred in the presence of acetone. Presumably the differences were due to the well known effect of photosensitizaton by the acetone or organic constituents of the natural waters. The main degradation products, in addition to the different isomers, were CPA, PBA together with smaller amounts of the corresponding aldehyde, and carbon dioxide, especially in the case of the cyano label. There was evidence of further degradation of CPA and PBA.

(b) Soil

Hall et al. (1981) studied the photodegradation of cypermethrin on the soil surface. Labelled cypermethrin, as used by Day & Leahey, was applied to very thin soil plates (0.5 mm) at a rate equivalent to about 200 g/ha. The plates were exposed to sunlight in the open air protected against rain by polythene sheeting, when necessary; the sheeting was transparent to the UV component of sunlight. The plates were extracted after an exposure period of 32 days and the extracts chromatographed. In the case of the cyclopropyl label, 63% of the radioactivity initially applied to the irradiated plate was recovered, compared with 103.5% from the plate that had been kept in the dark. The half-life of the cyclopropyl-labelled cypermethrin was reduced from > 32 days to 8-16 days by irradiation with natural light. The main degradation products appear to have been the amide, together with cis- and trans-CPA, and some unidentified (partly volatile) products. In the case of the benzyl label, the degradation products identified were mainly the amide analogue of cypermethrin and

various phenoxybenzyl derivatives, such as the alcohol, aldehyde, and acid. In these studies, the amide was the most prominent, even in the unirradiated sample, and in this respect, the results differ somewhat from those obtained in other soil incubation studies, where the main metabolite from benzyl-labelled cypermethrin was PBA, with the amide occurring only as a very minor product.

Takahashi et al. (1985a,b), working with the same products as they used for their study on water, applied the labelled products at 1.1 $\mu g/cm^2$ to half-millimetre layers of 3 different soils and found very rapid degradation in the irradiated soils compared with those kept in the dark. The half-lives ranged from between 0.6 and 1.9 days with sunlight and > 7 days in the dark. With regard to degradation products, the results were rather similar to those reported by Hall et al. (1981) in that the main degradation product was the amide of the otherwise intact isomers. In addition, they found smaller amounts of PBA, virtually no CPA, but occasionally small amounts of alpha carbamoyl- and alpha carboxyphenoxybenzyl alcohol. In one of the soils in which degradation was the highest, nearly half of the radio-labelled carbon was unextractable at the end of the exposure period. In contrast with the water study, there was very little evidence of isomerization of the parent isomers.

There is no obvious explanation for the different rates of degradation under the influence of irradiation and it is difficult to extrapolate the results of these studies to the practical situation. It appears likely that photochemical reactions will hasten the degradation of deposits of cypermethrin on exposed surfaces and possible residues in water, but there is little indication that they greatly change the degradation pathways.

4.3 Biological Degradation in Soil

Cypermethrin degrades relatively quickly in soils, primarily by biological processes involving cleavage of the ester linkages, to give the two main degradation products, CPA and PBA. These products are themselves subsequently mineralized. There is also evidence for the formation, as an intermediate, of the amide of the intact molecule and occasionally the 4-hydroxy phenoxy analogue. Neither of the latter products appears to persist in the soil (Leahey 1979; Sakata et al., 1986).

4.3.1 Mechanism

Chapman et al. (1981), who studied the effects of sterilization of soils on the rate of cypermethrin degradation

in the laboratory, demonstrated that degradation in the soil was essentially a biological process. Cypermethrin was added at 1 mg/kg to the soils (either untreated or sterilized) and the soils incubated for 16 weeks, by which time the sterilized soils were considered to have become contaminated. The experiment was conducted under strictly aerobic conditions. It was found that 84% of the added material had degraded in natural organic soil compared with only 8% in the sterilized organic soil. The corresponding values for the mineral soil were 96% and 7%. The small amounts of degradation in the sterilized soils presumably resulted from residual microbial activity, especially in the later stages of the study.

4.3.2 Degradation pathways (separate isomers)

In order to study degradation pathways, Roberts & Standen (1977, 1981) carried out a series of soil studies in the laboratory using either the racemic cis- or trans-isomers of cypermethrin or mixtures of the two. The compounds were ^{14}C-radio-labelled in either the benzyl or the cyclopropyl ring and were added to the soil at a rate of 2.5 mg/kg moist soil. Incubation with 3 different soils was carried out under either aerobic or anaerobic conditions, initially for 16 weeks and subsequently for a total of 52 weeks. Experiments were also conducted using biometer flasks, in order to measure the output of radio-labelled carbon dioxide. In the case of the cis-isomer, the main degradation products extracted from the soils were PBA, cis-CPA with small amounts of trans-CPA, and limited amounts of the 4-hydroxy derivative of cypermethrin. Between 25% and 30% of the added radioactivity could not be extracted with acetonitrile/water. A similar spectrum of degradation products was extracted in the trans-isomer experiments, except that the cis-isomer was absent. Some of the remaining radioactivity was identified in a further degradation product of CPA, the dicarboxylic acid.

A further study was undertaken by Roberts & Standen (1981) in which ring-labelled cis- and trans-isomers of CPA were added to a sandy loam soil at 2.5-13.5 mg/kg. In most cases, the soils were contained in loosely stoppered vessels but, in one experiment, a biometer flask fitted with a caustic potash trap was used, in order to measure carbon dioxide (CO_2) production. In spite of the production of labelled CO_2 in the initial study with cyclopropyl-labelled cypermethrin, very little was produced in the latter study and most of the radioactivity was shown to be still present in the soil. At the end of the 8-week exposure period, it was found that the greater part of the radioactivity in the soil was still associated with unchanged CPA, 33%-65% in the case of the trans-acid and 78% in the case of the cis-acid. There was

also evidence that some of the trans-CPA was transformed to the cis-isomer, but not vice-versa. This finding was analogous to that with the parent compound where a certain amount of cis-CPA was produced from trans-cypermethrin.

A similar series of studies was carried out by Sakata et al. (1986) who incubated 2 Japanese soils with the 1R cis-RS alpha and 1R trans-RS alpha isomers of cypermethrin for up to 168 days at 25 °C. While ester cleavage was the principal pathway of degradation, limited production of the amides of the intact esters and production of the 4-hydroxy derivatives (on the phenoxy group) were also reported. The latter were often present in greater amounts than the PBA or CPA fragments. The authors also reported the presence of small amounts of the desphenoxy derivative derived from ether cleavage, not previously reported for cypermethrin. However, the level of ^{14}C associated with extractable breakdown products was low (1-17% of the amount initially added, at 56 days) compared with that of bound radio carbon (14-58% at 56 days), the actual levels being very dependent on the type of soil under study. Since the trans-isomers degraded more readily than the cis-isomers and since the level of free degradation products was considerably lower for the trans- than the cis-isomers, it is possible that a substantial proportion of the bound radio carbon had reverted to the general carbon pool of the soil organic matter. A major proportion of the added label was recovered as carbon dioxide (16-48% at 56 days) and the amount was highest when the label was on the benzyl carbon, indicating, as Roberts & Standen had found, that the PBA was mineralized more readily than the CPA. Sakata et al. also found that, under comparable circumstances, the cis-isomers produced carbon dioxide more slowly than the trans-isomers.

The principal degradation products in soils, prior to breakage of the benzyl and cyclopropane rings, are shown in Fig. 2.

4.3.3 Rates of degradation

4.3.3.1 Laboratory studies

(a) Separate isomers

In the laboratory studies carried out by Roberts & Standen (1977, 1981), the half-lives of the cis-isomers were around 4 weeks, except in the inactive Los Palacios soils, where the figure was nearer to 10-12 weeks. The trans-isomer generally exhibited a much shorter half-life of less than 2 weeks and less than 4 weeks on the less active soil. After a year, the amounts of unchanged material left in the soils were very low

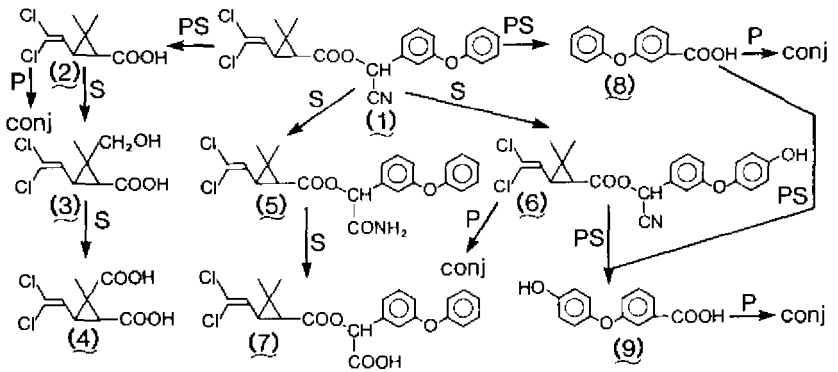


Fig. 2. Metabolic and degradation pathways of cypermethrin in plants and soils.
P = plant, S = soil, conj = sugar conjugate.

and nearly always below 10% of the amount applied. But, even at the low levels remaining after such a long interval, residues of the trans- were still substantially less than those of the cis-product.

Sakata et al. (1986) in their incubation studies reported half-lives of between 4.1 and 17.6 days for trans-cypermethrin and 12.5 and 56.4 days for the cis-isomer, under aerobic upland conditions. Degradation was much slower in one of the soils than in the other, as was also shown by Roberts & Standen (1977, 1981). Miyamoto & Mikami (1983) reported data on the half-lives in soil incubation tests for all 4 of the 1R isomers of cypermethrin. The alpha S isomers of both cis- and trans-isomers degraded much more rapidly than the alpha R isomers, sometimes nearly twice as fast. Again, the cis-isomers were slower to degrade than the trans-isomers. The greater readiness of the trans-isomers to degrade has been observed extensively by other workers, i.e., Kaufman et al. (1978), Chapman et al. (1981), Chapman & Harris, (1981), Harris et al. (1981). The Japanese studies did not produce data for the 1S isomers, but Chapman & Harris did not detect appreciable differences between the rates of degradation of the 1R and 1S isomers, either trans or cis. On the other hand, Harris et al. (1981) reported a substantial decrease in the 1S/1R ratio for trans-cypermethrin, as degradation in the soil proceeded suggesting that, in these studies, the 1S trans-isomers degraded more quickly than the 1R trans-isomers.

4.3.3.2 Field studies

(a) Cypermethrin, and separate isomers

Roberts & Standen (1981) showed that the rates of degradation of cypermethrin observed in the laboratory and in the field did not differ greatly. On the basis of their data, 2-4 weeks in the growing season would appear to be a typical half-life for the parent racemic cypermethrin, bearing in mind that the half-lives of the cis-isomers were often approximately twice those of the trans-isomers.

Shorter half-lives of less than 2 weeks on a mineral soil and about 3 weeks on a peat soil were reported by Chapman & Harris (1981). Harris et al. (1981) reported a half-life for cypermethrin in Plainfield sand of about 2.5 weeks. The persistence of the insecticidal activity of surface applications of cypermethrin, as measured by toxicity for cutworms was studied by Cheng (1984). Although these data cannot be expressed in terms of the half-life of cypermethrin, it is interesting to note that initial applications, giving 100% mortality, were only producing about 50% mortality after 12 days.

However, Chapman & Harris (1981) warned that a simple half-life expression was not necessarily a valid way of defining the rates of degradation of cypermethrin, because these tend to decrease with time. A possible explanation for this effect is that there is a gradual increase in the proportion of cis-isomers in the residues. Since these degrade more slowly, overall degradation rates are bound to decrease with time. But the results of Harris et al. (1981) cast doubt on whether this change in isomer ratio provides the sole explanation. These authors reported that, in their studies, the ratio of cis- to trans-isomers increased during the early part of their studies, but decreased substantially afterwards.

Chapman & Harris (1981) also reported that the degradation was slowed down by high soil contents of organic matter or clay (c.f., the slow rates of degradation reported by Roberts & Standen (1977, 1981) on the very high clay soil, Los Palacios) and by anaerobic conditions. Contrary to what might be expected in light of the behaviour of other pesticides, they reported that cypermethrin degraded more quickly on dry than on wet soils. They also identified the level of cypermethrin in the soil as a very important factor. Thus, degradation, expressed on a proportionate basis, was 2-3 times slower with an initial concentration in the soil of 10 mg/kg, than that with an initial concentration of 0.5 mg/kg. Kaufman et al. (1978) also reported faster degradation with lower rates of application.

(b) Metabolites

In studies on the 2 metabolites (PBA and CPA), Roberts & Standen (1977, 1981) reported that PBA was quicker to degrade than CPA.

In the Leiston soil, only about 2% of applied radioactivity was recovered as PBA after 16 weeks, though in the soil from Los Palacios, the figure was just under 30% for the soil treated with cis-cypermethrin and some 50% for the soil treated with trans-cypermethrin. The higher figure for PBA derived from trans-cypermethrin was, presumably, due to the more rapid rate of degradation of this parent isomer.

The degradation of PBA is an oxidative process and, under anaerobic conditions, its degradation was greatly retarded (Roberts & Standen, 1977).

The data of Roberts & Standen (1977) on CPA showed that, in Brenes soil treated with the parent cypermethrin cis-isomers, radioactivity recovered as CPA reached a maximum (about 17% of the total radioactivity initially added) at the 8th week. The maximum level of CPA from the trans-cypermethrin was reached at about the same time, but constituted nearly 50% of the radioactivity originally applied. Moreover, by the 52nd week, whilst CPA from the cis- product had practically disappeared, there was still a residue of CPA from the trans-isomers, equivalent to some 10% of the radioactivity originally applied.

The rate of decay of the unextractable radioactivity in soils previously treated by Roberts & Standen (1977) with labelled cypermethrin, as described above, was studied by incubating some of the soils (Brenes & Leiston soils) for a further 26 weeks in admixture with fresh soil. Substantial additional losses of radio carbon were observed. At the end of this time, 25-45% of the "bound" radioactivity initially present was lost. Perhaps unexpectedly, the losses from cypermethrin labelled in the cyclopropyl ring was almost double that from product labelled in the benzyl ring. It is clear from these studies that the binding of residues of breakdown products did not prevent their continued degradation. Although some of the evidence of Roberts & Standen relating to the rate of degradation of CPA itself appears to be anomalous, it can be inferred that cypermethrin degrades rapidly in the soil and that the subsequent degradation products are mineralized, as shown by the liberation of labelled carbon dioxide from cypermethrin labelled in either the cyclopropyl or benzyl rings. As Miyamoto (1981) concluded, there appears to be little likelihood of cypermethrin or its metabolites persisting for lengthy periods in soils.

4.4 Degradation in Water and Sediments

4.4.1 Laboratory studies

(a) Cypermethrin and separate isomers

Camilleri (1984), using 10^{-5}mol/litre solutions of the cis-2 isomer pair of enantiomers in dioxan-water, showed that, at alkaline pH values, cypermethrin is readily degraded by ester cleavage to give CPA and PBA. The alternative route of degradation, hydrolysis of the cyano group to amide, required a much higher energy of activation and could not be detected.

Takahashi et al. (1985a) demonstrated the effects of pH on the hydrolysis of 1R cis- or 1R trans-cypermethrin in abiotic buffered aqueous solutions. At acidic pH values, the half-life of the isomers was one or more years, but it was appreciably shorter at pH 7 and had fallen to a matter of minutes at pH 11 (all at 25 °C). In natural waters, sterilized by filtration and having a pH of about 8, the half-life was about 3 weeks at 25 °C. The trans-isomers were hydrolysed more readily than the cis-isomers.

The fate of cypermethrin under biotic conditions, simulating those in rivers and ponds, was studied by Rapley et al. (1981) using a radio-labelled product, with the label in either the cyclopropyl or benzyl ring. Samples of water and sediments from 3 rivers and a pond were used in a laboratory experiment in which mixtures of water and sediment were placed in pairs of glass cylinders. The insecticide was added at a rate equivalent to 140 g/ha and the vessels incubated at 16 °C for up to 60 weeks, periodic determinations being made of the level of cypermethrin remaining and the amount of labelled CO_2 evolved. One series of vessels was aerated and the other left undisturbed. Degradation was rapid in all cases, even in the non-aerated series. Some 50% of cypermethrin was lost in less than 2 weeks and 90% within 2-9 weeks. After approximately one year, 40-70% of the ^{14}C label from the benzyl-labelled material was lost as $^{14}CO_2$, but only 4% from the cyclopropyl-labelled material, though this proportion rose to 10% after 63 weeks. In the case of the cyclopropyl-labelled material, the main degradation product detected was CPA with a small amount of dicarboxylic acid. Subsequent degradation of the CPA was slow. When the label was in the benzyl ring, the main product was PBA though, in the sediment, precursors (aldehyde and to some extent the alcohol) were the most prominent, possibly because aeration was defective.

Muir et al. (1985) studied the behaviour of cis- and trans-cypermethrin isomers, labelled with ^{14}C in the cyclopropyl ring, in 3 bottom sediments (sand, a river silty clay, and a pond bottom clay). In each case, 0.064 or 0.64 mg

of the trans-isomers/kg or 0.012, 0.017, or 0.17 mg of the cis-isomers/kg was added to the sediment. Each sediment was covered with dechlorinated tap water and allowed to equilibrate for 24 h. The system was sampled at 6 and 24 h and the level of radioactivity determined in the sediment, pore water from the sediment (in a separate study), and in the supernatant water. The radioactivity was much less strongly absorbed on sediment treated with the trans-isomer than on that treated with cis-isomer, indicating that a substantial proportion of the radioactivity was associated with degradation products rather than with the parent compound, because it is unlikely that major differences in adsorption between the cis- and trans-isomers of the parent molecule would have been noticed.

4.4.2 Field Studies

(a) Cypermethrin

Crossland (1982) studied the effects of deliberately overspraying experimental ponds with cypermethrin at the rate of 100 g/ha. Water was sampled either from the surface (2.5-10 cm) or from a depth of 50 cm. Approximately 4 h after treatment, the concentration of cypermethrin in the surface was 0.1 mg/litre, but it fell to about a tenth of this value in 24 h. By 13 days, the surface concentration had fallen to 0.0007 mg/litre. Concentrations at a depth of 50 cm rose to a plateau of 0.0023-0.0026 mg/litre, 4 h after treatment, and then started to fall. By 13 days after treatment, the concentration had decreased to 0.0009 mg/litre. Residues were also found in the sediment at the bottom of the pond; these reached a concentration of 0.006 mg/kg by the thirteenth day.

In a second study with similar treatment, a procedure for surface sampling was introduced that enabled water films of only 0.05 mm to be sampled. In this extremely thin surface film, the initial concentration reached 24 mg/litre. There was a very rapid fall to around 50 µg/litre after the first week, and by the third week, none could be detected (the limit of determination was 1-2 µg/litre). In the subsurface water, where the limit of determination was only 0.1 µg/litre, concentrations reached 1 µg/litre shortly after treatment but fell rapidly to about a fifth of this value by the end of the first week. By the end of the fourth week, the concentration was below the limit of determination. Sporadic amounts were found in the sediments, but most had disappeared by the end of the study (16 weeks).

The effects of overspraying ponds or streams adjacent to arable fields in the United Kingdom and of treating vineyards in France with cypermethrin were studied by Crossland et al.

(1982). The fields in the United Kingdom were treated with a tractor-drawn sprayer at the rate of 70 g/ha and the French vineyards with mistblowers at the rate of 30-45 g/ha. One objective of this work was to determine the possible occurrence of the insecticide in the water as a result of spray drift from the treated areas. In the United Kingdom study, deposits on the soil where the spray had been applied were in the range of 4-7 mg/m^2, but those on the surface of the water of the adjacent pond were 4-5 orders of magnitude less. The concentration of cypermethrin in the surface layer of water (0.06 mm) was between 6 and 20 µg/litre but, after 24 h, only one of the 14 surface samples showed any cypermethrin, the concentration in this sample being 6 µg/litre. Residues in the subsurface layers reached between 0.01 and 0.07 µg/litre after 5 h but then declined; after 24 h, levels in most samples were below the limit of determination (0.01 µg/litre) with only the occasional sample reaching 0.03 µg/litre.

In the French vineyards, deposits on the surface of the water were considerably higher (0.04-0.5 mg/m^2). Concentrations in the surface water were initially between 0.14 and 1 mg/litre falling to 0.02 mg/litre within 3 h. Even in the subsurface samples, concentrations of up to 2 µg/litre were occasionally reached, but they fell rapidly and had generally decreased to 0.1 µg/litre or less within a few hours.

Further experiments along similar lines were carried out by Shires & Bennett (1985) who used a fixed wing aircraft to apply cypermethrin at 25 g/ha to a large field of winter wheat that was bordered on 3 sides by drainage ditches.

The deposit on the land was about 60% of the nominal rate of application, while on the water it was only about a tenth of this value (equivalent to 1.5 g/ha). Analysis of subsurface water showed that any spray drift reaching the ditches resulted only in very low levels ranging from below the level of determination of 0.01 µg/litre to a maximum of 0.03 µg/litre. By the fourth day, none could be detected.

It appears unlikely that spray drift during properly conducted spray operations will give rise to high concentrations of cypermethrin in adjacent surface waters. It is also evident that if cypermethrin residues do occur in natural waters, they are relatively short lived.

4.5 Bioaccumulation and Biomagnification

4.5.1 n-Octanol/water partition coefficient

In common with those of other synthetic pyrethroids, the n-octanol/water partition coefficient of cypermethrin is high; a value of 2×10^6 (log P_{ow} = 6.3) was obtained by

extrapolation from chromatographic data (Gray & Grayson, 1980). McLeese et al. (1980) reported a calculated log n-octanol/water partition coefficient of 2.44.

4.5.2 Bioaccumulation in fish

The accumulation by fish of cypermethrin from water and its subsequent elimination have been studied. In a preliminary study, rainbow trout were exposed to ^{14}C-benzyl-labelled cypermethrin in water at 14 °C for a period of 22 days. The initial concentration each day of 0.165 µg/litre decreased over the 24-h period to 0.064 µg/litre. Radioactivity in whole fish rose to a plateau equivalent to 0.083 mg cypermethrin/kg wet weight after approximately 11 days. During the steady state, at least 67% of the radioactivity was unchanged cypermethrin, but unidentified materials were also present. When the fish were transferred to clean water after 22 days, the concentration of radioactivity decreased to half the plateau level in about 11 days. According to this study, allowing for the cyclical nature of the exposure concentration, the best estimate of the accumulation factor is approximately 1000 (Baldwin & Lad, 1978b).

In a follow-up study, 2 groups of rainbow trout of different sizes were exposed to steady, low concentrations of unlabelled cypermethrin in a continuous-flow system. When exposed to a mean concentration of 0.19 µg cypermethrin/litre, residues in small trout (2-13 g) increased rapidly to approximately 0.15 mg/kg wet weight over 10 days and 0.23 mg/kg wet weight in 10-18 days. After 18 days, the fish were placed in clean water and depuration followed. Using a one-compartment mathematical model, it was calculated that the bioaccumulation factor at equilibrium was 1200. The calculated depuration half-life was approximately 8 days. In the larger trout (130-160 g), exposed to a mean concentration of 0.18 µg cypermethrin/litre in a continuous-flow system, the uptake was slower, and residues in whole fish reached 0.12 mg/kg wet weight after 24 days. Cypermethrin residues in fish were fairly uniformly distributed (mean values 1-2 mg/kg tissue), when expressed on a lipid-weight rather than a wet-weight basis, except that the brain contained lower residues than the other tissues (Bennett, 1981a).

Rainbow trout and common carp were exposed to cypermethrin concentrations of 0.4-1.9 µg/litre in a continuous-flow study for up to 21 days. It was found that residues in both species were very similar on a wet- and on a lipid-weight basis, but that there was only a small difference in residue burden between the fish that died and those that survived. The mean residue concentrations (mg/kg tissue) for trout and

carp were respectively: 0.91 (died) and 0.67 (survived), 0.68 (died) and 0.72 (survived), on a wet-weight basis and 44 (died) and 29 (survived), and 43 (died) and 25 (survived) on a lipid-weight basis, (Bennett, 1981b).

McLeese et al. (1980) studied the concentration factors for cypermethrin in salmon from various toxicity tests. The results are given in Table 4.

Table 4. Concentration factors for cypermethrin in salmon[a]

Concentration in water (µg/litre)	Exposure time (h)	Concentration fish (mg/kg)	CF[b]
12	12	0.04	3.5
7.8	21	0.02	2.6
3.0	62	0.02	6.7
1.4	96	0.01	7.1

[a] From: McLeese et al. (1980).
[b] CF = Concentration in fish/concentration in water.

The low CFs for cypermethrin may indicate rapid metabolism and elimination of the compound by salmon.

Accumulation of cypermethrin by fish exposed under field conditions was studied in rudd taken at various time intervals from a pond treated with 100 g cypermethrin a.i./ha (Table 5).

Table 5. Residues of cypermethrin in rudd and water from a pond treated at 100 g active ingredient/ha

Time after treatment	Concentration of cypermethrin in:	
	subsurface water (µg/litre)	rudd (µg/kg wet weight) (individual values)
1 day	1.0	50 and 41
1 week	0.21	45 and 49
2 weeks	0.06	42 and 65
4 weeks	0.01	26 and 30
8 weeks	0.01	19 and 5
16 weeks	-	5[a]

[a] Average of 8 fish.

These results show a rapid uptake of cypermethrin in the fish followed by elimination from the fish as the compound is lost from the water in the pond system. In such a dynamic situation, it is not possible to give a definite accumulation factor (Crossland et al., 1978).

In view of the very low concentrations of cypermethrin that are likely to arise in water from normal agricultural use and the rapidity with which concentrations decline, fish in the wild will not contain measurable residues of cypermethrin, in spite of the concentration factors reported.

4.5.3 Bioaccumulation in aquatic invertebrates

Muir et al. (1985) studied the accumulation of cypermethrin in sediment-dwelling larvae of the midge Chironomus tentans. These were allowed to establish themselves in the sediments or were kept suspended in the water under the conditions of the study described in section 4.4.1. Bioaccumulation factors were calculated for both the water and sediment larvae; these varied from 43 to 245 for the trans-compound and from 34 to 385 for the cis-, expressed as the ratios of total radioactivity per gram of larvae to that per ml of water.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental Levels

5.1.1 Air

No data are available.

5.1.2 Water

No data are available.

5.1.3 Soil

See section 4.3.

5.1.4 Food

Cypermethrin is used to control insect pests on a very wide range of crops, and residues of the parent compound can sometimes be found in agricultural commodities from treated crops. Foods of animal origin can also contain limited residues arising either from the use of the product for the control of ectoparasites or from the occurrence of residues in the animal feed.

5.1.4.1 Residues in food commodities from treated crops

A large body of information on the levels of residues arising in crop commodities where cypermethrin has been used according to Good Agricultural Practice (GAP), was available to the Task Group. The data had already been comprehensively reviewed by the FAO/WHO Joint Meeting on Pesticide Residues and summarized in their published Monographs of the meetings in 1979, 1981, 1982, and 1984. (FAO/WHO 1980b, 1982b, 1983b, and 1985c). As a consequence of their reviews, the JMPR were able to propose a series of Maximum Residue Limits (MRLs) for cypermethrin in a wide range of food commodities (treated according to GAP) below which the actual residue levels would be expected to fall. They range from 0.05 to 2 mg/kg. These MRLs are now at various steps in the Codex procedure and many have already been fully adopted by the Codex Alimentarious Commission, shown as step "CLX" in Table 6 (Codex Alimentarius Commission, 1986).

Dried tea is an exception to this range of levels in food commodities in that the level proposed is 20 mg/kg, but it was shown that only 0.1% of the residues in dried tea enter the infusion so that the brew, as drunk, will only contain negligible amounts (FAO/WHO 1985b). Cereal straws also fall

Table 6. Codex limits for cypermethrin residues in treated crops

Crop	MRL (mg/kg)	Step
Brassica leafy vegetables	1	CLX
Citrus	2	CLX
Lettuce	2	8
Oil seeds except peanuts	0.2	8
Peas	0.05	CLX
Root and tuber vegetables	0.05	CLX
Tomatoes	0.5	CLX
Wheat grain	0.2	8

outside this range in that the MRL is 5 mg/kg, but these are not foodstuffs.

In addition to these data, limited information on residues have been published by Lauren & Henzel (1977), Braun et al. (1982), Frank et al. (1982), and Awasthi & Anand (1983).

Research has also been carried out on the fate of residues in stored grain treated experimentally (Joia et al., 1985b; Noble & Hamilton, 1985). Residues proved to be relatively persistent and a knowledge of storage times and conditions would be required to estimate the levels that would occur in the grain trade, should this use of cypermethrin become accepted practice.

5.1.4.2 Residues in food of animal origin

Residues of cypermethrin can arise in foods of animal origin (milk or milk products, eggs, meat or meat products), either from topical application to livestock for the control of ecotoparasites or from residues in livestock rations. In the USA, the actual residues in meat and milk are expected to be less than the tolerances of 0.05 mg/kg per litre product (US EPA, 1984). By referring to available residue data, the JMPR was able to propose MRLs for carcass meat and meat products, eggs, and milk. Subsequently, the following Codex Limits (CLXs) were established (Codex Alimentarius Commission-1986) (Table 7).

Table 7. Codex limits for cypermethrin residues in foodstuffs

Commodity	Maximum Residue Limit mg/kg
Carcass meat (carcass fat)	0.2
Meat products	0.2
Eggs	0.05
Milk (whole milk)	0.01

5.2 General Population Exposure

Taking into consideration: (a) the levels of cypermethrin residues that may occur in food commodities from crops or in foods of animal origin, where cypermethrin has been used according to GAP; (b) the contribution of the relevant commodities to the diet; and (c) the losses that occur during the processing of these commodities, it can confidently be inferred that the daily intake of cypermethrin in the human diet will be well below the officially adopted Acceptable Daily Intake. However, no total diet or market basket studies are available.

5.3 Occupational Exposure

See section 9.2.2.

6. KINETICS AND METABOLISM

6.1 Absorption, Excretion, and Distribution

6.1.1 Oral

6.1.1.1 Rat

(a) Cypermethrin mixture

Three rats of each sex were given a single oral dose of 0.5 mg (approximately 1.2 mg/kg body weight for males and 2.1 mg/kg body weight for females) of a cis/trans mixture of ^{14}C-cyclopropyl-labelled cypermethrin. Three days after dosing, low concentrations of radioactivity were found for both sexes in the kidneys, muscle, brain, and blood. The level in the liver of male rats was 3 times higher than that in the liver of female rats (0.37 and 0.12 mg/kg tissue, respectively). The residues in the fat of the female rats were 2-3 times higher than those in the male rats (0.72 and 0.31 mg/kg tissue respectively). Concentrations in muscle, brain, and blood were < 0.05 mg/kg. The mean percentage recovery of the administered dose was more than 100% (Crawford, 1977; Crawford et al., 1981a).

Urinary excretion of the compound was rapid in both sexes; approximately 50-65% of the dose being excreted in 48 h. Elimination via the faeces was slower, the mean rate being approximately 30% of the dose in 3 days. The amount of radioactivity excreted via expired CO_2, measured in a separate study using one rat of each sex, was up to 0.1% of the dose in 15 days.

Studies with ^{14}C-cyclopropyl-labelled cypermethrin indicated that biliary excretion of the cyclopropyl moiety is a minor route of elimination (up to 2% in 4 h) (Crawford et al., 1981a).

The metabolism of cypermethrin in maize oil was studied in male and female Wistar rats following a single toxic oral dose of 200 mg/kg body weight of 2 radio-labelled forms (^{14}C-benzyl and ^{14}C-cyclopropyl) of the insecticide. Minimal amounts of $^{14}CO_2$ were expired from both types of labelled cypermethrin: viz < 0.005-0.06% of dose. The elimination of radioactivity within 7 days was 29-33% (^{14}C-benzyl label) and 41-56% (^{14}C-cyclopropyl label) in the urine and 55-59% and 34-46%, respectively, in the faeces. The differences between the sexes were small (Rhodes et al., 1984).

The distribution and tissue retention of cypermethrin was studied in 5 male and 5 female Wistar rats receiving daily oral doses of 2 mg (^{14}C-benzyl)-labelled cypermethrin/kg body weight for 28 days. Consistent with the lipophilic

nature of cypermethrin, the highest mean tissue concentration was found in the fat (4.1 mg/kg in males and 5.1 mg/kg in females). Concentrations in the liver, kidneys, adrenals, gut, ovaries, and skin were of the order of 0.4-0.9 mg/kg tissue. Small amounts of radioactivity (0.04-0.07 mg/kg) were detected in the muscle, spleen, and bone. Negligible concentrations (< 0.01 mg/kg) were detected in the brain (Rhodes et al., 1984). In a further study, the tissues identified as containing the highest concentrations of ^{14}C-benzyl-labelled cypermethrin (fat, liver, kidneys, skin, and ovaries) as well as whole blood and plasma were used to study the extent of accumulation and rate of elimination of cypermethrin. A total of 60 female rats were dosed orally with ^{14}C-benzyl-labelled cypermethrin at 2 mg/kg body weight per day, for up to 70 consecutive days. Levels in all tissues reached a plateau after 56 days of dosing. The extent of accumulation, expressed as mg equivalents of cypermethrin per kg tissue, was: fat, 3.91; liver, 0.97; kidneys, 0.69; ovaries, 0.03; skin, 1.89; whole blood, 0.35; and plasma 0.64. Analysis of fat samples, 24 h after the final dose, revealed that higher levels of the cis-isomer of cypermethrin had been retained than of the trans-isomer. The rate of elimination of radioactivity from fat was biphasic in nature, with rapid elimination of trans-cypermethrin (half-life = 3.4 days) and slower elimination of the less-readily hydrolysed cis-cypermethrin (half-life = 18.9 days). Levels of ^{14}C residues in the liver, kidneys, and blood reached control background levels within 29, 8, and 15 days, respectively, of the final dose. Apart from fat, the only other tissue that contained radioactivity was the skin; the rate of elimination of radioactivity from the skin was similar to that for fat. Accumulation in the sciatic nerve was also studied in rats dosed for 26 days. No appreciable bioaccumulation was found to occur (Jones, 1981; Rhodes et al., 1984).

Three Wistar rats of each sex, given a single oral dose of (^{14}C-cyano)-cypermethrin (4.3 mg/kg body weight), eliminated 30-66% of the dose in the faeces over 3 days. Urinary excretion of ^{14}CN-label was slow, accounting for 6-12% of the dose and elimination of expired $^{14}CO_2$ accounted for only 1.2-1.5% of the dose. Tissue retention in major organs apart from fat, was higher than that in similar studies involving ^{14}C-benzyl or ^{14}C-cyclopropyl labelling, thus reflecting metabolism typical of the ^{14}C-labelled cyanide moiety (Crawford et al., 1981a).

(b) Separate isomers

The fates of both cis- and trans-isomers have been studied separately. Groups of 3-6 Wistar rats of each sex were given

single oral doses (approximately 2.5 mg/kg body weight) of either the cis-isomer or the trans-isomer, both ^{14}C-labelled in the benzyl ring. Both isomers were rapidly eliminated. The greater part of the administered dose was excreted in the urine; 40% and 60% for males and females, respectively, of the cis-isomer and 70% and 80% of the trans-isomer within 48 h. Elimination of the cis-isomer in the faeces amounted to 26% and 48% for male and females, respectively; elimination of the trans-isomer was 24%. The results for the cis-isomer show a clear sex difference in the route of elimination. After 72 h, less than 5% of the administered dose of either isomer remained in the animal tissues with the exception of the intestines and skin. Fat and skin contained the highest concentrations (Crawford, 1976a,b; Crawford et al., 1981a). It has been demonstrated (Crawford & Hutson, 1977a, Crawford et al., 1981a) that the residue derived from cis-cypermethrin is eliminated more slowly from fat than from other tissues. In one study, 8 female rats were given (^{14}C-benzyl)-cis-cypermethrin at 2.5 mg/kg body weight orally, and elimination of radioactivity was measured in fat samples from 8 up to 42 days after dosing. The radioactivity was calculated to have a half-life of 11.7 (3.4-16.7) days. Ninety to 100% of the radioactivity still remaining in the fat at 25 days was present as unchanged cypermethrin. The residues in the liver and kidneys were much lower than those in the fat but were eliminated at a similar rate (Crawford et al., 1981a).

6.1.1.2 Mouse

(a) Separate isomers

Elimination of radioactivity was measured in male Swiss-Webster mice, dosed once orally with cis- or trans-cypermethrin, ^{14}C-labelled in either the benzyl (8 mg/kg body weight) or cyclopropyl (7 mg/kg body weight) moiety. The ^{14}C-benzyl-dosed mice eliminated 22% and 34% of the administered dose of cis-isomer in the urine and faeces, respectively, in one day; values for the trans-isomer were 41% and 16%, respectively. The ^{14}C-cyclopropyl-dosed mice eliminated 20% of the administered dose of cis-isomer in the urine and 50% in the faeces in one day; the values for the trans-isomer were 55% and 16%, respectively. Thus, radioactivity from the trans-isomer was mainly eliminated in the urine and that from the cis-isomer in the faeces. The ^{14}C-benzyl-treated mice were killed 1, 3, or 8 days after dosing; the ^{14}C-cyclopropyl-treated mice, 3 days after dosing. Residues of radioactivity from both labels, 3 days after dosing, were low in all tissues except for the fat. The sequence of the residues in different organs was fat > liver

≈ kidneys > blood ≈ muscle > brain. Residues fell rapidly during the ^{14}C-benzyl study, with the exception of the residues derived from the cis-isomer in fat, which did not decrease during the study period (Hutson, 1978a; Hutson et al., 1981). However, in a further study, radioactivity was measured in fat samples from 10 male mice taken up to 42 days after a single oral dose of approximately 8.8 mg/kg body weight (^{14}C-benzyl)-cis-cypermethrin. The residue was eliminated exponentially with a half-life of 13.1 (3.6-18.4) days. At 8 and 22 days after dosing, approximately 90% of the radioactivity present in two pooled fat samples was attributable to unchanged cis-cypermethrin (Crawford & Hutson, 1978; Crayford et al., 1980; Hutson et al., 1981).

6.1.1.3 Dog

(a) Cypermethrin mixture

Two male beagle dogs were given single oral doses of (^{14}C-cyclopropyl)-cypermethrin at 2 mg/kg body weight (Crawford, 1979a). Elimination of labelled material was rapid in both dogs, though a variable distribution between urine and faeces was observed between the 2 dogs, i.e., 21 and 57% in urine and 78 and 48%, respectively, in faeces. In a further study, one dog was dosed orally with (^{14}C-benzyl)-cypermethrin at 2 mg/kg body weight (Crawford, 1979b). Over 4 days, 80% of the radioactivity was recovered in the faeces and 11% in the urine. Analysis of tissues, 4 days after dosing, revealed that the gall bladder (1.5 mg/kg tissue) and renal fat (0.3 mg/kg tissue) contained the highest levels of radioactivity expressed as cypermethrin. Negligible amounts were detected in the brain (0.006 mg/kg tissue) and sciatic nerve (0.09 mg/kg tissue). In the liver, adrenals, bone marrow, pituitary gland, and mesenteric fat, levels of cypermethrin of 0.1-0.2 mg/kg tissue were found.

(b) Separate isomers

Administration of (^{14}C-benzyl)-cis-cypermethrin or (^{14}C-benzyl)-trans-cypermethrin separately to groups of 2 male dogs as a single (2 mg/kg body weight) oral dose resulted in 83.4% of cis-isomer and 88% of trans-isomer being recovered in the urine plus faeces over 6-7 days (Crawford, 1979b). Quantitative differences existed between the amounts eliminated via the 2 routes. As already mentioned, a variable distribution was found. These data are consistent with the results of the study involving ^{14}C-cyclopropyl-labelled cypermethrin (Crawford, 1979a), and the variation in amounts according to the route of elimination probably reflects the

inter-group differences in rates of absorption of labelled material.

6.1.1.4 Cow

Three studies were carried out on lactating cows fed diets containing 0.2, 5, or 10 mg ^{14}C-benzyl and/or ^{14}C-cyclopropyl-cypermethrin/kg feed, respectively, twice daily, for 7 or 21 days. The estimated daily intake was 2, 50, or 100 mg cypermethrin/cow. The radioactivity was rapidly eliminated following ingestion. Equilibrium between ingestion and elimination was reached after about 4 days. The amounts eliminated via the major routes were similar for both labels, i.e., approximately 50% in the urine, and approximately 40% in the faeces (mainly unchanged cypermethrin). Polar and acidic components were found in the urine. Up to 0.2% of the administered radioactivity was found in the milk, mainly in the cream phase (about 88%). Feeding 0.2, 5, or 10 mg/kg feed, the residues in the milk were 0.0006, 0.012, or 0.03 mg cypermethrin/litre, respectively. Radioactivity (expressed as mg cypermethrin/kg tissue) in the carcasses of the animals of the 3 groups at slaughter was not detectable in muscle and brain (< 0.001-< 0.04 mg/kg). Levels in other tissues were: blood < 0.04-0.07 mg/kg, liver 0.004-0.21 mg/kg, kidneys 0.003-0.11 mg/kg, and subcutaneous and renal fat 0.01-0.1 mg/kg (Croucher et al., 1985).

Swaine & Sapiets cf. FAO/WHO (1982b) dosed cows daily with 0.2, 5, or 50 mg cypermethrin (43% cis-isomers, 35% trans-isomers) per kg feed for up to 29 days. Residues in milk and tissues were comparable to those reported by Croucher et al. (1985).

6.1.1.5 Sheep

The elimination pattern in a single sheep, given one oral dose of a mixture consisting of unlabelled cypermethrin with ^{14}C-benzyl- and ^{14}C-cyclopropyl-labelled material (3.9 mg/kg body weight) in a gelatin capsule, showed that 41% of the administered dose was excreted in the urine and 20% was eliminated in faeces, within 48 h. Tissue residues, 2 days after treatment, were muscle, 0.04 mg/kg; and liver, kidneys, and renal fat approximately 0.4 mg/kg tissue (Crawford & Hutson, 1977b).

6.1.1.6 Chicken

^{14}C-phenoxy-labelled cypermethrin (cis:trans, 55:45) was administered orally to laying hens, daily for 14 days, at a rate equivalent to 10 mg/kg diet (about 0.7 mg/kg body weight).

Radioactivity in the eggs reached a plateau, equivalent to about 0.05 mg cypermethrin/kg, after 8 days. Most of the radioactivity was found in the yolk (up to 0.19 mg/kg) and about half of it was identified as cypermethrin. The rest was closely associated with neutral lipids and phosphatidyl cholines. Residues in the carcasses, at slaughter, were low; values were between 0.01 and 0.02 mg/kg in muscle tissue, about 0.08 mg/kg in the subcutaneous and peritoneal fat, and 0.37 mg/kg in the liver. The composition of residues in the liver was not conclusively established. Apart from small amounts of unchanged cypermethrin, the radioactivity was also associated with highly polar material. However, it is evident that the hen has a very effective mechanism for the metabolism of cypermethrin (Hutson & Stoydin, 1987).

Comparable results were obtained from non-labelled studies with laying hens in which dietary levels of up to 40 mg cypermethrin/kg diet were fed for 28 days (Wallace et al., 1982).

6.1.1.7 Man

Male volunteers were each given a single oral dose of 0.25, 0.5, 1, or 1.5 mg cypermethrin in corn oil in a capsule. Urinary excretion of cypermethrin metabolites was rapid. The subjects excreted an average 78% of the dose of trans-isomer and 49% of the cis-isomer within 24 h. These values did not differ from the results in rats. The ester cleavage was a major route of metabolism of cypermethrin in man. As reported in other animal species, the trans-isomer was metabolized more readily than the cis-isomer. Concentrations of both isomers excreted in the urine between 2 and 5 days after dosing 0.5 or 1 mg cypermethrin were below the limit of detection of 0.01 mg/litre (Eadsforth & Baldwin, 1983).

Groups of 2 male subjects were given cypermethrin in daily oral doses of 0.25, 0.75, or 1.5 mg/man, by capsule, for 5 consecutive days. During the dosing period and the following 5 days, 24-h urine samples were collected daily and analysed for the concentration of the cyclopropane carboxylic acid metabolite. The results showed that the respective percentages of the cis- and trans-isomers of cypermethrin, excreted in the 24-h period following each of the oral doses, were similar to the percentage excretion of these isomers measured in the single oral dose study. Therefore, no accumulation in the body occurred (van Sittert et al., 1985a).

6.1.2 Dermal

6.1.2.1 Cow

Two lactating cows were sprayed 3 times with 1.1 g cypermethrin/animal, with 2-week intervals between treatments. Milk samples were analysed during this period. Tissue samples were analysed approximately three weeks after the final spraying. The residues were: in whole milk, < 0.01 mg/litre; muscle, liver, and kidneys, ≤ 0.01 mg/kg tissue and in fat samples, 0.02 mg/kg tissue or less (Baldwin et al., 1977).

Comparable results were obtained when 2 barns were sprayed with either 0.05% or 0.1% of cypermethrin prepared from a 10% a.i. formulation. Cows were present during spraying. Milk was collected up to 4 weeks after spraying (0.05% application) or 4 days after spraying (0.1% application). Only the samples collected 4 days after the 0.05% treatment and 2 days after the 0.1% treatment contained detectable residues (0.005 mg/kg milk). No residues were found (≤ 0.002 mg/kg milk) in any of the other samples (Baldwin & Lad, 1978a).

Cows were dipped twice in approximately 170 mg cypermethrin/litre with a 10-week interval between treatments. The animals were sacrificed 4 or 14 days after the second dipping. Residues in muscle and liver did not exceed 0.01 mg/kg tissue. Fat samples contained detectable residues. The highest was 0.13 mg/kg in renal fat. The fat residue did not decline between 4 and 14 days after treatment (Baldwin, 1977a).

Cattle sprayed once with 0.1 and 0.2% a.i. showed the same level of residues (≤ 0.005 mg/kg tissue) in muscle, liver, and kidneys, and a level of < 0.01 mg/kg in fat samples, 1, 3, 8, and 15 days after treatment. In cattle treated twice, fat samples contained residues ranging from 0.01 to 0.05 mg/kg tissue (Bosio, 1979).

Many trials in which cows were sprayed with, or dipped in, cypermethrin solutions were carried out in Australia. The milk from cows sprayed with 0.1% cypermethrin did not contain any detectable residues. The highest residue (0.03 mg/kg) in butterfat was found one day after spraying. When the cows were dipped in a dipwash containing 75 mg cypermethrin/litre, residues in the milk determined 1, 3, and 7 days after dipping ranged from 0.01 to < 0.002 mg/litre. Omental fat contained the highest residue level (0.02 mg/kg) 3 and 4 days after dipping. Liver, kidneys, and muscle did not contain any detectable residues. A second dipping, 7 days after the first, did not cause any build-up of cypermethrin in the tissues of the cattle (FAO/WHO, 1982b).

Detectable residues of cypermethrin of up to 0.01 mg/kg butterfat were found in milk samples taken over 21 days from 5 of 10 cows wearing cypermethrin-integrated ear tags (Braun et al., 1985).

Taylor et al. (1985) found cypermethrin in the hair of cattle, in concentrations of up to 2.8 mg/kg, after application of impregnated ear tags.

6.1.2.2 Sheep

Two sheep were each treated dermally with a mixture consisting of unlabelled cypermethrin mixed with ^{14}C-benzyl- and ^{14}C-cyclopropyl-labelled material at 22 mg/kg body weight. The cypermethrin was slowly absorbed. Less than 0.5% of the dose was excreted in the urine within 24 h and only 2% over a 6-day period. Faecal elimination was also slow, 0.5% of the dose being eliminated in 6 days. Approximately 30% of the dose was recovered from the application area. Tissue residues, 6 days after treatment, were: muscle, 0.04; renal fat, 0.3; and liver and kidneys 0.12 mg/kg tissue (Crawford & Hutson, 1977b).

6.1.2.3 Man

A male subject was given a single dermal application of a ULV formulation of cypermethrin (50 mg cypermethrin in hexylene glycol/Shellsol AB) on the underside of the forearm. The majority of this application (35 mg) was removed from the skin after 4 h. Urine was monitored for residues of the acid metabolite [3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid] and its glucuronide, for a 96-h period after dosing. The metabolites were not detected over this period (Coveney & Eadsforth, 1982).

In a study by van Sittert et al. (1985b), 2 male volunteers were given a single dermal application of a ULV formulation, 25 mg cypermethrin in hexylene glycol/Shellsol A, on the underside of the forearm. An average of 53% of the original amount of cypermethrin applied was removed from the skin, 4 h after application. Approximately 0.1% was excreted as the urinary metabolite, cyclopropane carboxylic acid, during a 72-h period. Measurements were made using gas liquid chromatography - mass spectrometry, a method with a higher sensitivity and selectivity than gas liquid chromatography - electron capture detection, which was used in the previous study.

6.2 Metabolic Transformation

6.2.1 In vitro studies

In vitro studies on mouse liver homogenates have shown that ester cleavage is more extensive for the trans-isomer than for the cis-isomer. One µg of each of (1RS,trans)- and (1RS,cis)-cypermethrin was incubated with 2.2 ml of approximately 10% mouse microsome substrate at 37 °C for 30 min, under the following conditions: (a) tetraethyl pyrophosphate (TEPP)-treated microsomes (neither esterase nor oxidase activity); (b) normal microsomes (esterase activity); (c) TEPP-treated microsomes plus NADPH (oxidase activity); and (d) normal microsomes plus NADPH (esterase plus oxidase activity). Each esterase preparation hydrolysed about twice as much trans-cypermethrin as cis-cypermethrin. In contrast, cis-cypermethrin was metabolized more rapidly in an oxidation system than trans-cypermethrin. The major site of ring hydroxylation was the 4' position and the secondary site was the 5 position. The trans-methyl group was an important site of hydroxylation in the ester metabolites and cis-methyl oxidation was predominant in the ester-cleaved acid metabolites. The hydroxymethyl derivatives were further oxidized to the corresponding aldehydes and carboxylic acids.

3-Phenoxybenzaldehyde-cyanohydrin was detected as a minor metabolite. The preferred sites of hydroxylation were: with trans-cypermethrin, cis-methyl > 4' position > trans-methyl > 5 position; with cis-cypermethrin, trans > cis > 4' position > 5 position (Shone & Casida, 1978; Shone et al., 1979). With cis-cypermethrin, at least, cleavage of cypermethrin to cyanohydrin may result from both hydrolytic and oxidative mechanisms, since large amounts of the cleavage products were also evident in the oxidase system, which lacks esterase activity (Shono & Casida, 1978; Shono et al., 1979). However, at approximately 35-times higher substrate levels, the hydrolysis rate of cypermethrin isomers was depressed (Söderlund & Casida, 1977).

In studies on the metabolism of ^{14}C-cypermethrin by rat liver microsomes, the overall rates of metabolism of cis- and trans-cypermethrin were similar, though their metabolic routes differed. The cis-isomer was metabolized almost exclusively by an NADPH-dependent oxidative pathway to 4'hydroxy-cis-cypermethrin with subsequent oxidative ester cleavage. The predominant route for the metabolism of the trans-isomer was hydrolysis to the trans-acid by microsomal carboxylesterase (Crawford, 1979c). The in vitro esteratic capacity was determined in rat, rabbit, and human liver microsomes using p-nitrophenyl acetate and cypermethrin as substrate. The relative ability to hydrolyse cypermethrin was rabbit > man

> rat. Rabbit and rat microsomes metabolized the trans-isomer 6 times faster than the cis-isomer. Human microsomes showed a similar capacity for metabolizing both cis- and trans-isomers (Croucher et al., 1982a,b).

6.2.2 In vivo studies

The identification of the metabolites of cypermethrin has been studied in mice (Hutson, 1978b, Casida et al., 1979; Hutson et al., 1981), rats (Crawford & Hutson, 1977a; Casida et al., 1979; Hutson, 1979a,b; Crawford et al., 1981b; Rhodes et al., 1984), dogs (Crawford, 1979d,e), and cows (Swaine & Sapiets, 1980a,b; Croucher et al., 1985).

Overall, metabolism in these species is similar. Differences that occur are related to the rate of metabolite formation rather than to the nature of the metabolites formed. The only major differences between species relate to conjugation reactions.

Cypermethrin (both isomers) is metabolized via cleavage of the ester bond. The cyclopropane carboxylic acid moiety is mainly excreted as the glucuronide conjugate; hydroxylation of the methyl group occurs only to a limited extent (Crawford, 1979e; Rhodes et al., 1984). The 3-phenoxy-benzyl product of the ester hydrolysis is converted to PBA. The cyanide moiety is metabolized to thiocyanate (Hutson, 1979b). The PBA moiety is mainly excreted as a glutamic acid conjugate in the cow (Croucher et al., 1985), as a taurine conjugate (N-(3-phenoxy-benzoyl)taurine) in 2 strains of mouse (Hutson & Casida, 1978; Hutson, 1978b, 1979a; Hutson et al., 1981), and as a glycine conjugate in the rat and dog (Crawford & Hutson, 1977a; Crawford, 1979d) and in the sheep, cat, and gerbil (Huckle et al., 1981a). PBA is further metabolized (rat > mouse > dog) via the 4'-hydroxylation to 3-(4'-hydroxyphenoxy)benzoic acid and its sulfate conjugate (Crawford & Hutson, 1977a; Hutson, 1978b; Crawford, 1979d). Glucuronic acid conjugates of PBA and its 4'hydroxy derivative are the major urinary metabolites in the marmoset, rabbit, guinea-pig, and hamster. The rat was unique among the animal species tested in utilizing sulfuric acid for the conjugation of the 4'-hydroxy derivative (Huckle et al., 1981a). The major route of excretion for cypermethrin metabolites is via the urine; unchanged cypermethrin accounted for the majority of radioactivity found in faeces in radiolabel studies. The amount of cyclopropyl-radioactivity eliminated in the bile (1%) suggests that the biliary-intestinal-faecal route is of minor importance for this moiety (Crawford & Hutson, 1977a; Crawford, 1979e; Rhodes et al., 1984). Biliary excretion of PBA occurred as glucuronide and that of 4'-OH-PBA as ether and ester glucuronic acid conjugates. Very little was eliminated

in the faeces, indicating that the biliary glucuronides decompose and/or are enzymatically cleaved in the gastro-intestinal tract to the respective benzoic acids. The latter are subsequently reabsorbed and undergo further metabolism, principally to the sulfate ester, which is excreted in the urine (Huckle et al., 1981b). As already noted, the major urinary metabolite of cypermethrin in cows is N-(3- phenoxy-benzoyl)glutamic acid. This metabolite is also found in the organs and tissues with only a small quantity of unchanged cypermethrin. The residues in body fat consist mainly of cypermethrin. An unidentified polar metabolite, present in the liver and kidneys, is suspected of being a conjugate of 3-(4'-hydroxyphenoxy)benzoic acid. The small portion of radioactivity appearing in milk was associated with lipid components and consisted mainly of unchanged cypermethrin (Croucher et al., 1985). The metabolic pathway of cypermethrin is shown in Fig. 3.

As in other mammals, ester cleavage and elimination of the cyclopropyl acid moieties in the free and glucuronidated form is a major route of metabolism of cypermethrin in man (Eadsforth & Baldwin, 1983).

6.2.3 Metabolism of the glucoside conjugate of 3-phenoxy-benzoic acid

Studies have been carried out on rats on the metabolism of the glucoside conjugate of 3-phenoxybenzoic acid, which occurs occasionally as a metabolite in plants (Crayford, 1978). The results indicated that the rat hydrolyses the glucoside and then metabolizes the 3-phenoxybenzoic acid in virtually the same way as it would metabolize PBA liberated during the metabolism of cypermethrin.

The same conclusion was also reached by Mikami et al. (1985). During this study involving the metabolism of the glucoside conjugate of PBA, it was noticed that the skin and carcasses contained high residues (4-7% of the administered dose) of radioactivity. To characterize the metabolites of PBA in the skin and carcasses, rats were given (^{14}C-benzyl) 3-PBA in a single oral dose (0.8 mg/kg body weight) or a higher dose (totalling approximately 750 mg/kg body weight) for 7 consecutive days. Two components were identified in the skin: unchanged PBA and a mixture of 3-phenoxybenzoyl-dipalmitins. The components were present in the skin of the high-dose animals in the approximate ratio of 3:7 and in the carcasses at 9:1 (Crayford & Hutson, 1979, 1980).

6.3 Metabolism in Plants

Lettuce plants were sprayed outdoors with ^{14}C cypermethrin labelled in the cyclopropyl ring (Wright et al.,

1980; Roberts, 1981). The plants were sprayed twice, at a rate equivalent to 0.3 kg/ha, and harvested for analysis 21 days after the last treatment. Most of the residue was in the form of unchanged cypermethrin (33% of the total label present) and polar materials (54%), which were shown to be mainly conjugates of trans-CPA. One of these conjugates was identified as the β-D-glucopyranose ester. Evidence for this was obtained from studies on abscised cotton leaves. The acid, trans-CPA was shown to be readily converted into a mixture of the β-D-glucopyranose ester, an acidic derivative of this, and disaccharide derivatives, including the glucosyl arabinose ester and the glucosylxylose ester.

Small apple trees were grown in cages outdoors (Roberts, 1981) and the cis- or trans-isomers, labelled in either the cyclopropyl or the benzyl rings, were applied to either the leaves or fruit. In the leaves, it was shown that the main component of the residue was cypermethrin itself with smaller amounts of sugar conjugates that gave rise on hydrolysis to the 3-phenoxybenzyl alcohol, 3-phenoxybenzyl aldehyde, or PBA. A small amount of 4-hydroxy cypermethrin was also detected. There was also evidence that some 30% of the cis-cypermethrin was converted to the trans-isomer, though the conversion of trans- to cis- was not observed. Less extensive metabolism occurred in the apple fruit. More than 98% of the total label recovered was associated with the peel. Of this, up to 77% was cypermethrin. Small amounts of the other free compounds, together with polar compounds, were detected (Roberts, 1981).

Furuzawa et al. (1986) treated young cabbage plants in the greenhouse with known amounts of either cis- or trans-cypermethrin labelled in either the cyclopropyl or benzyl rings. After 42 days, 4-6% of the applied dose was found on the surface of the leaves, 57-63% in the acetone extract of the whole leaves, and 13-26% was present as a bound residue. The observed half-lives were 4-5 days for the trans- and 7-8 days for the cis-cypermethrin. Isomerization was carefully followed in these studies. First, there was practically no change in the ratio of alpha-R to alpha-S isomers. On the other hand, both of the 1R isomers (cis and trans) were converted, in part, to the corresponding 1S isomers, though the transformation appeared greater where cis- had been the starting material, compared with trans-cypermethrin. However, the position was complicated by the simultaneous conversion of trans to cis-isomers. Apparently, these changes were much less in the case of the extracts from the whole leaf and the authors considered that this isomerization, as well as the 1R-1S epimerization, were probably photochemical. These findings on the conversion of cis to trans are consistent with the formation of trans-cypermethrin from cis- reported by Cole

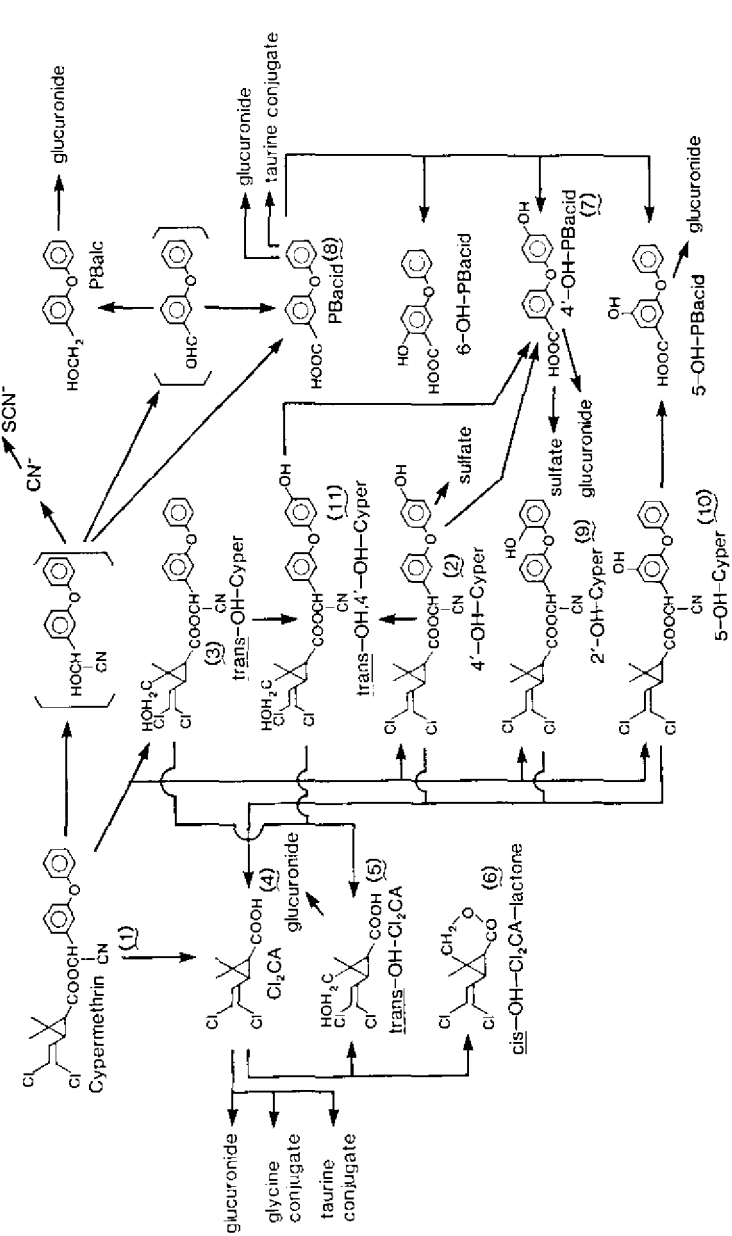


Fig. 3. Metabolic pathways of cypermethrin in mammals.

Notes on Fig. 3.

1. (RS)-α-cyano-3-phenoxybenzyl (1 RS) cis- or trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.
2. 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid[a].
3. 3-phenoxybenzoic acid (PBAcid).
4. (RS)-α-cyano-3-phenoxybenzyl (1 RS)-cis- or trans-3-(2,2-dichlorovinyl)-2-hydroxymethyl-2-methylcyclopropanecarboxylate.
5. 3-(2,2-dichlorovinyl)-2-hydroxymethyl-2-methyl-cyclopropanecarboxylate.
6. N-(3-phenoxybenzoyl) taurine.
7. N-(3-phenoxybenzoyl) glycine.
8. N-(3-phenoxybenzoyl) glutamic acid.
9. 3-(4-hydroxyphenoxy) benzoic acid.
10. 4-(3-carboxyphenoxy)-phenyl sulfate.
11. (RS)-α-cyano-3-(4-hydroxyphenoxy)-benzyl (1 RS)- or trans-3-(2,2-dichlorvinyl)-2,2-dimethylcyclopropanecarboxylate.

[a] This numbering is approved by SCI Publications, Chemical Abstracts, and IUPAC.

et al. (1982) in bean and cotton leaves in the greenhouse. These authors also considered this to be a photochemical reaction. Roberts (1981) reported the conversion of cis- to trans-cypermethrin on apple leaves, but not of trans to cis.

The results of studies by Furuzawa et al. (1986) showed that, in the intact ester, there was some hydration of the cyano group to the amide, and subsequently to the corresponding acid, as well as hydroxylation at the 4-benzyl or one of the gem methyl groups in the cyclopropyl moiety. However, by far the most important metabolites were glycoside conjugates of 4'-OH-PBA and CPA (with a limited degree of isomerization from cis to trans and vice versa). Hydroxylated CPA, either free or conjugated, was a relatively minor metabolite.

More et al. (1978) studied the uptake of ^{14}C radiolabelled PBA in the abscised leaves of a range of different plants, which were dipped in aqueous solutions. The PBA was labelled in the benzyl ring. Mainly cotton plants and vines were studied, but broad beans, tomatoes, lettuce, peas, and soybeans were also included. In the case of cotton, some of the leaves were exposed to ^{13}C-labelled CO_2 and allowed to take up the labelled PBA after a 2-h period of photosynthesis; the ^{13}C label was used to assist identification by mass spectroscopy. A large part of the PBA in the cotton leaves was conjugated within a few hours; it was shown that most of the conjugated material was the glucose ester. It was also shown, in the $^{13}CO_2$ study, that at least a part of the glucose moiety had been derived from recent photosynthesis. On more prolonged exposure, other conjugates were formed. In the case of vine leaves, these proved to be a series of disaccharides that contained pentose sugars as well as glucose. The evidence suggested that these had been formed by the addition of the pentose sugar to the glucose conjugate rather than by the PBA becoming conjugated with the preformed disaccharide. The conjugates in the other plant species were not always positively identified, but the authors commented that the interspecies differences were likely to be mainly of degree rather than of any fundamental differences in process.

Mikami et al. (1984) studied the metabolism of PBA in abscised leaves of cabbage, cotton, cucumber, kidney bean, and tomato plants. PBA was rapidly converted into more polar products by esterification with glucose, malonylglucose, gentiobiose, cellobiose, glycosylxylose, and tri-glucose. The main metabolites were malonyl glucoside in cabbage, kidney bean, and cucumber, and the glucosylxylose ester in cotton. The gentiobiose and tri-glucose esters were predominant in tomato. The metabolism of cypermethrin in plants is summarized in Fig. 4.

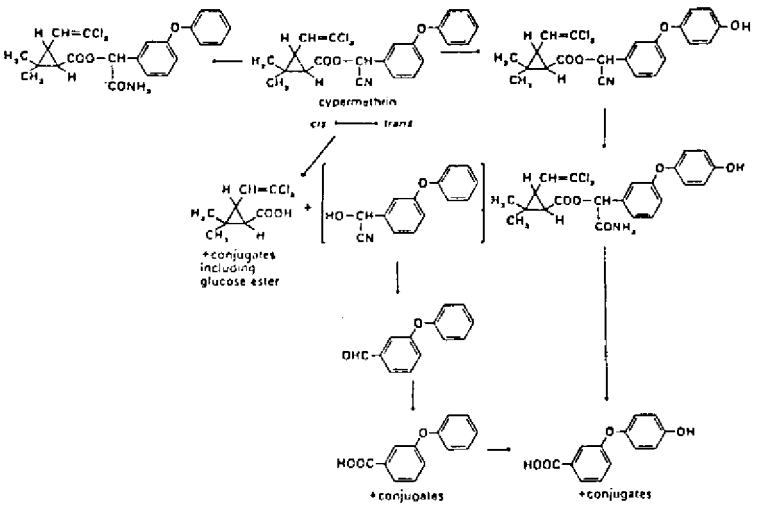


Fig. 4. The metabolic pathway of cypermethrin in plants. From: Roberts (1981).

6.4 Metabolism in Fish

The metabolism of cis-cypermethrin (^{14}C-labelled in either the acid or the alcohol moiety) in trout was studied by Edwards & Millburn (1985a). In contrast with that in other animals (frogs, mice, and quail), ester cleavage of cypermethrin was very slow, and the main metabolic pathway was hydroxylation to give the 4-hydroxyphenoxy derivative, which was excreted in the bile as the glucuronide. Edwards & Millburn (1985b) identified the glucuronide of CPA and the ether glucuronide and sulfate of 4-hydroxy PBA, but only as minor metabolites.

Trout liver microsomes metabolize both cis- and trans-isomers of cypermethrin to the 4'-hydroxy derivatives of the intact esters and their corresponding ether glucuronic acid conjugates at comparable rates. There are indications, derived from studies with other pyrethroids, that the liver microsomes of the carp are more able to metabolize pyrethroids than those of the salmonids (Edwards & Millburn, 1985b).

7. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Leahey (1985) and Smith & Stratton (1986) give extensive reviews on this matter.

7.1 Microorganisms

Effects of cypermethrin on microbial activity in the soil have been investigated under laboratory conditions. Cypermethrin was applied to a sandy loam soil at a rate of 2.5 or 250 mg/kg soil. No effect was found on the rate of carbon dioxide evolution (Cook, 1978a) or oxygen uptake (Loveridge & Cook, 1978a) at the lower rate. With 250 mg/kg, slight, but significant, inhibition of the CO_2 evolution and a decrease in oxygen uptake were noted after long incubation periods. Nitrogen fixation was assessed by the acetylene reduction method (Loveridge & Cook, 1978b). No significant effects were found. Ammonification and nitrification were studied in soils, either alone, or amended with urea or ammonium chloride. Again, no significant effects were found, even at the high rate of application (Cook, 1978b). Finally, glucose utilization was studied in the short term (2 days) and after pre-incubation with cypermethrin for up to 38 weeks. No significant effects were noted, even at the high rate (Bromley & Cook, 1979).

A second series of experiments, in which cypermethrin was applied to a sandy loam at 0.5 or 5 mg/kg soil has been reported. Antimicrobial activity was observed in the early stages of incubation with fungal population numbers returning to normal within 2-4 weeks, and with a subsequent stimulation of microbial growth. There was no inhibition of acetylene reduction activity at either dosage. Nitrification and microbial respiration were increased at both dosages, suggesting microbial degradation of cypermethrin. Dehydrogenase activity was not affected, while urease activity was stimulated. This study indicates that cypermethrin may exert transient effects on the populations and activities of microflora, but they are short-lived and minor in nature (Tu, 1980).

The toxicity of cypermethrin for 4 pathogens of soybean and for the nodulation organism Rhizobium has been investigated. In a paper disc inhibition test, cypermethrin proved non-toxic for Rhizobium, the EC_{50} exceeding 10 000 mg/litre. The toxicity for the pathogens was higher, EC_{50} values ranging from 390 to 1700 mg/litre (Tu, 1982).

7.2 Aquatic Organisms

7.2.1 Fish

7.2.1.1 Acute toxicity

In common with other pyrethroids, cypermethrin is very toxic for fish in clean water under laboratory conditions. The available data are summarized in Table 8. The data demonstrate a similar high acute toxicity for both cold- and warm-water species of fish. Certain of these data have been reviewed by Stephenson (1982e).

There is no evidence of a significant effect of temperature on toxicity, though a negative temperature coefficient has been claimed for certain pyrethroids (Kumaraguru & Beamish, 1981). Furthermore, the toxicity of pyrethroids for fish was not influenced by the hardness or pH of the water (Mauck et al., 1976).

To determine the acute toxicity of cypermethrin for Tilapia nilotica, an EC formulation of cypermethrin (25 g/litre) was sprayed on the surface of static water held in stainless steel tanks in a glasshouse. The concentration of cypermethrin in the water was determined over a 96-h period. Depending on the application rate, the concentration of cypermethrin in the water rose rapidly during the first 24 h after application and decreased slowly over the following 3 days. The tanks each contained 5 fish and water to a depth of 30 cm. Water temperatures were 23-26 °C. No fish deaths occurred when the peak concentration of cypermethrin was less than 1.5 µg/litre, while all fish died when the concentration exceeded approximately 5 µg/litre (Stephenson, 1981a).

To study the influence of suspended solids on water concentrations and the toxicity for fish of cypermethrin, Rainbow trout were exposed to nominal concentrations of 2 or 5 µg cypermethrin/litre, which was added to microfiltered mains water or to pond water containing 14.5 mg suspended solids/litre. The actual concentrations were measured for water samples taken 30 min after initial mixing. Two samples of pond water were taken. One was analysed as such while the second was centrifuged (60 min at 3000 rev/min) to precipitate the suspended solids; the clear supernatant liquid was then analysed. The results are summarized in Table 9.

The data from this study show that suspended solids absorb 40% of the cypermethrin initially present. Fish exposed to an actual concentration of 4.9 µg cypermethrin/litre in mains water died within 24 h, those in pond water containing an actual concentration of 2.5-4 µg/litre survived (Reiff, 1978a).

Table 8. Acute toxicity of cypermethrin for fish

Species	Weight (g) (or age)	Vehicle	Temperature (°C)	96-h LC_{50} (µg a.i./litre)	Reference
Brown trout (Salmo trutta)	5 - 8	technical, dispersed via DMSO	15	2 - 2.8	Reiff (1976)
	5 - 8	technical, absorbed on pumice	15	1.2[a,b]	Reiff (1976)
Rainbow trout (Salmo gairdneri)	1 - 11	technical, absorbed on pumice	10 - 15	0.5[a,b,c]	Reiff (1978b)
	1 - 2	technical, via acetone	10	0.5	Stephenson (1982b)
	3.3	technical, via acetone	15	2.8	Stephenson (1982b)
	3	emulsifiable concentrate (40% ai)	10	11 [d,a]	Coats & O'Donnell-Jeffery (1979)
	3	technical, dispersed via acetone	10	55 [d]	Coats & O'Donnell-Jeffery (1979)
Common carp (Cyprinus carpio)	4 - 10	technical, absorbed on pumice	10	0.9[a,b,c]	Reiff (1978b)
	4 - 10	technical, absorbed on pumice	20 - 25	1.1[a,b,c]	Reiff (1978b)
	8 - 10	technical, via acetone	10	0.9	Stephenson (1982c)
	2.1	emulsifiable concentrate (5% a.i.)	22 - 26	3.4[f]	Stephenson (1982c) Stephenson et al. (1984)

Table 8.(contd).

Rudd (*Scardinius erythrophthalmus*)	9 - 10	technical, absorbed on pumice	15	0.4[a,b,c]	Reiff (1978b)
Atlantic salmon (*Salmo salar*)	5.3	technical, dispersed via ethanol	10	2 - 7.4[b]	McLeese et al. (1980)
	9.4	1-R-*cis*-	10	0.74	Zitko et al. (1979)
Tilapia nilotica	1 - 3	technical, absorbed on pumice	25	2.0[a,b,c]	Stephenson (1981b) Stephenson et al. (1984)
Fathead minnow (*Pimephales promelas*)	0.74 (juvenile)	technical, absorbed on pumice	23 - 25	1.2[a,b]	Stephenson (1982d)
Mugil cephalus	0.1 30 days	30% EC	?	24 [g]	Tag El-Din et al. (1981)
Gambusia affinis	4 weeks	30% EC	25	6.6 [g]	El-Sebae et al. (1983)

[a] Flow-through system. Otherwise, static test.
[b] Measured concentration. Otherwise, nominal.
[c] The data quoted have been recalculated from the primary data given in the original reports following current statistical methods.
[d] 24-h LC_{50}.
[e] Lethal threshold value (geometric mean of lowest concentration with and highest concentration without mortality).
[f] 48-h LC_{50}.
[g] Formulation.

Remark: In most tests, the pH of the water was 7.5 - 8.5; the hardness was 260 mg/litre as $CaCO_3$ (except for a few cases).

Table 9. Influence of suspended solids on the toxicity of cypermethrin for Rainbow trout

Source	Suspended solids (mg/litre)	Initial cypermethrin concentration (µg/litre)			Response of Rainbow trout
		nominal	actual total	actual in water	
Microfiltered mains water	0	2	1.7	1.7	1/6 fish dead at 48 h
		5	4.9	4.9	6/6 fish dead at 24 h
Pond water	14.5	2	1.2	0.65	no symptoms or deaths
		5	4.0	2.5	at 7 days

The high degree of adsorption of cypermethrin on soils was demonstrated by Riley & Hill (1983) in their studies on the toxicity of cypermethrin for Daphnia and other aquatic organisms. The addition of soil to the system reduced the toxicity of the aqueous solution by 200-350 times.

The stainless steel tank study with Tilapia nilotica was repeated with the water initially containing 100 mg suspended solids/litre. In this study too, the presence of suspended solids reduced the toxic effects of cypermethrin (about 2-fold) (Stephenson, 1982a).

7.2.1.2 Long-term toxicity

The effects of cypermethrin on the most sensitive stage in the life cycle of the Fathead minnow (Pimephales promelas) were investigated using a flow-through system. Total hardness, pH, concentration of dissolved oxygen, and temperature were controlled. Within 24 h of fertilization, eggs were exposed to nominal concentrations of 0, 0.03, 0.1, 0.3, or 1.0 µg/litre (mean exposure concentration 0, 0.03, 0.12, 0.17, and 0.79 µg cypermethrin/litre), for a total of 34 days. Hatching occurred between the 3rd and 6th day, while egg hatch was not affected at the highest concentration. No fry survived day 34. Survival was reduced at concentrations of 0.3 and 0.1 µg/litre but not at 0.03 µg/litre. On the basis of the most sensitive parameter, i.e., survival of young fry, the no-observed-adverse-effect level for cypermethrin lay between 0.03 and 0.12 µg/litre (Stephenson, 1982d).

7.2.2 Invertebrates

7.2.2.1 Acute toxicity

Aquatic invertebrates show a wide range of susceptibility to cypermethrin. The data in Table 10 are from static, clean water test systems and some of these data have been reviewed by Stephenson (1982e). It can be seen that snails do not show any effects at 5 µg/litre (close to the water solubility of cypermethrin), while some insects show behavioural changes, but no mortality at this level. Crustacea, particularly marine decapod Crustacea, are highly susceptible to cypermethrin, mortality occurring at levels below 0.05 µg/litre. Water mites are also very susceptible (Zitko et al., 1979).

In addition to these static water tests, continuous-flow tests in clean water have been undertaken with 2 sensitive species (Stephenson, 1980b) (Table 11).

It can be concluded that effects can be expected when concentrations of cypermethrin of the order of 0.01 µg/litre are maintained in the water phase for more than 96 h.

It has been shown that, at 100 µg/litre, cypermethrin does not affect the growth of the single-celled green alga Selenastrum capricornutum, over a period of 2-4 days (Stephenson, 1982b).

7.2.2.2 Long-term toxicity

The effects of cypermethrin on the survival, growth, and reproduction of Daphnia magna were investigated, over 21 days, in a static water test with daily renewal of test solutions. The nominal concentrations tested were 0, 0.003, 0.01, 0.03, 0.1, and 0.3 µg/litre. Cypermethrin affected all 3 parameters at a nominal concentration of 0.3 µg/litre, but no effects were noted at 0.1 µg/litre. Chemical analysis suggested that the Daphnia were exposed to about 50% of the nominal concentration, two-thirds in solution, the remainder adsorbed on suspended solids. These results show that the no-observed-adverse-effect level of cypermethrin throughout the life cycle for Daphnia is of the order of 0.05 µg/litre (Garforth, 1982).

7.2.3 Field studies

7.2.3.1 Deliberate overspraying

This subject has received wide attention, and various aspects have been reviewed in a number of publications (Crossland & Stephenson, 1979; Crossland, 1982; Crossland et

Table 10. Acute toxicity of cypermethrin for aquatic invertebrates in static tests

Species	Stage	Temperature (°C)	Solvent	24-h EC_{50} (µg/litre)[a]	24-h LC_{50} (µg a.i./litre)	Reference
Fresh-water						
Crustacea						
Water flea (*Daphnia magna*)	up to 24 h old	22	acetone		4.2	Reiff (1977)
		18	water	2	2	Stephenson (1980a)[b]
		20	acetone	1.2	-	Stephenson (1982b)
		20	acetone	0.3[c]	-	Stephenson (1982b)
Water hog louse (*Asellus* spp.)	3 - 8 mm	15	water	0.02	0.2	Stephenson (1980a)
Freshwater shrimp (*Gammarus pulex*)	3 - 8 mm	15	id	0.04	0.1	Stephenson (1980a)
Insecta						
Mayfly (*Cloeon dipterum*)	larvae	15	id	0.07	0.6	Stephenson (1980a)
Whirligig beetle (*Gyrinus natator*)	adult	15	id	0.07	$\geq$ 5	Stephenson (1980a)
Bloodworm (*Chironomus thummi*)	larvae	15	id	0.2	$\geq$ 5	Stephenson (1980a)
Mosquito (*Aedes aegypti*)	larvae	18	id	0.03	1	Stephenson (1980a)
Midge (*Chaoborus crystallinus*)	larvae	15	id	0.03	0.2	Stephenson (1980a)

Table 10 (contd).

Water boatman (*Corixa punctata*)	adult	15	water	0.7	> 5	Stephenson (1980a)
Water boatman (*Notonecta* spp.)	adult	15	id	0.3	> 5	Stephenson (1980a)
Arachnida						
Water mite (*Piona carnea*)	adult	15		0.02	0.05	Stephenson (1980a)
Mollusca						
Snail (*Lymnaea peregra*)	< 8 mm	15	id	> 5	> 5	Stephenson (1980a)
Marine						
Crustacea						
Lobster (*Homarus americanus*)	450 g	10	ethanol	-	0.04[g]	McLeese et al. (1980)
	450 g	10	id	-	0.0003[d,f,g]	Zitko et al. (1979)
Shrimp (*Crangon septemspinosa*)	1.3 g	10	id	-	0.01[d,e]	McLeese et al. (1980)

[a] EC_{50} values are based on effects, usually immobilization, other than death.
[b] Stephenson (1980a) used cypermethrin (85% a.i.) dissolved in acetone and absorbed on pumice.
[c] 48-h EC_{50}.
[d] 96-h LC_{50}.
[e] Dispersed via ethanol.
[f] 1-R-*cis*-.
[g] Salinity, 30%.

Remark: In most tests, the pH of the water was 7.5 - 8.5; and the hardness, 260 mg/litre as $CaCO_3$.

Table 11. Acute toxicity of cypermethrin for aquatic invertebrates in continuous-flow tests

Species	Stage size	Temperature (°C)	EC_{50} (µg/litre)		LC_{50} (µg/litre)	
			24-h	96-h	24-h	96-h
Freshwater shrimp (Gammarus pulex)	3 - 8 mm	15	0.005	0.004	0.030	0.009
Mayfly (Cloeon dipterum)	larvae 0.5 - 1 cm	15	0.008	0.004	0.070[a]	0.020

[a] 48-h LC_{50}.

al., 1982; Crossland & Elgar, 1983; Shires, 1983a; Stephenson, 1983).

The effects of field applications of cypermethrin on fish were studied in a preliminary study by Crossland & Bennett (1976). A small pond was deliberately oversprayed with 100 g cypermethrin/ha as an EC formulation. The peak concentration of cypermethrin in the water was 2.6 µg/litre. Wild populations of fish and amphibia were not affected by this treatment. Large numbers of young fish seen during the 2 weeks following treatment did not appear to be affected.

In a second study at the same rate of application, the peak concentration of cypermethrin was 1.4 µg/litre. There was no observed mortality among 12 small rudd that had been placed in the pond 12 days before treatment, and no effects of treatment were noted in wild populations of rudd or newts (Crossland et al., 1978).

Observations on invertebrates were included in these two pond studies. In the first study, which lasted 2 weeks, populations of Crustacea, mites, and insects were severely reduced. Surface breathing insects were affected most rapidly, within hours of treatment. Free-swimming dipterous larvae were not noticeably affected for 24 h, while zooplankton were killed between 1 and 2 days after treatment. Bottom dwelling invertebrates, including chironomid larvae, snails, leaches, and flatworms, did not appear to be affected, though the numbers in the last 2 groups were low in pre-treatment samples.

The second study was continued for 15 weeks after treatment. Initial results were similar to those reported above. Macro-invertebrates were markedly reduced in numbers, 2 weeks after treatment. However, both numbers and diversity returned to normal levels after 15 weeks. Snails and flat-

worms (again numbers low in this group in pretreatment counts) were unaffected, but no arthropods were present in the samples taken at 2 weeks. Recolonization by flying insects (beetles and chironomids) commenced 4 weeks after treatment. The Crustacean Asellus had not reappeared by the end of the study.

No daphnids or copepods were found in the zooplankton samples, 1 week after treatment, and they only reappeared in the 8-week post-treatment sample. Populations returned to normal levels in 10-12 weeks. Some 2 weeks after treatment, an increase in filamentous algae was noted, and this persisted until the end of the study. It was inferred that this was a secondary effect following from the elimination of known feeders on algae, for instance, the mayfly, Cloeon dipterum, and the daphnid, Simocephalus sp. (Crossland & Bennett, 1976; Crossland et al., 1978).

7.2.3.2 Monitoring of drift from ground and aerial applications

Two field studies were undertaken to assess the fate and effects in adjacent waters of spray drift from ground-based agricultural applications of cypermethrin.

(a) Mistblower applications on vines (France)

Three sites were chosen, each with vines planted up to the banks of adjacent streams. One application of cypermethrin was monitored at each site and a second application at one of the sites. A diluted EC formulation of cypermethrin was applied at 30 g a.i./ha using a backpack, swinging-head mistblower, and at 45 g a.i./ha using a tractor-mounted, fixed-head mistblower.

The deposition on the ground and an adjacent stream of 0.37-4.5 g/ha led to peak concentrations in the subsurface water ranging from 0.17 to 1.7 µg/litre during the first hour after spraying; the concentrations decreased to less than 0.1 µg/litre within a few hours. No effects on fish, tadpoles, or frogs were observed. Some aquatic invertebrates in adjacent streams were seen to be hyperactive or immobilized during the first 2 h after application. This was most obvious with mayfly larvae, water boatmen, water beetles, pond skaters, and syrphid larvae. During the first 3 h following application, there was an increase in the number of invertebrates caught in drift nets. However, there were no significant population effects in zooplankton or macroinvertebrates (Bennett et al., 1980).

(b) Boom-and-nozzle applications to row crops (United Kingdom)

Two sites were chosen each with row crops (potatoes or sugarbeet or both) planted up to within 1-3 m of the edge of ponds. Two applications of cypermethrin were monitored at each of 3 ponds. In each case, a diluted EC formulation of cypermethrin was applied at 70 g a.i./ha using tractor-mounted, boom-and-nozzle equipment. Deposition on the ground and over the pond was estimated. The deposition led to peak concentrations in subsurface water in the range of 0.01- 0.05 µg/litre. In one case, the concentration in subsurface waters after 24 h was 0.02-0.03 µg/litre. In all other cases, this value was at, or below, 0.01 µg/litre, the limit of detection. No effects on fish were observed. No residues of cypermethrin were found in fish (limit of detection, 5 µg/kg wet weight). The only effects on invertebrates in adjacent waters were noted in the corner of 1 pond. Some pond skaters, one water-boatman, and 2 syrphid larvae were found immobilized. They had recovered by the next day. There was no evidence from zooplankton or sweep-net samples of any effects on invertebrate populations (Shires et al., 1980).

(c) Aerial application to winter wheat (United Kingdom)

A large field of winter wheat was chosen, which was surrounded on 3 sides by drainage ditches. An EC formulation of cypermethrin was applied at 25 g a.i./ha by fixed-wing aircraft. Up to 6% of the nominal dose was deposited on the water surfaces, resulting in maximum levels in subsurface waters of 0.03 µg/litre, which declined rapidly after spraying. No effects were observed on caged or wild fish, and no significant residues of cypermethrin were found in the fish. A few air-breathing water boatmen and water mites, which are very susceptible, showed minor short-term reductions in abundance (Shires & Bennett, 1982, 1985).

(d) Application for rice insect control (Korea, Spain)

An EC formulation of cypermethrin was applied to rice paddies in Korea, in which carp had been caged, by hand-spraying at 15 or 40 g a.i./ha. Mortality at the higher rate was significantly higher than that in the control, i.e., 15 and 7%, respectively (Stephenson, 1982c).

Another field study was carried out in Spain. Cypermethrin was applied by air to paddy rice and also to caged fish (Cyprinus carpio) within the area. The application rate was 15-40 g a.i./ha. The limited toxic effects of cypermethrin on fish under field conditions were confirmed in this study.

Aerial overspraying of the rice paddies at 25 g a.i./ha did not produce any mortality (Stephenson et al., 1984).

(e) Applications for tsetse fly control (Nigeria)

Field studies have been reported on the assessment of the environmental impact of the application of cypermethrin for tsetse fly control in Nigeria. Searches for affected fish were made in areas that had been selectively sprayed from the ground with an EC formulation of cypermethrin at 2-3 g a.i./litre, or sprayed from the air with an oil-based solution of cypermethrin at 100 g a.i./ha in 1977 and at 60 and 150 g a.i./ha in 1978. The ground spray application was successful in controlling the tsetse fly, but only the highest rate applied from the air approached a satisfactory level of tsetse control. None of these searches revealed any dead fish in the rivers within the areas sprayed with cypermethrin. Pre- and post-treatment net samples of aquatic invertebrates were taken in an area sprayed at 100/150 g a.i./ha. Acute mortality occurred in terrestrial and aquatic arthropods, such as the water beetle and Crustaceans. Shrimps and mayfly larvae disappeared from river benthos after spraying, but reappeared one year later (Smies et al., 1980).

7.3 Terrestrial Organisms

7.3.1 Laboratory studies

7.3.1.1 Acute toxicity

(a) Birds

The acute oral toxicity of cypermethrin for birds is summarized in Table 12.

In the first study (Coombs et al., 1976), 4 birds of each species were observed for a 3-week period after dosing; no deaths or toxic signs were noted at the highest dosages applied. In the second study (Rose, 1981), clinical signs of cypermethrin intoxication, including ataxia and lethargy, were noted at dosages of 3000 mg/kg body weight and above. One male duckling, out of 28 of each sex, died at the top dosage of 10 000 mg/kg body weight.

7.3.1.2 Short-term toxicity

(a) Birds

Six laying hens were given 5 successive daily oral doses of 1000 mg cypermethrin/kg body weight in DMSO followed after

Table 12. Acute oral toxicity of cypermethrin for birds

Species	Age	Vehicle	Observation period	LD_{50} (mg/kg body weight)	Reference
Domestic fowl (Gallus domesticus)	adult	40% DMSO	21 days	> 2000	Coombs et al. (1976)
French partridge (Allectoris rufa)	adult	40% DMSO	21 days	> 3000	Coombs et al. (1976)
Mallard duck (Anas platyrhynchos)	2 - 6 months	40% emulsifiable concentrate	14 days	> 10 000	Rose (1981)

3 weeks by a second 5-day dosing regime and were observed for a further 3 weeks. Control hens did not receive any treatment. No signs of intoxication or histological changes in nervous tissue were noted at any time (Owen & Butterworth, 1977).

Cypermethrin was administered for 5 consecutive days to Mallard ducks at dosages of 5000 or 10 000 mg/kg diet. No deaths or clinical signs of intoxication were noted during the feeding period or over a subsequent 40-day holding period. Food intake and body weights were slightly depressed during the feeding period, though most ducks had regained or exceeded their initial body weights by the end of the holding period (Rose, 1981).

Riviere et al. (1983) studied the influence of cypermethrin on the microsomal drug metabolizing enzymes in Japanese quail (Coturnix coturnix). Cypermethrin had no or only a very weak inducing effect.

(b) Honey bees

Cypermethrin was highly toxic for worker honey bees (Apis mellifera) in laboratory tests (24-h oral LD_{50} 0.035 µg a.i. per bee) (Table 13). Cypermethrin applied on the dorsal side of the thorax was more toxic for honey-bees at lower breeding temperatures, i.e., at 12-20 °C, the toxic level was 0.01-0.02 µg/bee and at 32 °C, 0.02-0.03 µg/bee. In addition, the sensitivity of the bees to cypermethrin increased with age (Delabie et al., 1985).

An aqueous dispersion of cypermethrin was sprayed directly on worker honey bees. Only 5% of the bees sprayed with a 0.01 g/litre solution were killed. All bees sprayed with 0.1 and 1 g/litre died (Harris & Turnbull, 1978).

First indications that cypermethrin might not be hazardous for bees under field conditions were obtained in cage tests. Worker honey bees were exposed for 2 h to residues produced by treating flowering Solidago (Golden rod) to run-off with a spray containing 0.5 g cypermethrin/litre and aging the residue for 1 h. Some knock-down of the bees (up to 9%) was noted during the first 8 h following initial exposure. However, most bees recovered, and mortality after 1 day and 10 days did not differ from that in untreated control bees. Higher mortality had been noted in an earlier study using the same technique but with a higher dosage rate of 1.5 g cypermethrin/litre (Gerig, 1979, 1981).

Table 13. Toxicity of cypermethrin for worker honey bees

Formulation	24-h LD_{50} (mg/bee)		Reference
	Topical application	Oral administration	
Technical	0.02	0.035	Badmin & Twydell (1976)
Technical	0.053	0.12	Knight (1982)
Technical	0.056	-	Smart & Stevenson (1982), Westlake et al. (1985)
Emulsifiable concentrate (40%)	-	0.031	Badmin & Twydell (1976)

(c) Predatory and parasitic species

Cypermethrin has also been evaluated against a number of predatory or parasitic insects and mites. Laboratory data are available for a number of predators (Coleoptera) and parasites (Hymenoptera) of insect pests.

The available data indicate that cypermethrin can show useful selectivity between insect predators and parasites and the relevant pest species (Mulla et al., 1978; du Toit, 1978; Waddill, 1978; Abdel-Aal et al., 1979; Coats et al., 1979; Holden, 1979; Leake et al., 1979; McDonald, 1979; European Patent Office, 1980; Harris & Turnbull, 1980; Hagley et al., 1981; Jordan & Chang, 1981; Saad et al., 1981; Ascher et al., 1982; Baicu, 1982; Bayoumi, 1982; Chang & Jordan, 1982; Osman et al., 1982; Rajakulendran & Plapp, 1982; Surulivelu & Menon, 1982; Brempong-Yeboah et al., 1983; Chang & Jordan, 1983;

El-Guindy et al., 1983; El-Minshawy et al., 1983; El-Sebae et al., 1983; Ho et al., 1983; Ishaaya et al., 1983; Watters et al., 1983; Abbassy et al., 1984; Bariola & Lingren, 1984; Brempong-Yeboah et al., 1984 a,b,c; Cheng & Hanlon, 1984; Dai & Sun, 1984; El-Sayed & Knowles, 1984; Ewen et al., 1984; Fabellar & Heinrichs, 1984; Hopkins et al., 1984; Liu et al., 1984; Mani & Krishnamoorthy, 1984; Meisner et al., 1984; Le Patourel & Singh, 1984; Riskallah, 1984; Scott & Georghiou, 1984; Wilde et al., 1984; Zohdy et al., 1984; Ahmed et al., 1985; Abou-Awad & El-Banhawy, 1985; Bostanian & Belanger, 1985; Bostanian et al., 1985; Corbitt et al., 1985; Edwards et al., 1985; El-Sebae et al., 1985; Harris et al., 1985; Knapp et al., 1985; Knowles & El-Sayed, 1985; McKee & Knowles, 1985; Pree & Hagley, 1985; Suhas & Devaiah, 1985; Tewari & Krishnamoorthy, 1985; Vekaria & Vyas, 1985; Barlow et al., 1986).

(d) Earthworms

The toxicity of cypermethrin for the earthworm (Eisenia foetida) has been assessed in an artificial soil test system. Worms were exposed to dosages of 0, 0.1, 1.0, 10, or 100 mg/kg soil for 14 days. No mortality was found (Inglesfield & Sherwood, 1983; Inglesfield, 1984).

The LC_{50} for cypermethrin in Eisenia foetida was found to be 26.1 µg/cm² (16.3-44.4 µg/cm²) (Roberts & Dorough, 1984).

(e) Higher plants

In studies on effects of cypermethrin on seed germination in the soybean, seedling emergence and survival were not reduced by levels of up to 5000 mg/litre (Tu, 1982). Cypermethrin has been demonstrated not to be phytotoxic for crops when applied at recommended dosages (Hargreaves & Cooper, 1979).

7.3.2 Field Studies

7.3.2.1 Applications for tsetse fly control in Nigeria

Field trials in Nigeria of cypermethrin against Tsetse flies (Glossina palpalis (RD) and Glossina tachnoides Westw.) were carried out, over a 2-year period by Spielberger et al. (1979). Ground applications of cypermethrin (0.3%) were made on fly-resting sites in vegetation using pressurized knapsack sprayers. Populations of both species were eradicated after a single application. Levels of over 150 g/ha were needed for complete eradication by residual spraying from a helicopter.

The effects on the general insect population of aerial applications of cypermethrin for tsetse fly control were studied by Smies et al. (1980). Within a few hours of application, dead and dying insects were found, exemplifying the rapid knockdown effect of cypermethrin. Insect fallout, as assessed by funnel traps, was markedly increased for 1 day by 100 g cypermethrin a.i./ha, and for 3 days by 150 g a.i./ha. General insect activity as assessed by Malaise trap catches was not affected by 150 g cypermethrin a.i./ha (Smies et al., 1980).

7.3.2.2 Honey bees

This subject has been reviewed by Shires & Debray (1982) and Shires (1983b).

The hazard of practical field applications of cypermethrin for worker honey bees was assessed in 2 field trials. In both trials, cypermethrin was applied to flowering oilseed rape, by helicopter, at a time when the crops were being actively worked by bees from nearby colonies, thus representing a worst case exposure of the bees. The rate of application in both trials was 25 g a.i./ha. Of the 8 hives, placed adjacent to the treated crops, 6 had been fitted with dead bee traps and 2 with pollen traps. Observations were made on bee mortality, pollen collection, foraging activity, hive populations, and brood areas. In addition, in the second trial, cypermethrin residues were determined in the bees, pollen, wax, honey, and in the leaves and flowers of the treated crop (Pearson & Shires, 1981; Shires, 1982b).

In the first trial, only a small increase in bee mortality was noted, following the cypermethrin treatment (Table 14). Cypermethrin appeared to be repellent to honey bees foraging the crop, but the duration of this effect could not be established because of poor weather during the first few days following treatment. Cypermethrin did not have any effects on hive populations of adult bees or brood areas.

In the second trial, a slight increase in bee mortality was found at the time of treatment (Table 14). Cypermethrin had a repellent effect on honey bees for up to 24 h after application. Following this period, foraging activity and pollen collection returned to normal. Cypermethrin residues in dead bees, collected on the day of spraying and on the following morning, were higher than would be expected to be lethal. However, residue levels in dead bees collected after this period were considerably lower than those required to produce toxic effects, confirming that they represented the natural mortality level. Very low levels of cypermethrin were found in live bees and levels in honey and wax were close to

Table 14. Mean number of dead bees per hive during large-scale field trials with cypermethrin[a]

Treatment compound (dosage)	Time from treatment				
	-2 to -1 days	-1 to 0 days	0 to +4 h	+1 to +2 days	+3 to +4 days
Winter-sown rape; cypermethrin (25 g a.i./ha)	65	6	260	40	2
water control	75	17	0	26	15
Spring-sown rape cypermethrin (25 g a.i./ha)	9	36	310	2	13

[a] From: Shires (1983b).

the limit of detection. Concentrations of cypermethrin in flowers and pollen declined rapidly after treatment. Again, cypermethrin did not have any effects on hive populations of adult bees or of brood areas (Shires, 1982b).

In glasshouse studies, in which insecticide treatment was carried out during foraging by spraying the rape with 0.12 ml of Cymbush in 100 ml water (equivalent to 50 g a.i./ha), high mortality was observed 2 days after treatment, but no residual mortality appeared during the following 2-month period. In this study, oilseed rape flowers were not attractive to bees for at least 2 days following treatment.

A field test was carried out on a 38-ha field of oilseed rape. The insecticide was sprayed on a central area of 13 ha during the morning, at a rate of 50 g a.i./ha. The weather was sunny and the temperature about 18 °C. A high level of mortality occurred only on the 3 days following treatment. The results also showed that the bees avoided visiting the flowers as soon as the treatment was made, especially during the first 2 days. From the third day after the treatment, the repellent effect decreased, and the visits to the rape flowers increased reaching normal on the fifth day. It was suggested by the authors that the repellent effect appeared to be due to the formulation ingredients.

No residues of cypermetherin were found in hive products (pollen, wax, or honey) (Delabie et al., 1985).

In a study by Gerig (1981), cypermethrin was repellent to worker honey bees for a short period after spraying. Flowering Phaselia plants, within a flight tent, were treated

with a spray containing 0.5 g cypermethrin/litre. Honey bee visits to the treated flowers were very few over the first 0.5 h following treatment and remained at a reduced level during the remaining 5.5 h of observation on the day of treatment. Flower visits returned to normal levels on the following day (Gerig, 1981).

7.3.2.3 Soil fauna

This topic has been reviewed by Shires (1980).

In an initial study on the effects of cypermethrin on the soil surface fauna and earthworms, cypermethrin was applied at 100 g a.i./ha to small plots of spring wheat. This treatment did not have any effect on earthworm populations or on leaf litter breakdown, which is an indirect indicator of earthworm activity. The general population of soil surface predators, mainly beetles and spiders, was reduced to about 50% of the control value soon after treatment, but increased to a higher level than that in the controls after 5 weeks. A subsequent secondary decrease in predator populations was probably related to the efficiency of control of cereal aphids by cypermethrin (Shires et al., 1979). In a second study, cypermethrin was applied at 25 g a.i./ha to newly-emerged winter barley to control the aphid vectors of barley yellow dwarf virus. Populations of non-target arthropods were assessed using pitfall and water traps. Populations of soil Collembola were only slightly affected by cypermethrin. Populations of predators (beetles, spiders, and centipedes) were already declining because of the season, but there were significantly fewer predators in the cypermethrin plots compared with the controls at the end of the trial. Cypermethrin treatment did not affect the numbers of invertebrates collected from the water traps (Sherwood & Shires, 1981).

Two studies have been reported on the summer application of cypermethrin for aphid control in winter wheat. In France, ground applications of cypermethrin at 50 and 75 g a.i./ha were made in June and effects on the fauna in the air, on the crop, and on the soil surface were studied. Cypermethrin proved effective against the phytophagous (pest) species. Effects on non-target organisms were only minor, with the exception of spiders. In the second study in the United Kingdom, cypermethrin was applied in June using a fixed-wing aircraft at 25 g a.i./ha. Again, cypermethrin proved effective against the pest species, while, generally, effects on non-target organisms were minor and short-lived (Shires, 1982a,c).

Similar results have been obtained in studies on the aerial application of cypermethrin at 25 g a.i./ha on oilseed

rape and at 50 and 75 g a.i./ha on maize, in France (Inglesfield, 1982; Garforth, 1983).

7.3.2.4 Foliar predators and parasites

The relative toxicity of cypermethrin for pests and their parasites and predators is such that the balance between host/prey and parasites/predators may not be adversely affected in the field. However, care should be taken where predatory mites are important in pest management. The high toxicity of cypermethrin for predatory mites has been confirmed under field conditions (Wong & Chapman, 1979; Aliniazee & Cranham, 1980; Shires & Tipton, 1982).

The effects of cypermethrin treatments, included in a spray programme for cotton insect control, on white fly parasitism have been studied in the Sudan. The treatment regime that gave the consistently highest level of control of parasitism included cypermethrin at 40 g a.i./ha in 4 early season sprays (Shires & Tipton, 1982).

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

Leahey (1985) and Smith & Stratton (1986) have reviewed the available literature on this subject.

8.1 Single Exposures

8.1.1 Oral

The acute oral toxicity of cypermethrin (mixture of cis-/trans-isomers) in experimental animals is of a moderate order (Tables 15, 16). Signs of intoxication, indicative of an action on the central nervous system consist of sedation, ataxia, splayed gait, tip-toe walk, with occasional tremors and convulsions. These signs of toxicity appear within a few hours following dosing, and survivors show clinical recovery within 3 days (Coombs et al., 1976).

Table 16 shows the effects of the ratio of cis-:trans-isomers on the acute oral toxicity (FAO/WHO, 1980b).

Factors known to influence the oral LD_{50} value of cypermethrin include concentration, vehicle, temperature, age of the animals, and the animal strain used (Coombs et al., 1976; Dewar & Owen, 1979). The acute toxicity of cypermethrin was approximately 3 times greater in 3-week-old, than in 12-week-old rats (Rose & Dewar, 1978). The cis-:trans-ratio plays a role in determining acute toxicity, the cis-isomers being more toxic than the trans-isomers. The oral LD_{50} of the cis-isomers in rats (Carworth Farm E strain) was 229 mg/kg body weight while, with the trans-isomers, no deaths were found at 2000 mg/kg body weight (Brown, 1979a,b).

8.1.2 Dermal

The acute dermal toxicity of technical cypermethrin is of a low order. There were no deaths in CFE rats at any dose level tested up to 1600 mg/kg body weight using 20% w/v xylene as the vehicle (Coombs et al., 1976). The dermal LD_{50} for the cis-isomer of cypermethrin, applied to the skin of rats as a 10% solution in DMSO, was 219 mg/kg body weight (Brown, 1979a).

The acute dermal toxicity of cypermethrin for the rabbit is > 2460 mg/kg body weight (US EPA 1984).

8.1.3 Intraperitoneal

The intraperitoneal (ip) LD_{50} (20% w/v solution in corn oil) for technical cypermethrin in CFI mice is 485 mg/kg body weight (Coombs et al., 1976). In rats, the LD_{50} is between

Table 15. Oral LD_{50} values for technical cypermethrin

Species	Concentration and vehicle	LD_{50} value (mg a.i./kg body weight) (with 95% confidence limits)	Reference
rat	5% in corn oil	251 (203 - 295)	Coombs et al. (1976)
rat	5% in dimethylsulfoxide	303 (277 - 329)	Coombs et al. (1976)
rat	5% in dimethylsulfoxide	570 (485 - 823)	Price (1981a)
rat	40% in dimethylsulfoxide	approximately 4000	Rose (1982)
rat	5% in glycerol formal	200 - 400 (male); approximately 200 (female)	Coombs et al. (1976)
rat	10% in aqueous suspension	400 - 800 (male); approximately 400 (female)	Coombs et al. (1976)
rat	50% in aqueous suspension	3423 (2815 - 4328)[a]	Rose (1982)
mouse	5% in corn oil	82 (68 - 116)	Rose (1982)
mouse	5% in dimethylsulfoxide	138 (105 - 199)	Coombs et al. (1976)
mouse	50% in aqueous suspension	657 (439 - 1003)	Rose (1982)
Syrian hamster	10% in corn oil	approximately 400 (male and female)	Coombs et al. (1976)
Chinese hamster	5% in corn oil	203 (144 - 255)	Coombs et al. (1976)
guinea-pig	20% in corn oil	approximately 500 (male); > 1000 (female)	Coombs et al. (1976)
bovine calves	15% formulation in Shellsol A	142 - 284 (male)	Cassidy (1979)
piglets	15% formulation in Shellsol A	> 600 (male)	Cassidy (1979)
lamb	15% formulation in Shellsol A	283 - 567 (male)	Cassidy (1979)

Table 15 (contd).

Species	Concentration and vehicle	LD_{50} value (mg a.i./kg body weight) (with 95% confidence limits)	Reference
domestic fowl	40% in dimethylsulfoxide	> 2000	Coombs et al. (1976)
partridge	40% in dimethylsulfoxide	> 3000	Coombs et al. (1976)

[a] 40:60 cis/trans.

Table 16. Effects of cis-:trans-ratio on the acute toxicity of cypermethrin[a]

Species	Sex	Vehicle	cis-:trans-ratio	LD_{50} (mg/kg)
rat	male, female	dimethylsulfoxide	cis-only	160 - 300
rat	male, female	dimethylsulfoxide	trans-only	> 2000
rat	female	corn oil	90:10	367
rat	female	corn oil	40:60	891

[a] From: FAO/WHO (1980b).

198 and 315 mg/kg body weight (administered as 5% solution in DMSO) (Price, 1981a).

8.1.4 Inhalation

Groups of CD rats (4 of each sex) were exposed for 4 h to an aqueous spray of cypermethrin as a 400 g/litre emulsifiable concentrate. The liquid phase contained 3 g cypermethrin/litre and the atmospheric concentration of droplets in the vicinity of the rats was calculated to be 0.7 mg/litre. The median droplet size was 130 µm with a geometric standard deviation of 1.6 µm, comparable with the droplet spectrum of a field-spraying device. (It should be

noted that this droplet size is nearly not inhalable). The rats became thoroughly soaked during the exposure, thereby indicating a significant dermal exposure with probable oral exposure during post-exposure grooming. Immediately after the exposure, the female rats showed the abnormal gait and urinary incontinence typical of pyrethroid intoxication. Recovery took place within 3 days. No deaths or other adverse signs occurred during the exposure period or the subsequent 14-day observation period (Blair & Roderick, 1976).

In another study on possible effects on the peripheral nerves, rats (8 of each sex) were exposed for 4 h to an aqueous spray of cypermethrin as a 400 g/litre emulsifiable concentrate under conditions similar to those in the previous study. Half of the rats were necropsied immediately after exposure and the others after 66 h. Examination of the sciatic nerves from all of the rats did not reveal any abnormalities, even though signs of intoxication had been observed (Blair et al., 1976).

8.1.5 Skin and eye irritation

Technical cypermethrin was moderately irritant to occluded rabbit skin (both intact and abraded) and to the eyes of New Zealand white rabbits. In both cases, recovery was complete in a few days. The severity of the irritation depended on the formulation and the solvent used (Hine & Zuidema, 1970; Coombs et al., 1976).

The skin on the backs of guinea-pigs was treated with cypermethrin. The animals responded by licking, rubbing, scratching, or biting the sides tested. This reaction may be associated with skin sensory effects characterized by transient itching and tingling sensations (Cagen et al., 1984).

8.1.6 Sensitization

A skin sensitization test on guinea-pigs (maximization procedure of Magnusson & Kligman) indicated that technical cypermethrin may have a mild skin sensitizing potential (Coombs et al., 1976; US EPA, 1984).

8.2 Short-Term Exposures

8.2.1 Oral

8.2.1.1 Rat

Groups of 6 male and 6 female Charles River rats were fed diets containing 0, 25, 100, 250, 750, or 1500 mg cypermethrin/kg feed for 5 weeks. In the 1500 mg/kg group,

reduced body weight gain and food intake, piloerection, nervousness, incoordinated movement, increased liver weight, and increases in blood urea and haemoglobin concentrations were observed, but there were no pathological changes. No changes were detected in the groups receiving 750 mg/kg or less (Coombs et al., 1976).

Groups of Charles River rats, 12 of each sex (24 of each sex as controls), were fed dietary concentrations of 0, 25, 100, 400, or 1600 mg cypermethrin/kg feed for 3 months. Signs of intoxication, such as hypersensitivity and abnormal gait, were observed in the 1600 mg/kg group, during the first 5 weeks, and one animal died. The survivors showed clinical recovery in the second half of the study. However, body weight gain was reduced, liver and kidney weights increased, and there were increases in plasma-urea concentrations and plasma-alkaline phosphatase activity, and decreases in haemoglobin concentrations and the red blood cell count in females, and in the kaolin cephalin clothing time in males and packed cell volume were observed. Two out of 4 male rats, killed prematurely, showed axonal breaks and vacuolization of myelin in the sciatic nerve. None of the survivors showed nerve lesions, and no other pathological effects were found. In the 400 mg/kg group, males showed increased kidney weights but no histopathological changes. No effects were found in the 100 mg/kg group (Hend & Butterworth, 1976).

Male and female rats (20 in each group) were fed cypermethrin (cis-:trans- = 44:56) with a purity of 92% in the diet at levels of 0, 75, 150, or 1500 mg/kg diet, for 90 days. Haematology and the results of urinalysis were normal. Both males and females receiving 1500 mg/kg diet showed reduced body weight and reduced food consumption during the first month of the study. Increased liver microsomal oxidase activity was noted in both males and females in the 1500 mg/kg group and in the males in the 150 mg/kg group. These changes were substantially reversed within the 4-week recovery period. Gross and microscopic (including electron microscopic) examination of the tissues and organs did not reveal any signficant differences between the treated groups and the controls. Examination of the sciatic nerve of animals in the control and the 1500 mg/kg groups did not reveal any changes that could be directly attributed to cypermethrin (Glaister et al., 1977b).

Groups of rats (6 male and 6 female rats per group and 14 of each sex as controls) were fed trans-isomer at concentrations of 0, 30, 100, 1000, or 3000 mg/kg diet, for 5 weeks. No gross or microscopic findings were observed and mortality did not occur. Changes in several haematological parameters, alkaline phosphatase activity, and liver, spleen, and kidney weight were observed at the 2 highest dose levels.

Special histopathological studies of the sciatic nerve did not show any damage (Hend & Butterworth, 1977a).

Groups of rats (6 male and 6 female rats per group and 10 of each sex used as controls) were fed concentrations of the cis-isomer at 0, 30, 100, 300, 750, or 1500 mg/kg diet for 5 weeks (protocol similar to that described above). Mortality was observed at the 1500 mg/kg level as well as neurotoxic signs of poisoning. Growth was reduced at the 750 mg/kg level. Significant reductions in food intake were also noted at doses of 300 mg/kg or more, during the initial phase of the study. Relative kidney weights showed a statistically-significant increase at doses of 300 mg/kg or more and an increase in liver weight was observed at 750 mg/kg. Histopathological examinations revealed substantial degeneration in both the liver and sciatic nerve at 1500 mg/kg. No lesions were observed in the brain or spinal cord (Hend & Butterworth, 1977b).

8.2.1.2 Dog

Beagle hounds (4 of each sex per dose level) were fed diets containing 0, 5, 50, 500, or 1500 mg cypermethrin/kg diet for 13 weeks. At 1500 mg/kg, severe signs of intoxication consisting of diminished food intake, weight loss, diarrhoea, anorexia, licking and chewing of the paws, whole body tremors, a stiff exaggerated gait, ataxia, incoordination, and hyperaesthesia were observed. Half of the dogs in this group were necropsied because of severe clinical signs of intoxication. However, no changes in haematology, organ weight, or histopathology were observed and despite the severe signs of intoxication, no lesions of the sciatic nerves were observed in the dogs. No effects were seen at 500 mg/kg feed (Buckwell & Butterworth, 1977).

8.2.2 Dermal

8.2.2.1 Rabbit

Groups of 10 male and 10 female New Zealand white rabbits received occluded dermal applications (abraded and non-abraded skin) of 2, 20, or 200 mg cypermethrin/kg body weight in polyethylene glycol (PEG 300) for 6 h per day, 5 days per week, for 3 weeks. A control group was similarly treated with the vehicle only (PEG 300). Slight-to-moderate skin irritation was observed in rabbits receiving 2 and 20 mg/kg body weight; those receiving 200 mg/kg body weight showed slight-to-severe irritation. In the rabbits treated at 200 mg/kg, reductions were observed in food intake, body weight gain, and weight of gonads. No other changes were

noticed. No such effects were found at 20 mg/kg body weight (Henderson & Parkinson, 1981).

8.2.3 Intraveneous

8.2.3.1 Rat

Lock & Berry (1981) found biochemical changes in the rat cerebellum after a single iv administration of 25 mg cypermethrin/kg body weight. Signs of toxicity included: salivation, clonic convulsions, and sinuous writhing movements. The concentrations of cerebellar amino acids and cyclic nucleotides were determined at these stages of toxicity. Treatment with cypermethrin resulted in an increase in cerebellar cyclic GMP at the earliest stage, without changing cyclic AMP. Levels of blood- and cerebellar-glucose, lactate, and ammonia were also increased in most of the stages of toxicity. No changes were seen in concentrations of glutamate, glutamine, gamma-aminobutyrate, creatine, phosphate, or ATP in the cerebellum. The increase in cerebellar cyclic GMP did not appear to be related to the convulsive state of the animal or to the muscarinic cholinergic stimulation.

8.3 Long-Term Exposures

8.3.1 Rat

Wistar rats (24 of each sex per dose level and 48 of each sex as controls) were fed dietary concentrations of 0, 1, 10, 100, or 1000 mg cypermethrin/kg diet for 2 years. Additional groups (6 or 12 rats of each sex per dose level) were fed the diets for only 6, 12, or 18 months.

Throughout the 2-year study, the control and cypermethrin-treated animals were similar in terms of behaviour; no compound-related clinical signs were observed, except for a significantly-reduced growth rate in both males and females fed 1000 mg/kg diet. Survival was not affected by cypermethrin. No clinical-chemical, haematological, or histopathological changes were observed. The sciatic nerves from a number of animals of all groups, sacrificed after 6, 12, 18, or 24 months, showed a small number of nerve fibres exhibiting Wallerian degeneration. The incidence increased with age, but there was no difference in severity between the control and treated groups. It is concluded that doses of 100 mg cypermethrin/kg diet or less did not produce significant toxicological effects in rats over a 2-year period (McAusland et al., 1978).

Assays of liver microsomal enzyme activity in 6 rats of each sex fed 0 or 1000 mg cypermethrin/kg feed for 2 years

showed cypermethrin to be a weak inducer of the microsomal enzyme hepatic p-nitroanisole-O-dimethylase (PNOD), used as an index of monooxygenase activity (Potter & McAusland, 1980).

Five groups of Wistar rats, each composed of 52 males and 52 females, were given diets containing 0 (2 groups), 20, 150, or 1500 mg/kg diet (equivalent to 0, 1, 7.5, and 75 mg/kg body weight) for 2 years. Satellite groups of 12 male and 12 female rats were sacrificed at 52 weeks. For the first 6 weeks of the study, the rats in the 1500 mg/kg group received 1000 mg/kg. The purity of the cypermethrin was between 88% and 93% (cis-:trans- ratio; 55:45). After 104 weeks at the highest dose level, body weight loss, increased liver weight, increased smooth endoplasmatic reticulum in hepatocytes, and some haematological and other slight clinical changes were observed. No other changes or increase in the incidence of tumours were found. The dose of 150 mg/kg diet was considered to be the no-observed-adverse-effect level in this study (only a summary is given) (US-EPA, 1984).

8.3.2 Mouse

The effects of cypermethrin were investigated in groups of 70 male and 70 female Swiss mice fed diets containing 0 (2 groups), 100, 400, or 1600 mg/kg feed (equivalent to 0, 15, 60, or 240 mg/kg body weight) for up to 101 weeks. The purity of the cypermethrin was between 91.5 and 94.2%; cis-:trans- ratio; 53:47 or 54:46. Ten males and 10 females per group were killed at 52 weeks for interim haematological evaluation. Appearance, behaviour, and survival were similar in all groups. Body weight gain was reduced in mice fed 1600 mg cypermethrin/kg diet compared with the combined control groups. Food intake of both males and females was not significantly changed. Several haematological changes, consistent with a mild anaemia, were found in the 1600 mg/kg group of animals at the interim kill (decreased haemoglobin, haematocrit, and red blood cell counts in males; decreased mean cell volume and mean cell haemoglobin concentration in females) but were not found at termination. Thrombocytosis and increased liver weight were also observed in this group, at both the interim and terminal kills. There were no accompanying histopathological changes (for carcinogenic potential, see section 8.7). No effects were observed at dose levels of 400 mg/kg diet or less (Lindsay et al., 1982).

8.3.3 Dog

Cypermethrin (dissolved in corn oil) was administered to 4 groups of 8 beagle dogs of each sex at dose levels of 0, 1, 5, or 15 mg/kg body weight per day, by capsule, for a period of

52 weeks. The purity of the cypermethrin was 90.6% (cis-: trans- ratio; 54:46). The dogs in the highest dose group exhibited loss of appetite, tremors, gait changes, incoordination, disorientation, and hypersensitivity. No other abnormalities were found in the composition of the blood or urine or in organ weights. Dogs receiving 5 mg/kg or more showed liquid stools by this mode of administration. However, this effect was not found when cypermethrin was fed in the diet for 2 years. No effects were seen at 1 mg/kg (but only a summary is given) (US-EPA, 1984).

Groups of 4 male and 4 female Beagle hounds were fed diets containing 0, 3, 30, or 300 mg cypermethrin/kg feed for 2 years. An additional group received 1000 mg/kg feed but, because of severe intoxication signs, the dose was decreased to 750 mg/kg. The signs of intoxication consisted of licking and chewing of the paws, a stiff high-stepping gait, whole body tremors, head shaking, incoordination, ataxia, and convulsions. After 3 weeks of feeding at 750 mg/kg, the animals received the control diet, until signs of intoxication could no longer be seen. The dogs were then fed a diet containing 600 mg cypermethrin/kg from week 8 until termination at 2 years. No signs of intoxication were observed in dogs fed diets containing 0, 3, 30, or 300 mg/kg during the course of the study. There was reduced body weight gain in male dogs in the 600 mg/kg group. Clinical chemistry and haematological investigations, performed at 6-week intervals for 2 years, did not reveal any consistent differences between treated groups and controls. The minor changes in absolute organ weight observed in the brain and thyroid in the 300 mg/kg group were not present when the differences were corrected for terminal body weight. Furthermore, a dose relationship was not apparent, and there were no accompanying histopathological changes. Opthalmological observations performed during the course of the study did not reveal any ocular differences between treated groups and control. No abnormalities were found in the sciatic nerves, brain, or spinal cord in any of the treated groups. The feeding of diets containing up to 600 mg cypermethrin/kg diet to dogs for 2 years did not reveal any treatment-related gross or histopathological effects, although the dogs receiving diets containing 1000 mg/kg decreased to 600 mg cypermethrin/kg showed reduced body weight gain. Cypermethrin did not produce any toxicological effects in dogs fed dietary concentrations of 300 mg/kg feed or less, over 2 years (Buckwell, 1981).

8.4 Special Studies

8.4.1 Synergism/potentiation studies

8.4.1.1 Organophosphate mixture

In a study on rats, designed to determine whether an organophosphate insecticide, monocrotophos, potentiated the neurotoxic effect of cypermethrin, 5 groups of 7 or 8 male and 7 or 8 female rats were given 7 consecutive oral doses of monocrotophos (100 g/litre), cypermethrin (25g/litre), or a mixture of monocrotophos and cypermethrin (100 g/litre and 25 g/litre, respectively). Signs of intoxication and neurotoxic effects (biochemical changes consistent with very sparse axonal degeneration in sciatic/tibial nerves) were found to be wholly attributable to the monocrotophos component of the mixture, and there was no evidence of potentiation of neurotoxic effects (Rose & Dewar, 1979a).

8.4.1.2 Organochlorine mixture

The oral and dermal toxicities of cypermethrin and endosulfan for rats were determined both individually and combined. No evidence for enhancement of toxicity was found for either cypermethrin or endosulfan when administered as a 1:1 mixture in corn oil (Price, 1981b).

8.4.2 Neurotoxicity

8.4.2.1 Characterization of the neurotoxic effects

During preliminary short-term studies on cypermethrin, 2 observations were made:

(a) high doses of cypermethrin given orally to rats caused an unusual gait in intoxicated animals; and

(b) at lethal or near-lethal dermal or oral doses, histopathological changes (swelling and/or disintegration of axons of the sciatic nerve of rats) were observed; such observations have been reported to occur with other synthetic pyrethroids (Okuno et al., 1976a) and natural pyrethrins (Okuno et al., 1976b).

As a consequence of these findings, an extensive programme of work has been undertaken to characterize the neurotoxic effects of cypermethrin.

8.4.2.2 Neuropathological studies

(a) Rat

Single oral doses of cypermethrin in corn oil were given to groups of 6-12 rats of each sex at 100, 200, or 400 mg/kg body weight. All rats showed signs of intoxication, which varied in severity according to the dose level. At 400 mg/kg, severe clinical signs were seen within 2 days of dosing. Most of the animals showed swelling of the myelin sheaths and breaks of some of the axons of the sciatic nerves. At 200 mg/kg, 8 rats of each sex died or were killed within 48 h of dosing, and the remaining 4 of each sex survived the 9 days of the study. Nearly half of the animals showed lesions of the sciatic nerve. At 100 mg/kg, all rats survived 9 days of the trial. Only one female out of 12 showed minimal lesions of the sciatic nerve. Neuropathological changes were found in a number of animals dosed with 200 mg cypermethrin/kg body weight or more. Dose-related increases in signs of intoxication and neuropathy were observed; however, neuropathy was not detected in all the animals showing signs of intoxication (Carter & Butterworth, 1976).

Groups of rats (10 males per group) were fed dietary levels of cypermethrin (*cis*-:*trans*- = 45:55) at 0, 1250, 2500, or 5000 mg/kg diet for 14 days. Mortality was observed at the 2 higher doses and growth inhibition was seen in all treated groups. Clinical signs of neurotoxicity were characterized by an impaired ability to walk, splayed hind limbs, ataxia, and paralysis. Other clinical signs were hypersensitivity, gross disorientation, and convulsions. The neurotoxic signs of poisoning observed at 1250 mg/kg diet were reversible. Remission of ataxia at 2500 mg/kg diet was also noted. Ultrastructural changes in the sciatic nerve were observed in a small number of animals at the 2 highest dose levels. Some evidence of axonal damage in the myelinated nerves was observed, mainly in these groups (Glaister et al., 1977a).

In another study, rats were fed dietary concentrations of 0, 1, 10, 100, or 1000 mg cypermethrin/kg diet for 2 years (section 8.3). At the 12-month interim kill, part of the sciatic nerve was removed from 6 males and 6 females in both the control and 1000 mg/kg group. The dissected nerves were divided and teased into a fan shape, allowing each fibre to be examined. No significant difference was found in the incidence of abnormal nerve fibres in the control and the 1000 mg/kg group (Trigg et al., 1977; McAusland et al., 1978).

(b) Hamster

Groups of 6 male and 6 female Syrian hamsters were given single oral doses of cypermethrin in corn oil at 0, 794, 1000, and 1260 mg/kg body weight. Signs of intoxication (generally tiptoe walking, tremors, irregular movements) occurred in all groups receiving cypermethrin. Animals died or were killed at times varying from a few hours to 9 days after dosing. Of the 31 animals of the different test groups that were examined, 3 had nerve lesions, axonal swelling, and axonal breaks in the sciatic and posterior tibial nerves (many animals died within a few hours) (Butterworth & Clark, 1977).

(c) Chicken

In a delayed neurotoxicity study on 6 adult domestic hens, cypermethrin in DMSO did not cause histological lesions in the nervous system (brain, spinal cord, and sciatic nerves) or signs of intoxication at an oral dose of 1000 mg/kg body weight per day for 5 days, compared with a positive control group. No delayed neurotoxicity was observed (Owen & Butterworth, 1977).

8.4.2.3 Biochemical and electrophysiological studies

Biochemical and electrophysiological studies have been carried out because the sparse axonal degeneration described above is difficult to demonstrate by conventional histopathological techniques. Furthermore, evidence was required to quantify the neurological dysfunction attributable to cypermethrin. The rationale for measuring the activities of beta-glucuronidase and beta-galactosidase in conjunction with an assessment of "mean slip angle" and "mean landing foot spread" as markers for axonal degeneration has been described by Dewar (1977a,b).

(a) Rat

Using biochemical markers, it has been shown that, at high oral doses of cypermethrin, sparse axonal degeneration occurs in the sciatic/posterior tibial nerves (Dewar, 1977b; Rose & Dewar, 1983), and the trigeminal nerve and trigeminal ganglion of Wistar rats (Dewar & Moffett, 1978a).

Three studies involving repeated oral administration of cypermethrin to rats at 150 mg/kg body weight for 5 or 7 days and 0, 25, 50, 100, or 200 mg/kg body weight for 5 or 7 days have been carried out. Mortality occurred from 100 mg/kg body weight onwards. A dose-related transient functional impairment, assessed by means of the inclined plane test, was

found in the first week. Significant increases in beta-glucuronidase or beta-galactosidase activity of the sciatic, tibial, or trigeminal nerves only occurred with 5 or 7 doses of 150 or 200 mg/kg body weight. The sensitivity of these nerves is comparable. Complete functional recovery occurred within 26 days. Increased activity of the enzymes in the distal portion of nerves was found but, even in the most severely intoxicated animals, the magnitude of the increases was less than that induced by the known neurotoxic agent methylmercury chloride (Dewar, 1977b; Dewar & Moffett, 1978a; Rose & Dewar, 1983).

Biochemical changes, consistent with primary axonal degeneration, were detected in rats aged 3, 6, or 12 weeks. Cypermethrin was more acutely toxic for 3-week-old rats than for 12-week-old rats and the dose required to cause a sparse axonal degeneration, as demonstrated by biochemical changes, was proportionally smaller for the younger rats (Rose & Dewar, 1978).

The time-course for development and recovery from axonopathy was investigated in groups of rats (5 of each sex) at periods of 2-12 weeks after the start of dosing. The daily doses were 150 mg/kg body weight for the first 11 doses and 100 mg/kg body weight for the subsequent 9 doses, over a period of 4 weeks. More than half of the animals died and more than 80% of the treated animals showed clinical signs of intoxication, characterized by abnormal gait, ataxia, salivation, lethargy, chromodacryorrhoea, piloerection, and hypersensitivity to external stimuli. Maximum enzyme activities in the sciatic posterior tibial nerves were found after 5 weeks and had returned to control values by 12 weeks. In a second phase of the study, 10 male and 10 female rats were given 20 oral doses of cypermethrin at 37.5, 75, or 150 mg/kg body weight per day, (concurrent control group dosed with DMSO), over a 4-week period. The animals given 75 and 150 mg/kg showed clinical signs of intoxication. Mortality also occurred at the highest dose level. The behaviour and appearance of animals in the 37.5 mg/kg body weight per day group were similar to those of the controls. Five weeks after the initial dose, biochemical changes, which were indicative of a mild axonal degeneration, were observed in animals in the highest dose group. No consistent or biologically significant neurobiochemical changes were found in the 37.5 or 75 mg/kg body weight groups. The results of this study demonstrated that 20 oral doses of cypermethrin at 75 mg/kg body weight per day administered over a 4-week period, produced mild clinical signs of intoxication; however, no biochemical changes which were indicative of peripheral neuropathy were seen (Rose, 1983).

Further evidence to support the minor nature of the nerve lesions has been afforded by electrophysiological studies on rats. In these studies, measurements of the maximal motor conduction velocities and conduction velocity of slower fibres in the sciatic and tail nerves of Wistar rats were made before, and at intervals of up to 5 weeks after, exposure to single (200 mg/kg body weight) or repeated doses (7 doses of 150 mg/kg body weight) of cypermethrin. Even at near-lethal doses, cypermethrin did not cause any effects on these parameters (Dewar & Deacon, 1977).

The ability of the major metabolite of cypermethrin, PBA, to produce axonal changes has been investigated. Four groups of 8 male and 8 female rats given 7 consecutive daily oral doses of 0, 25, 77, or 375 mg/kg body weight did not show any biochemical changes indicative of peripheral nerve damage. The sparse axonal degeneration observed with high doses of cypermethrin is, therefore, not caused by PBA (Rose & Dewar, 1979b).

(b) Hamster

In 3 studies, Chinese hamsters were given oral doses of 5-30 mg cypermethrin/kg body weight per day, for 5 consecutive days. Clinical signs of intoxication were observed and tests made to assess whether the compound produced degenerative changes in peripheral nerves and sensory ganglia. Beta-glucuronidase, and beta-galactosidase activities were measured in the sciatic/posterior tibial nerves and trigeminal ganglion. A positive control group received 7.5 mg methylmercury chloride/kg body weight per day, for 5 consecutive days.

The most striking feature in the hamsters treated with doses exceeding 5 times 20 mg/kg body weight was a marked loss of fur in the facial area, neck, and back, due to repeated scratching. The results of the enzyme determinations suggest that the Chinese hamster like the rat developed sparse axonal degeneration following oral doses in excess of 5 times 10 mg/kg body weight (Dewar & Moffet, 1978b)

(c) Rabbit

Rabbits were administered capsules with 0 (corn oil), 75, 150, or 300 mg cypermethrin (93.5%)/kg body weight in corn oil, 5 times a week, for 6 weeks. At the end of the 6th week, electroencephalographic records were taken. The waves of the complex EEG activity as well as the performance of the 6 constituting bands of different frequency were computer analysed. No significant alterations were found (Desi et al., 1986a).

8.4.2.4 Appraisal

Repeated oral administration of cypermethrin to rats, at doses sufficiently high to produce significant mortality in a group of animals, produced biochemical changes in peripheral nerves that were consistent with sparse axonal degeneration. The magnitude of the biochemical changes was similar to that of changes produced with either a single (Dewar, 1977b) or repeated doses of shorter duration (Dewar & Moffet, 1978a), thus demonstrating a lack of cumulative effect. The magnitude of change was substantially less than that encountered with established neurotoxic agents and the site of maximal enzyme change (distal portion of the nerve) suggests that the degeneration is more likely to be of a Wallerian type rather than segmental demyelination. The short time required to produce ataxia and/or abnormal gait rules out a causal relationship between ataxia and axonopathy. The clinical signs are consistent with a pharmacologically-mediated effect whereas the axonopathy is a minor reversible lesion that occurs several days after exposure and has also been detected in animals that do not show clinical signs.

Histopathological lesions of some fibres of the sciatic nerve have only been demonstrated in rats or hamsters receiving extremely high, lethal or near lethal, oral doses of cypermethrin (Carter & Butterworth, 1976; Butterworth & Clark, 1977). Compound related histopathological changes have not been observed in rats exposed to cypermethrin through inhalation (Blair et al., 1976) or in rats fed diets containing 1000 mg cypermethrin/kg over a 1-2 year period (Trigg et al., 1977; McAusland et al., 1978). Furthermore, dogs fed 1500 or 600 mg cypermethrin/kg diet for 3 or 24 months, respectively, did not have any compound-related lesions of the sciatic nerve (Buckwell & Butterworth, 1977; Buckwell, 1981).

The results of biochemical studies, used as sensitive indicators of change, confirmed that minor changes that occur after massive exposure to cypermethrin are reversible and are not necessarily associated with clinical signs (Dewar, 1977b; Dewar & Moffet, 1978a; Rose, 1983). There was no direct correlation between the time course of the neuromuscular dysfunction and the neurobiochemical changes (Rose & Dewar, 1983). The metabolite of cypermethrin, PBA, did not produce any biochemical changes in peripheral nerves (Rose & Dewar, 1979b).

8.4.3 Immunosuppressive action

Stelzer & Gordon (1984) studied the in vitro effects of pyrethroids on the mitogenic responsiveness of murine splenic

lymphocytes to concornavalin A and lipopolysaccharide. The results of these studies showed that at concentrations of the order of 1-10 µmol/litre, inhibition of murine splenic lymphocytes to both B and T cell mitogens was found. These results support the possibility of immune suppression by pyrethroid (cypermethrin) exposure.

Desi et al., (1985, 1986a) studied the short-term effects of 6.25, 12.5 or 25 mg cypermethrin (93.5%)/kg body weight in rats, on the immune system by measuring the autologous rosette formation of T-lymphocytes and determining the ovalbumin titre. These studies were performed over a period of 6 or 12 weeks.

The humoral immune response after vaccination with Salmonella typhimurium and the cell-mediated immune response were determined in rabbits. The antibody titre was measured by tube-agglutination and complement-binding tests and the tuberculin skin test was used for the immune response test. The dose levels in this study were 75, 150, or 300 mg/kg body weight, for 7 weeks. A significant dose-dependent decrease was observed in both the anti-ovalbumin titre of the blood-serum and in the autologous rosette formation of the T-lymphocytes. In rabbits, the 2 highest dose levels induced a significant dose-dependent decrease in serum antibody titres and the tuberculin skin test showed the same dose-dependent tendency.

8.5 Reproduction, Embryotoxicity, and Teratogenicity

8.5.1 Reproduction

Cypermethrin was fed to Wistar rats (30 male and 30 female per group) at dietary concentrations of 0, 10, 100, or 500 mg/kg for 5 weeks, after which the males and females (10 weeks of age) from each treatment group were mated. Two successive litters were produced from each pair. The first of these litters was discarded, and randomly-selected male and female pups of the second litters were mated to produce the next generation. The study was continued until 2 litters from each of 3 successive generations had been bred. The parent animals in the 500 mg/kg group consumed less food than the controls and this was accompanied by a reduction in body weight. Otherwise, the parent animals of control and treatment groups behaved similarly. Cypermethrin did not cause any adverse effects on the reproductive performance of the rats or on the survival of the offspring. No consistent changes were observed in mean litter weight between birth and weaning in any treatment group, with the exception of a reduction in total litter weights in the 500 mg/kg F_{1a} litters on days 4, 14, and 21. There was also a statistically-significant

decrease compared with controls in total litter weights and size in the F_{1b} litters at 500 mg cypermethrin/kg diet. In the 500 mg/kg F_0 group, one animal showed a squamous cell carcinoma of the skin. However, this was considered not to be related to the compound, because no increase in tumour incidence was found in the long-term studies on rats and mice. No changes were observed in rats administered 100 mg/kg diet (Hend et al., 1978).

8.5.2 Embryotoxicity and teratogenicity

8.5.2.1 Rat

Groups of pregnant female Sprague Dawley CD rats (25 animals per group) were administered cypermethrin orally as a 1% solution in corn oil at doses of 0, 17.5, 35, or 70 mg/kg body weight per day, from days 6 to 15 (inclusive) of gestation. Cypermethrin at 17.5 mg/kg body weight per day did not affect maternal performance or fetal survival and development. At the higher doses of 35 and 70 mg/kg body weight, respectively, slight and significant retardation of maternal body weight gain was recorded. In addition, at 70 mg/kg per day, slight to severe neurological disturbances were observed in nearly half of the females including: slight splaying of the hind legs while walking ranging to severe splaying of all limbs, involuntary movements of the jaws, convulsive spasms, and hypersensitivity to noise. Despite this maternal toxicity, there were no indications of any embryotoxic or teratogenic effects of cypermethrin (Tesh et al., 1978).

8.5.2.2 Rabbit

Groups of pregnant female Banded Dutch rabbits (30 controls and 20 for each dose group) were dosed orally with 0, 3, 10, or 30 mg cypermethrin/kg body weight per day in corn oil (by gelatin capsule) during days 6-18 (inclusive) of gestation. No influence was found on growth, pre-implantation losses, resorptions, fetal deaths, or numbers and sizes of fetuses. The incidence of fetal visceral and/or skeletal abnormalities was comparable to that in the vehicle control group, except for a slight increase in the mean percentages of fetuses showing visceral and/or skeletal abnormalities in the group receiving 30 mg/kg body weight per day. No teratogenic effects were found in this study (Dix, 1978).

8.6 Mutagenicity and Related End-Points

8.6.1 In vitro studies

8.6.1.1 Microorganisms

Using bacterial assays, no increases in the reversion rates of Escherichia coli WP2, E. coli WP2 uvrA, Salmonella typhimurium TA 1535, TA 1537, TA 1538, TA 98, and TA 100 were detected with cypermethrin (concentrations of up to 2 mg per plate) in the presence or absence of a rat liver microsomal activation system. Exposing Saccharomyces cerevisiae JD1 in liquid culture to cypermethrin at concentrations of up to 5 mg/ml, both in the presence and absence of a rat liver microsomal activation system, did not result in any increase in the rate of mitotic gene conversion (Brooks, 1980).

In a study in which cypermethrin was tested for mutagenicity in Salmonella typhimurium TA 100 or TA 98, in the presence or absence of a rat liver activation system, using the plate incorporation assay, concentrations of up to 1 mg/plate gave negative results. The same was true with the fluctuation test, with concentrations of up to 10 µg/ml (Pluymen et al., 1984).

8.6.1.2 Mammalian cells

Cypermethrin was tested for mutagenicity in V_{79} Chinese hamster cells. No cytotoxicity was observed when the assay was carried out in the presence of rat hepatocytes. Cypermethrin was found not to be mutagenic for either genetic locus (OUA' and TG') in V_{79} cells, when tested in concentrations up to 20 µg/ml, in the presence or absence of rat hepatocytes (Pluymen et al., 1984).

8.6.2 In vivo studies

8.6.2.1 Host-mediated assay

There was no increase in the rate of mitotic gene conversion in Saccharomyces cerevisiae JD1 harvested from male mice following a single oral dose of cypermethrin at 25 or 50 mg/kg body weight for 2 days (Brooks, 1980).

8.6.2.2 Dominant lethal assay

No evidence of dominant lethality was found when male CD1 mice (3 groups of 12 animals and a control group with 36 animals) were given single oral doses of 6.25, 12.5, or 25 mg cypermethrin/kg body weight. Two other groups were given 5

consecutive daily oral doses of 2.5 or 5 mg/kg body weight (controls received the vehicle DMSO). A significant reduction in fetal implants during the second week of mating was noted and a marginal increase in early fetal deaths was observed at 5 mg/kg per day. This effect was not confirmed in a second study using oral doses of 2.5, 5, 7.5, or 10 mg/kg body weight for 5 consecutive days, when no effects were found on reproductive capability or the histopathology of the testes and epididymis. The marginal differences found in the 5 mg/kg per day group in the second study were considered not to be related to the compound.

In summary, cypermethrin did not show detectable dominant lethality after administration of doses of up to 10 mg/kg body weight per day, for 5 days, or as a single oral dose of 25 mg/kg body weight (Dean et al., 1977).

8.6.2.3 Bone marrow chromosome study

Chinese hamsters (12 of each sex per group) were orally dosed with 20 or 40 mg cypermethrin/kg body weight, in DMSO, for 2 successive days. The incidence of chromosome abnormalities in bone marrow cells, 8 and 24 h after dosing, did not differ from that in the DMSO control animals. The positive control group (100 mg/kg cyclophosphamide) showed many chromosomal aberrations (Dean, 1977).

The effects of cypermethrin on sister chromatid exchange were studied in the bone marrow cells of 3-month-old mice. Cypermethrin was injected subcutaneously at 0.75, 1.5, or 3 mg/kg body weight or 2.5, 5.0, or 10 mg Ripcord/kg body weight. Both the technical and the formulated products showed a dose-related increase in sister chromatid exchanges in the dividing cells at all dose levels. The highest doses of both cypermethrin and Ripcord completely inhibited mitotic division (Seehy et al., 1983).

8.6.2.4 Micronucleus test

The induction of micronuclei was studied in mouse bone marrow. Cypermethrin was administered by 3 routes: intraperitoneal, oral, and dermal. Cypermethrin showed mutagenic potential after oral administration of 900 mg/kg diet for 7 and 14 consecutive days. No effects were seen after ip administration of a single injection of 60 or 180 mg/kg body weight or double and triple injections of 60 mg/kg body weight.

Up to 4 dermal treatments with 360 mg cypermethrin/kg body weight resulted in a significant increase in the frequency of polychromatic erythrocytes with micronuclei (Amer & Aboul-Ela, 1985).

8.7 Carcinogenicity

8.7.1 Oral

8.7.1.1 Rat

Wistar rats (24 of each sex per dose level and 48 of each sex as controls) (section 8.3) were fed dietary concentrations of 0, 1, 10, 100, or 1000 mg cypermethrin/kg for up to 2 years in a combined long-term/carcinogenicity study. No evidence for carcinogenicity was found in this study (McAusland et al., 1978) (section 8.3.1).

No increase in tumour incidence was seen when Wistar rats were given diets containing 0, 20, 150, or 1500 mg cypermethrin/kg diet (equivalent to 0, 1, 7.5, or 75 mg/kg body weight) for 2 years. The purity of the cypermethrin (*cis*-:*trans*- ratio; 55:45) was between 88% and 93% (section 8.3.1) (US EPA, 1984).

8.7.1.2 Mouse

Swiss mice (70 male and 70 female) were fed diets containing 0 (2 groups), 100, 400, or 1600 mg cypermethrin/kg feed for up to 101 weeks. Effects consisted of increased liver weights at 400 and 1600 mg/kg diet and decreased body weight, thrombocytosis, and mild anaemia at 1600 mg/kg diet (section 8.3.2).

There were no compound-related changes in non-neoplastic histopathology or increases in tumours of types that are not commonly associated with the mouse strain used. The incidence of tumours was similar in all groups with the exception of a slightly increased incidence of benign alveolar lung tumours in the females in the 1600 mg/kg group. However, the magnitude of this increased incidence was insufficient when compared with concurrent and historical control incidence, to warrant concern. There was no evidence for a decreased latency of benign alveolar lung tumours in the female mice receiving the highest dose, and this tumour type was not accompanied by any increase in malignancy. There was also no evidence of a carcinogenic response in the male mice in this study. Furthermore, benign alveolar lung tumours are know to occur in both sexes at a high and variable incidence in this strain of mouse. Therefore, it is considered that the occurrence of benign alveolar lung tumours in the female mice receiving the highest dose was not related to treatment with cypermethrin. Feeding cypermethrin at levels of up to 1600 mg/kg diet to mice for a life-time did not produce any evidence of carcinogenicity (Lindsay et al., 1982).

8.8 Mechanisms of Toxicity - Mode of Action

In the classification in the Appendix, cypermethrin is classified among the Type II compounds, which cause toxic signs of choreoathetosis with salivation (CS-syndrome) in the rat (Verschoyle & Aldridge, 1980) and bursts of spikes in the cercal motor nerve of the cockroach (Gammon et al., 1981). Pyrethroids having α-cyano-3-phenoxy-benzyl alcohol, such as cypermethrin, do not induce repetitive firing in the cercal sensory nerves of the cockroach in vivo or in vitro, but cause different signs including a pronounced convulsive phase (Gammon et al., 1981).

The intravenous toxicity of 1RS-cis-, and 1RS-trans-cypermethrin for the rat has been examined. Both compounds cause the CS-syndrome, which is characterized by initial pawing and burrowing behaviour, followed within 2-5 min by profuse salivation, coarse whole-body tremor, increased startle response and abnormal locomotion involving the hind limbs. The coarse tremor progresses into sinuous writhing (choreoathetosis) of the whole body, which gradually becomes more violent and is enhanced by sensory stimuli. Clonic seizures are occasionally observed as a terminal event. No increase in core temperature occurs and, in fact, it may fall. In the electroencephalogram (EEG) during the CS-syndrome, poisoned rats showed generalized spike and wave discharges, prior to choreoathetosis (Verschoyle & Aldridge, 1980). The primary site of action resulting in the CS-syndrome has not yet been decided.

It has been suggested (Van den Bercken, personal communication, 1981) that the facial skin sensations experienced by people who handle cypermethrin or other pyrethroids (section 9.2.2) are brought about by repetitive firing of sensory nerve terminals in the skin. In the opinion of the author, this is a strictly local effect that may occur as soon as the pyrethroid concentration on or in the skin reaches a certain level and is not a sign of general intoxication. It is considered by the author that the occurrence of these skin sensations are a warning signal indicating that exposure has occurred. No undue hazard is likely, provided the pyrethroid does not reach the blood in any significant concentration. In this connection, it was stressed that, although cypermethrin is among the least toxic insecticides when administered orally, it may become highly toxic, whenever it reaches the nervous system in sufficient concentrations.

The question remains whether there is a causal relation between the intense repetitive activity induced by α-cyano pyrethroids (of which cypermethrin is an example) and the nerve damage that occurs in experimental animals after

prolonged exposure to nearly lethal concentrations of these compounds. Because of the large number of different chemicals, most of which do not cause repetitive activity in the nervous system but are known to cause serious nerve damage, such a correlation is hardly expected. Furthermore, the extensive literature on DDT (which causes the same type of repetitive activity in sense organs and in sensory nerve terminals as the non-cyano pyrethroids) does not contain any indication that this insecticide may cause axonal degeneration. However, in theory, there is a possibility that repeated occurrence of intense repetitive firing will eventually lead to dysfunction of sensory nerve terminals and sense organs, and, finally, to degeneration of sensory nerve fibres (Van den Bercken, personal communication, 1981; Van den Bercken & Vijverberg, 1980[a]).

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[a] Van den Bercken, J. & Vijverberg, H.P.M. (1980) Letter (personal communication) to WHO concerning "Mode of action of pyrethroid insecticides in the vertebrate nervous system" (dated April, 1980).

9. EFFECTS ON MAN

9.1 General Population Exposure

9.1.1 Acute toxicity: poisoning incidents

One report of accidental intoxication has been described. A family who ate food cooked in 10% cypermethrin developed nausea, prolonged vomiting with colicky pain, tenesmus, and diarrhoea within minutes of ingestion. One male adult had convulsions, passed into coma, and died due to respiratory paralysis. The symptoms were less severe in other members of the family (Poulos et al., 1982). There is some doubt whether this was a cypermethrin intoxication (Suthers, personal communication).

9.1.2 Controlled human studies

Flannigan & Tucker (1985) studied the differences in the extent of paraesthesia induced by a number of pyrethroids. Field strength formulated cypermethrin (0.13 mg/cm^2) was applied (0.05 ml) to a 4 cm^2 area of the earlobe of volunteers on 5 occasions. Distilled water was applied to the opposite earlobe. 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 other pyrethroids. Cypermethrin (as the other pyrethroids) induced sensation. The paraesthesia developed with a latency period of approximately 30 min, peaked by 8 h and deteriorated as early as 24 h. Dl-alpha tocopheryl acetate markedly inhibited the occurrence of the paraesthesia.

9.1.3 Epidemiological studies

No information is available.

9.2 Occupational Exposure

9.2.1 Acute toxicity: poisoning incidents

No information is available.

9.2.2 Effects of short- and long-term exposure

Laboratory workers and field operators handling natural and synthetic pyrethroids, including cypermethrin, have noticed a transient sensation (described as "tingling" or

"burning" sensations) of the skin in the periorbital area of the face and of other sites after direct skin exposure. The skin sensations have been interpreted (section 8.8) as being caused by spontaneous repetitive firing of local sensory nerve fibres or nerve endings, with thresholds that have been transiently lowered by the compound (Wouters & Van den Bercken, 1978). There is a delay of about 30 min before onset of these symptoms following pyrethroid exposure; the sensation generally lasts only a few hours and does not persist for more than one day after exposure (Van den Bercken & Vijverberg, 1980[a], Le Quesne et al., 1980).

In a clinical and electrophysiological assessment of these skin sensations (paraesthesia), 23 laboratory workers, who had been exposed to synthetic pyrethroids during the preceding months, were examined. Nineteen of the 23 workers had experienced at least one or more episodes of facial sensations. Neurological signs were not observed and electrophysiological studies of selected motor and sensory nerves in the legs and arms of the 23 subjects showed no abnormalities (Le Quesne et al., 1980).

Field studies have been performed in the Côte d'Ivoire in which cypermethrin was sprayed on cotton using a hand-held, ultra-low-volume (ULV) commercial spraying machine. This method of application represented a situation of high potential exposure. The first study, in which 17 workers were involved, concerned a single exposure to cypermethrin (Prinsen & Van Sittert, 1978), while a second study was conducted in which 7 workers took part in 7 consecutive spray sessions (Prinsen & Van Sittert, 1979). Skin exposure to cypermethrin was assessed by quantitative measurement of the compound deposited on aluminium foil pads on the body of the sprayer during the spraying operation. The rate of dermal exposure of the operators during spraying ranged from 1.5 to 46.1 mg/h. Total absorption of cypermethrin in the body was monitored by urinary analysis for 2,2-dichlorovinyl-3,3-dimethylcyclopropane-1-carboxylic acid, a metabolite of cypermethrin. In most of the samples, the excretion was below the limit of detection (0.05 mg/litre), indicating a low level of absorption. It was estimated that approximately 3% of the total dermal dose was absorbed. General medical, extensive clinical blood chemistry, and electrophysiological examinations were carried out of selected motor and sensory periph-

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[a] Van den Bercken, J. & Vijverberg, H.P.M. (1980) Letter (personal communication) to WHO concerning "Mode of action of pyrethroid insecticides in the vertebrate nervous system" (dated April, 1980).

eral nerves in the legs and arms, of the trigeminal nerve, and of the facial nerve. No effects were found.

In another field study in India, 18 workers, including spraymen (spraying an emulsifiable concentrate formulation by mist-blower or knap-sack), mixers, and loaders, handled cypermethrin daily for 5 consecutive days. Medical examination, with special attention to the sensory function of the peripheral nervous system, was carried out before, during, and after spraying (Suthers & Marlow, 1981). No compound-related adverse clinical effects of peripheral neuropathy were noticed in any of the workers. The urinary excretion of the cypermethrin metabolite (methyl ester of the cyclopropane carboxylic acid moiety) increased from day 1 to 5 of the study, but decreased 24 h after spraying had ceased. On the fifth day, concentrations of up to 0.18 mg (average 0.1 mg) were found in the 24-h urine of workers using the mist-blower. Concentrations were lower in workers using the knap-sack sprayer.

A field study was carried out on Indian workers in the Satara district in India prior to, during, and after spraying cotton with the synthetic pyrethroid formulations, permethrin (Ambush) and cypermethrin (Cymbush). The formulations were applied using a mist-blower or knap-sack spray. Exposure of 7 spraymen and 2 loaders/mixers was monitored by measuring the 24-h urinary excretion of 3-(4'-hydroxyphenoxy)-benzoic acid, and medical assessments were carried out by 4 medical doctors. The sensory function of the peripheral nervous system was also assessed. The formulations were applied at the recommended rates; Ambush, 150 g a.i./ha and Cymbush, 70 g a.i./ha. Average exposure was approximately 8 h per day for 5 days. No compound-related adverse clinical effects were noticed. The average urinary excretion of 3-(4'-hydroxyphenoxy)-benzoic acid increased from day 1 to day 5, but then decreased 24 h after spraying had ceased (Hart et al., 1982).

In another study, two agricultural pilots and five mixer/loaders were monitored for dermal exposure during aerial "ultra-low-volume" (ULV) applications of cypermethrin in vegetable oil to cotton. This study was conducted in Greenwood, Mississippi. The mixer/loaders wore protective equipment. The actual dermal exposure for pilots was 0.67 mg/8 h and for mixer/loaders 2.43 mg/8h. The exposure of pilots was predominantly of the hands, whereas that of mixer/loaders was more uniform (hands were protected). The urinary excretion of cypermethrin metabolites was very low; between 4 and 22 µg cypermethrin equivalents/day. This study demonstrates that exposure of pilots and mixer/loaders during the aerial ULV applications of cypermethrin is minimal and that skin absorption is very slight (Chester et al., 1986).

Desi et al. (1986b) carried out a biological monitoring and health surveillance study on 11 workers spraying organophosphate carbamate and pyrethroid pesticides in greenhouses during the whole year in comparison with 10 control persons. During the work, protective clothing and masks were worn before and after a regular spraying period with pyrethroids (including cypermethrin). Extensive medical examinations, such as urinalysis, haematology, immunoglobulin levels, whole blood cholinesterase activity, serum-gamma-glutamyltransferase activity, chromosome analysis and electrocardiography were performed over a period of 3 months. The amount of cypermethrin in the blood was just at the limit of detection. No health injuries or other significant changes in the parameters studied were found.

10. EVALUATION OF HEALTH RISKS FOR MAN AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation

Cypermethrin, an α-cyano pyrethroid consisting of a mixture of 8 stereo-isomers, is a highly active insecticide effective against a wide range of pests in many food and non-food commodities.

It is stable to light and heat, it has a low vapour pressure and is more stable in acidic than in alkaline media. Sensitive analytical methods for the determination of residues in food and the environment are available.

When cypermethrin is applied to crops, residues may occur in soils and surface waters, but biological degradation is fairly rapid and residues do not accumulate in the environment. Photodegradation is unlikely to play an important role. The main route of degradation is cleavage of the ester linkage to give 2 main degradation products containing the cyclopropane, and the phenoxybenzyl moiety. The half-lives in the soil are determined by many factors, but are in the range of 2-4 weeks. Cypermethrin is strongly adsorbed by soil and downward leaching is negligible. Because of its rather fast breakdown forming less toxic products, and the low dose rates used in good agricultural practice, it is unlikely that cypermethrin will attain significant levels in the environment.

Bioaccummulation in certain organisms, such as fish, took place under laboratory conditions, but levels declined on cessation of exposure and there are indications that, under natural conditions, fish will not contain measurable residues.

When applied according to good agricultural practice, the levels of cypermethrin residues in food commodities are generally low. Total diet studies are not available, but from the available residue information, it can be inferred that the oral intake by man is well below the ADI.

High dose levels of cypermethrin may exert transient effects on the soil microflora. Earthworms and other soil organisms are generally rather resistant to cypermethrin, while fish and other aquatic invertebrates are very sensitive. Because of its strong adsorption on soil, only low levels of cypermethrin may leak into surface water. These may have transient effects, mainly on surface breathing insects.

The toxicity of cypermethrin for birds is low. Bees appear to be very sensitive in laboratory tests. Under field conditions, the effect on bees is minimal, because cypermethrin seems to have a repellent effect for bees.

Absorption and elimination of cypermethrin has been rapid in the different mammalian species tested. The major metabolic reaction is cleavage of the ester bond followed by hydroxylation and conjugation of the cyclopropane- and phenoxybenzyl moiety. The highest levels are found in body fat, which is consistent with the lipophilic nature of cypermethrin. The half-life in the fat of the rat is about 12-19 days for the cis-isomer and 3-4 days for the trans-isomer. Breakdown products in plants are bound as glucosides.

The acute toxicity of cypermethrin for mammals is of a moderate order. The oral LD_{50} for the rat ranges from 200 to 4000 mg/kg body weight. Short-term and long-term toxicity studies on rats, mice, and dogs have shown effects on growth, on the liver and kidneys, and the nervous system, and on haematology. A no-observed-adverse-effect level of 7.5 mg/kg body weight has been adopted by the Task Group.

Cypermethrin was not carcinogenic for mice or rats fed diets containing high levels of the material over a 2-year period. Cypermethrin did not induce teratogenic effects in either rats at 70 mg/kg body weight or rabbits at 30 mg/kg body weight. It was also shown not to have any effects on reproductive performance during a 3-generation reproduction study in rats administered 100 mg/kg diet. In a variety of mutagenicity studies, cypermethrin was shown to be mainly without mutagenic activity.

The mechanism of the action on the nervous system has been extensively studied. From these studies and the occupational studies available, it seems that the skin sensation seen in workers handling cypermethrin, generally lasts only a few hours and does not persist for more than one day after exposure. Other neurological signs were not observed. These skin sensations can be considered to be an early warning that exposure has occurred and that work practice should be reviewed. Cypermethrin may cause eye irritation and may be a sensitizer for certain persons.

10.2 Conclusions

It can be concluded that:

General population: When applied according to good agricultural practice, exposure of the general population to cypermethrin is negligible and is unlikely to present a hazard.

Occupational exposure: With reasonable work practices, hygiene measures, and safety precautions, the use of cypermethrin is unlikely to present a hazard to those

occupationally exposed to it. The occurrence of "facial sensations" is an indication of exposure. Under these circumstances work practice should be reviewed.

Environment: With recommended application rates it is unlikely that cypermethrin or its degradation products will attain levels of environmental significance. Notwithstanding its high toxicity for fish and honey bees, this is only likely to cause a problem in the case of spillage and overspraying.

11. RECOMMENDATIONS

- Cypermethrin should be included among the residues looked for in surveillance, market-basket, or total diet studies.

- Attention should be paid to the implications for the welfare of human beings of animal studies indicating immune suppression.

- Further follow-up studies into the facial effects in human beings should be conducted, in order to better understand this phenomenon.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

Cypermethrin was discussed at meetings of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) during the period 1979-84 (FAO/WHO, 1980a,b; 1982a,b; 1983a,b; 1984; 1985a,b,c; Vettorazzi & Van den Hurk, 1984). In 1981, the JMPR established an Acceptable Daily Intake (ADI) for cypermethrin of 0-0.05 mg/kg body weight.

The Pesticide Development and Safe Use Unit, Division of Vector Biology and Control, WHO, classified cypermethrin as "irritant to eyes and sensitizer of skin" in the list of "technical products unlikely to present an acute hazard in normal use" (Plestina, 1984; WHO, 1979; WHO, 1985). The same division published a data sheet on cypermethrin, No. 84.58 (WHO/FAO, 1975-85).

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APPENDIX

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 (Van den Bercken et al., 1979; WHO, 1979; Verschoyle & Aldridge, 1980; Glickman & Casida, 1982; Lawrence & Casida, 1982). The same distinction was found in studies on cockroaches (Gammon et al., 1981).

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 (Gammon et al., 1982; Gammon & Casida, 1983; Lawrence & Casida, 1983; Lawrence et al., 1985).

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 (Van den Bercken et al., 1973). 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 (Van den Bercken, 1977). 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 (Vijverberg et al., 1983).

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 (Flannigan & Tucker, 1985).

In the isolated node of Ranvier, allethrin causes prolongation of the transient increase in sodium permeability of the nerve membrane during excitation (Van den Bercken & Vijverberg, 1980). 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 (Vijverberg et al., 1983).

The effects of cismethrin on synaptic transmission in the frog neuromuscular junction, as reported by Evans (1976), 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 (Van den Bercken et al., 1973, 1979; Vijverberg et al., 1982b).

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 intermittantly, cause large depolarizing afterpotentials, and evoke repetitive

firing with minimal effect on the resting potential (Lund & Narahashi, 1983).

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 (Ruigt & Van den Bercken, 1986).

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 (Vijverberg et al., 1982a). 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 (Vijverberg & Van den Bercken, 1979; Vijverberg et al., 1983).

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 (Vijverberg & Van den Bercken, 1979; Vijverberg et al., 1983). 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 (Lund & Narahashi, 1983).

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 (Gammon et al., 1982).

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 (Lawrence & Casida, 1983).

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 (Lawrence et al., 1985).

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 (Gammon & Casida, 1983).

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 (Ruigt & Van den Bercken, 1986).

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 (Wouters & Van den Bercken, 1978; WHO, 1979).

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 (Vijverberg & Van den Bercken, 1982).

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