

IPCS International Programme on Chemical Safety

*Environmental Health  
Criteria 96*

d-Phenothrin



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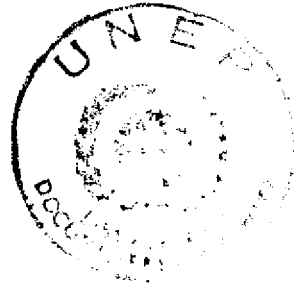
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## **Environmental Health Criteria 96**

# d-PHENOTHRIN

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World Health Organization  
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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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FOR D-PHENOTHRIN**

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## NOTE TO READERS OF THE CRITERIA DOCUMENTS

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

\* \* \*

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

\* \* \*

The proprietary information contained in this document cannot replace documentation for registration purposes, because the latter has to be closely linked to the source, the manufacturing route and the purity/impurities of the substance to be registered. The data should be used in accordance with para. 82-84 and recommendations para. 90 of the Second FAO Government Consultation (1982).

## ENVIRONMENTAL HEALTH CRITERIA FOR D-PHENOTHRIN

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

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

The first draft of this document was prepared by Dr J. MIYAMOTO and Dr MATSUO of Sumitomo Chemical Company, with the assistance of the staff of the National Institute of Hygienic Sciences, Tokyo, Japan. Dr I. Yamamoto of the Tokyo University of Agriculture and Dr M. Eto of Kyushu University, Japan, assisted with the finalization of this draft. The second draft was prepared by Dr J. SEKIZAWA, NIHS, Tokyo, incorporating comments received following circulation of the first draft to the IPCS contact points for Environmental Health Criteria documents. Dr K.W. Jager and Dr P.G. Jenkins, both members of the IPCS Central Unit, were responsible for the technical development and editing, respectively, of this monograph.

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

## 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, 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 Elliott (1977), Miyamoto (1981), Miyamoto & Kearney (1983), and Leahey (1985).

## 1. SUMMARY, EVALUATION, CONCLUSIONS, AND RECOMMENDATIONS

### 1.1 Summary and Evaluation

#### 1.1.1 Identity, physical and chemical properties, analytical methods

Racemic phenothrin was first synthesized in 1969. Chemically, it is an ester of chrysanthemic acid (2,2-dimethyl-3-(2,2-dimethylvinyl)-cyclopropanecarboxylic acid) and 3-phenoxybenzyl alcohol (PBalc). It is a mixture of four stereoisomers, i.e., the [1R,trans], [1R,cis], [1S,trans], and [1S,cis] isomers. d-Phenothrin is the 1:4 mixture of the [1R,cis] and [1R,trans] isomers and is nowadays the only technical product commercially available. The [1R,trans] isomer is the most insecticidally active isomer, followed by the [1R,cis] isomer.

Technical grade d-phenothrin is a pale yellow to yellow-brown liquid and is 92.5-94.5% pure. The specific gravity is 1.058-1.061 at 25°C, and the vapour pressure is 0.16 mPa at 20°C. It is sparingly soluble in water (2 mg/litre at 25°C) but is soluble in organic solvents such as acetone, xylene, and hexane. It is fairly stable in air but is unstable to light, although it is not photodegraded as rapidly as natural pyrethrins. It is unstable in alkaline media.

Residue analysis can be carried out by determination using high-performance liquid chromatography with UV detector, the minimum detectable concentration being 0.05 mg/kg. A gas chromatograph equipped with flame ionization detector is used for the analysis of the technical product.

#### 1.1.2 Production and use

d-Phenothrin has been in use since 1977. It is estimated that 70-80 tonnes of d-phenothrin are used annually worldwide, mainly to control noxious insects in the household and insects of public health concern and to protect stored grain. It is used either alone or in combination with other insecticides and/or synergists, and it is formulated in aerosols, oil, dust formulations, and emulsifiable concentrate. d-Phenothrin is also used to control human lice, in which case it is formulated as a powder, shampoo, or lotion.

#### 1.1.3 Human exposure

Conventional household aerosol spraying is not expected to lead to aerial levels of d-phenothrin greater than 0.5 mg/m<sup>3</sup>. Residues of up to 4 mg/kg might be present in stored wheat, but this decreases, after milling, to 0.8 mg/kg in flour and to 0.6 mg/kg after baking.

To control lice, d-phenothrin is applied to human hair, e.g., three doses of 32 mg at 3-day intervals. No data are available on occupational exposure to d-phenothrin.

The exposure of the general population is expected to be very low, but precise data are lacking.

#### 1.1.4 Environmental fate

Phenothrin degrades readily, with a half-life of less than 1 day, on plants and other surfaces. There is little translocation of d-phenothrin or its degradation products to the untreated parts of the plants. Limited uptake of radiolabelled products into bean plants took place from soils treated with  $^{14}\text{C}$ -phenothrin. When soils were treated with [1R,*trans*]- or [1R,*cis*]-phenothrin (1 mg/kg), both isomers decomposed rapidly with initial half-lives of 1-2 days, but under flooded conditions the degradation was much slower, with initial half-lives of 2-4 weeks (*trans* isomer) and 1-2 months (*cis* isomer). Very little movement (approximately 2%) of either *trans*- or *cis*- phenothrin was observed through soil columns when leaching was started immediately or 14 days after treatment with the insecticide.

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

#### 1.1.5 Kinetics and metabolism

After rats were given single or repeated oral exposure or dermal treatment with radiolabelled phenothrin, the radiolabel was rapidly and almost completely excreted in urine and faeces within 3-7 days. The major metabolic pathways of both *trans*- and *cis*-phenothrin in rats were ester cleavage and oxidation at the 4'-position of the alcohol moiety or the isobutenyl group of the acid moiety. Ester-cleaved metabolites (excreted mainly in the urine) were the principal products of the *trans* isomer, whereas ester-form metabolites (excreted mainly in the faeces) were mostly formed from the *cis* isomer.

#### 1.1.6 Effects on organisms in the environment

Phenothrin has been tested on few groups of non-target organisms and on only a few species within each group. The 96-h  $\text{LC}_{50}$  for racemic phenothrin and (1R) stereoisomers in fish ranged from 17 to 200  $\mu\text{g}/\text{litre}$ . A single study on aquatic invertebrates demonstrated 3-h  $\text{LC}_{50}$  values for *Daphnia pulex* of 25-50 mg/litre for all isomers and for racemic phenothrin.

A single field study applying phenothrin to ponds showed no effect on aquatic arthropods.

Toxicity to birds is low with an acute oral  $\text{LD}_{50}$  for bobwhite quail of >2500 mg/kg body weight and a dietary  $\text{LC}_{50}$  for mallard duck and bobwhite quail of >5000 mg/kg diet.

Since phenothrin breaks down rapidly in sunlight and is used principally on stored grain, environmental exposure is expected to be very low. Therefore, effects on the environment are extremely unlikely.

### 1.1.7 Effects on experimental animals and in vitro test systems

The acute toxicity of d-phenothrin is extremely low, the LD<sub>50</sub> being >5000 mg/kg body weight in the rat and mouse (via the oral, subcutaneous, dermal, and intraperitoneal routes) and the inhalation LC<sub>50</sub> >3760 mg/m<sup>3</sup> in the rat. d-Phenothrin causes a poisoning syndrome of hyperexcitability, prostration, tremor, ataxia, and paralysis. From these symptoms and the results of electrophysiological studies of cockroach cercal sensory nerves, it is classified as a Type I pyrethroid.

When rats were exposed to d-phenothrin by inhalation at concentrations of up to 210 mg/m<sup>3</sup> for 4 h per day for 4 weeks or orally for 5 consecutive days at a dose level of 5000 mg/kg body weight, no adverse toxicological effects were observed.

Several feeding studies of phenothrin (racemic or d-phenothrin from 200 to 10 000 mg/kg diet) in rats and mice, with exposure periods of 6 months to 2 years, have been performed. The no-observed-effect levels (NOEL) obtained in these studies were 300-1000 mg/kg diet, which correspond to approximately 40-160 mg/kg body weight per day. In two studies on dogs in which d-phenothrin was given at doses of 100-3000 mg/kg diet, with exposure periods of 26-52 weeks, the NOEL was 300 mg/kg diet, corresponding to 7-8 mg/kg body weight per day.

d-Phenothrin is not mutagenic in a variety of *in vivo* and *in vitro* systems that test for gene mutations, DNA damage, DNA repair, and chromosomal effects.

In 2-year studies, d-phenothrin was not oncogenic to rats and mice at dietary levels of up to 3000 mg/kg diet.

Neither teratogenicity nor embryotoxicity was observed in fetuses of rabbits and mice orally administered d-phenothrin at up to 1000 and 3000 mg/kg body weight, respectively. In a 2-generation rat reproduction study, the NOEL was 1000 mg/kg diet.

Rats exposed by inhalation to very high doses of d-phenothrin (up to 3760 mg/m<sup>3</sup>) for 4 h or orally to a dose of 5000 mg/kg body weight per day for 5 days showed no myelin degeneration or axon disruption in the sciatic nerve.

### 1.1.8 Effects on human beings

Although d-phenothrin has been in use for more than 10 years, no cases of human poisoning have been reported.

There are no indications that d-phenothrin, when used as recommended, has an adverse effect on human beings.

## 1.2 Conclusions

### 1.2.1 General population

The exposure of the general population to d-phenothrin is expected to be very low and is not likely to present a hazard when it is used as recommended.

### *1.2.2 Occupational exposure*

With reasonable work practices, hygiene measures and safety precautions, d-phenothrin is unlikely to be an occupational hazard.

### *1.2.3 Environment*

The rapid breakdown of phenothrin in sunlight and its use principally on stored grain imply that environmental exposure should be very low. Environmental effects of the compound are, therefore, extremely unlikely.

## **1.3 Recommendations**

When d-phenothrin is used as recommended, exposure levels are expected to be very low. However, monitoring studies should be continued.



## 2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

### 2.1 Identity

Molecular formula:  $C_{23}H_{26}O_3$

Chemical structure:

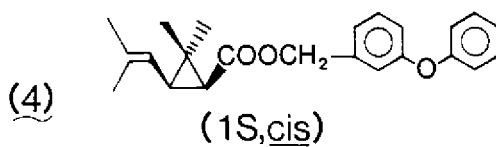
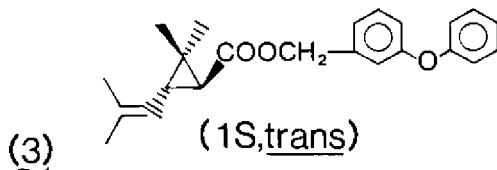
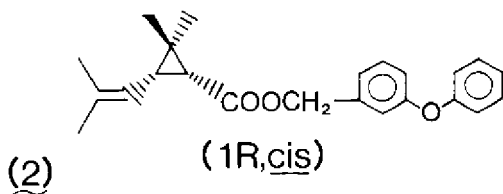
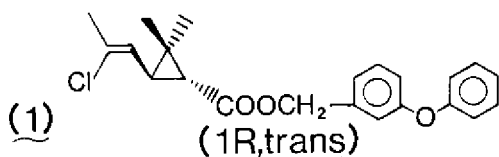
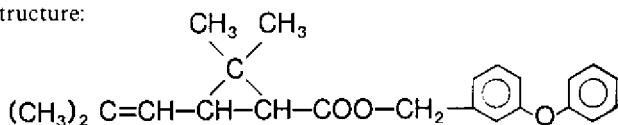


Fig. 1. Chemical structure of the four stereoisomers of d-phenothrin

Table 1. Chemical identity of racemic phenothrin and d-phenothrin

Common name/ CAS Registry no./ RTECS Registry no. <sup>a</sup>	CAS Index name (9CI)/ Stereospecific name <sup>b,c</sup>	Stereoisomeric composition <sup>d</sup>	Synonyms and trade names
Phenothrin (racemic) 26002-80-2 GZ1975000	Cyclopropanecarboxylic acid, 2,2-dimethyl-3-(2-methyl-1-propenyl)-, (3-phenoxyphenyl)methyl ester	(1)(2)(3)(4) =4:1:4:1	Phenoxothrin, S-2539
	3-Phenoxybenzyl (1RS, <i>cis. trans</i> )-, 2,2-dimethyl-3-(2,2-dimethylvinyl)- cyclopropanecarboxylate or 3-Phenoxybenzyl (1RS, <i>cis. trans</i> )- chrysanthemate		
(+)- <i>cis. trans</i> - Phenothrin GZ2002000	Cyclopropanecarboxylic acid, 2,2-dimethyl-3-(2-methyl-1-propenyl)-, (3-phenoxyphenyl)methyl ester	(1)(2) =4:1	Sumithrin, S-2539 Forte d-Phenothrin
	3-Phenoxybenzyl (1R, <i>cis. trans</i> )- chrysanthemate		

<sup>a</sup> (NIOSH, 1983).

<sup>b</sup> (1R), d, (+) or (1S), l, (-) in the acid part of the compound signify the same stereospecific conformation, respectively.

<sup>c</sup> Chrysanthemic acid is a name of the acid which forms the acid part of the compound.

<sup>d</sup> Numbers in parentheses identify the structures shown in Fig. 1.

Racemic phenothrin was first synthesized by Itaya et al. (1969). It is prepared by esterifying (1*R*,*cis*,*trans*)-2,2-dimethyl-3-(2,2-dimethylvinyl)cyclopropanecarboxylic acid (chrysanthemic acid) with 3-phenoxybenzyl alcohol (Fujimoto et al., 1973). Phenothrin is thus a mixture of four stereoisomers (Fig. 1). The *cis:trans* isomer ratio is 1:4 and the optical ratio of 1*R*:1*S* is 1:1 (racemic). Thus the isomers 1, 2, 3, and 4 are present in the approximate ratio of 4:1:4:1 (Table 1). *d*-Phenothrin is the (1*R*,*cis*,*trans*) preparation (i.e., a mixture of isomers 2 and 1), the *cis:trans* ratio being 1:4. The technical grade is 92.5-94.5% pure. The major impurities found in seven *d*-phenothrin preparations (average purity, 94.0%) were ethyl chrysanthemate (2.31%), 3-phenoxy-6-bromobenzyl *cis:trans*-chrysanthemate (0.66%), 3-phenoxy-toluene (0.43%), and 4-phenoxybenzyl *cis:trans*-chrysanthemate (0.39%) (Miyamoto et al., 1984).

## 2.2 Physical and Chemical Properties

Certain physical and chemical properties of *d*-phenothrin are given in Table 2. It is poorly soluble in water, but is soluble in organic solvents. *d*-Phenothrin is fairly stable in air but unstable to light and in alkaline media. However, it is not photodegraded as rapidly as the natural pyrethrins (FAO/WHO, 1980; Worthing & Walker, 1987).

Table 2. Some physical and chemical properties of *d*-phenothrin

Physical state	liquid
Colour	pale yellow to yellow-brown
Relative molecular mass	350.5
Water solubility (25°C)	2 mg/litre
Solubility in organic solvents	soluble <sup>a</sup>
Relative density	$d_{20}^{25}$ 1.058-1.061
Vapour pressure (20°C)	0.16 mPa

<sup>a</sup> Hexane (>1 kg/kg), acetone, methanol (>1 kg/kg), xylene (>1 kg/kg).

## 2.3 Analytical Methods

Examples of residue and product analyses of racemic phenothrin and *d*-phenothrin are shown in Table 3.

To analyse technical grade racemic phenothrin or various formulations, Sakaue et al. (1981) dissolved the product in acetone, together with di-(2-ethylhexyl) phthalate (an internal standard), and injected the solution into a gas chromatograph equipped with a flame

ionization detector (GC-FID). d-Phenothrin was separated as a single peak in the analysis of formulations by a high-performance liquid chromatography with UV detector (HPLC-UV) system (utilizing a  $\mu$ -Bondapak phenyl column eluted with acetonitrile as water mobile phase). Murano (1972) and Papadopoulou-Mourkidou et al. (1981) analyzed technical grade phenothrin, and separated the cis and trans isomers of racemic or d-phenothrin by GC-FID with a AW-DMCS chromosorb W column or by HPLC-IR with a Partisil 10 column, respectively.

The Joint FAO/WHO Codex Alimentarius Committee has published recommendations for methods of analysis of d-phenothrin residues (FAO/WHO, 1985b).

Table 3. Analytical methods for racemic phenothrin

Sample	Sample preparation		Determination	MDC <sup>b</sup> (mg/kg)	% Recovery (fortifi- cation level, mg/kg) <sup>c</sup>	Refef- enced
	Extraction solvent	Partition Clean up column elution				
<i>Residue analysis</i>						
apple	<i>n</i> -hexane acetone (1/1)	ext.sol. <sup>a</sup> /H <sub>2</sub> O silica gel	CH <sub>2</sub> Cl <sub>2</sub> HPLC UV-206nm, 25cm ODS, propan-2-ol, 1 ml/min as for apple	0.05	62(0.1), 92(1.0)	1
pear		silica gel	CH <sub>2</sub> Cl <sub>2</sub> as for apple	0.05	85(0.1), 96(1.0)	
cabbage		silica gel	CH <sub>2</sub> Cl <sub>2</sub> as for apple	0.05	72(0.1), 88(1.0)	
potato		silica gel	CH <sub>2</sub> Cl <sub>2</sub> as for apple	0.05	77(0.1), 98(1.0)	
wheat grain		methanol <i>n</i> -hexane alumina	HPLC, 235nm, 30cm, uBondapak C18, methanol/H <sub>2</sub> O (4/1), 2.5ml/min		87(2.0)	2
cooked rice		petroleum ether ethanol	colorimetric method, 680nm		87(3.1) 91(1.9)	3

Table 3 (contd).

Sample	Sample preparation		Determination	MDC <sup>b</sup> (mg/kg)	% Recovery (fortification level, mg./kg) <sup>c</sup>	Reference <sup>d</sup>
	Extraction solvent	Partition Clean up column elution				
<i>Product analysis</i>						
Technical grade		acetone	FID-GC, 1m, 2% PEG-20M 210°C			4
Technical grade		acetone	FID-GC, 1m, 2% PEG-20M or 2% DEGS-H <sub>3</sub> PO <sub>4</sub> (total d-phenothrin)			5
Technical grade		acetone	FID-GC, 2m, 2% QF-1 (separation of geometrical isomers)			
Technical grade		acetone	HPLC, 230 nm, 50cm Sumipax OA-2000 hexane/1,2-dichloroethane (500/1) (separation of optical isomers)			

*a* extraction solvent  
*b* minimum detectable concentration  
*c* fortification level indicates the concentration of d-phenothrin added to control samples for the measurement of recovery  
*d* 1. Baker & Bottomley (1982), 2. Noble et al. (1982), 3. Desmarchelier (1986), 4. Sakaua et al. (1981), 5. Doi et al. (1985)

### 3. SOURCES AND LEVELS OF HUMAN AND ENVIRONMENTAL EXPOSURE

#### 3.1 Industrial Production

Racemic phenothrin was first marketed in 1977 (Hayashi, 1977), but is no longer commercially available. As for d-phenothrin, although no production data are publicly available, the annual world-wide production level is probably 70-80 tonnes.

#### 3.2 Use Patterns

The main use of d-phenothrin is in aerosol formulations to control household and public health insects, alone or in combination with other insecticides (e.g., tetramethrin or d-allethrin) or synergists (e.g., piperonyl butoxide). Oil and dust formulations are used for the same purpose, as are emulsifiable concentrates. d-Phenothrin is also formulated in powders, shampoos, and lotions, mixed with a synergist (e.g., piperonyl butoxide), to control human lice. In addition, it is used to protect stored grains.

#### 3.3 Residues in Food

Phenothrin, being photodegradable, has a relatively short residue time on plants.

Many residue studies (e.g., post-harvest treatment of stored grains) have been carried out (FAO/WHO 1980, 1988a).

In supervised trials on several crops, emulsifiable formulations of racemic phenothrin (0.375-0.50 kg ai/ha) were applied to rice, green pepper, and cabbage, 3 to 9 times with 3 to 10 days interval (Takimoto et al., 1977). The resultant residues were 0.005-0.008 mg/kg in cabbage (3-21 days after treatment), 0.125-1.26 mg/kg in green pepper (1-7 days after treatment), and 0.86-2.54 mg/kg and 0.012-0.25 mg/kg in straw and hulled rice, respectively (7-14 days after treatment in both cases).

Analyses of residues of racemic phenothrin and d-phenothrin used for the protection of stored grains (e.g., wheat, barley, and sorghum) have been carried out. The [1R,trans] or [1R,cis] isomer of [methylene-<sup>14</sup>C]-phenothrin was applied at 4 mg/kg to wheat grains (11% moisture content) and stored at 15°C or 30°C in the dark. Both trans and cis isomers decomposed slowly; 79% and 87%, respectively, of the applied radiocarbon remained intact in the grain after it had been stored for one year at 30°C. The joint application of either *trans*- or *cis*-phenothrin with piperonyl butoxide (20 mg/kg) or piperonyl butoxide plus fenitrothion (4 mg/kg) did not significantly affect the residue levels of either isomer over a period of 12 months. The phenothrin isomers and their decomposition products were mainly located in the seed coat after storage for one year, and the residue levels of both isomers in

flour and bran were 0.77 and 11.4 mg/kg, respectively. The phenothrin residues in flour decreased somewhat during the baking process, leaving 0.57 mg/kg in bread (Nambu et al., 1981).

After wheat in a silo was treated with approximately 0.55 mg d-phenothrin/kg, there was no evidence of residue loss during storage for 25 weeks. Residue levels in white flour ranged from 0.15-0.22 mg/kg (approximately one third of the residues in grain), and in white bread from 0.06-0.17 mg/kg. The decline in phenothrin residues during baking was almost all accounted for by dilution (Turnbull & Ardley, 1987; Ohnishi et al., 1987).

### **3.4 Residues in the Environment**

No data are available on actual residue levels in air and water.



#### 4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

##### *Appraisal*

*Phenothrin undergoes rapid photodegradation under outdoor conditions. It is transported to a very minor extent from the site of application on plants and in soils. However, very limited movement of phenothrin and its degradation products from soil into bean plants was detected using radiolabelled compounds. Phenothrin remains almost intact on stored grains in the dark for up to 12 months.*

The degradation pathways of phenothrin under environmental conditions are summarized in Fig. 2.

##### 4.1 Transport and Distribution between Media

The degree of leaching of [1RS,*trans*]- or [1RS,*cis*]-phenothrin has been studied under laboratory conditions. Very little movement (less than 2%) of *trans*- and *cis*-phenothrin through soil columns occurred when leaching was started either immediately or 14 days after treatment (Nambu et al., 1980).

##### 4.2 Photodegradation<sup>a</sup>

Although d-phenothrin is more resistant to photolysis than pyrethrin I, allethrin, and resmethrin (due to a more stable alcohol moiety), it still possesses the photo-labile isobutenyl group in the molecule and therefore is easily photodecomposed.

Ruzo et al. (1982) investigated the photodegradation of [1RS,*trans*]-phenothrin (5)<sup>a</sup> in oxygenated benzene solution ( $10^{-3}$  mol/litre) under UV light (360 nm) or in a thin film (0.1-0.3 mg/cm<sup>2</sup>) under sunlight (Fig. 2). Exposure to sunlight resulted in 30% conversion, the major photoproducts being:

- the (1RS) epoxides (21) (22% of the reaction mixture), the alcohol (22) (9%), and the aldehyde (23) (13%) derivatives from oxidation at the (E)-methyl group;
- the caronaldehyde derivative (7) (4%) from ozonolysis;
- the hydroperoxide (25) (27%) from hydroperoxidation, including migration of the double bond at the 1'-position of the isobutenyl moiety (Fig. 2).

<sup>a</sup> The numbers in brackets following a chemical name refer to the numbers given in Fig. 2.

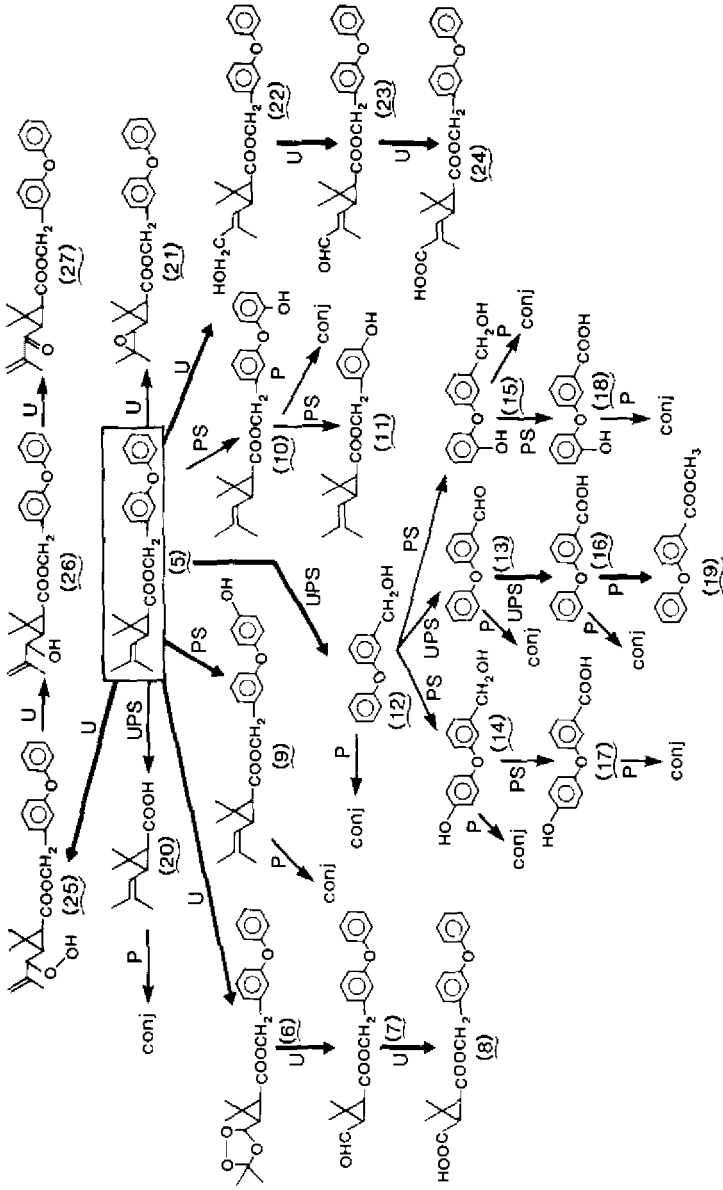


Fig. 2. Degradation pathways of racemic phenofrin in plants and soil and under the action of UV light.  
U = UV light, P = plant, conj = sugar conjugate, S = soil.

Minor products (26) and (27) (3%) resulted from further oxidation of the hydroperoxide (25) and from *cis/trans* isomerization and ester cleavage. Trace amounts of *trans*-chrysanthemic acid (20) were detected. 3-Phenoxybenzyl alcohol (12) underwent further oxidation to form the aldehyde (13) and carboxylic acid (16). Unidentified photo-products accounted for 16.6% of the total. A similar product distribution was obtained in benzene solution.

### 4.3 Degradation in Plants and Soils

In studies by Nambu et al. (1980), <sup>14</sup>C-methylene-labelled [1*R*,*trans*]- or [1*R*,*cis*]-phenothrin (each 10 mg/kg) disappeared from the treated leaves of kidney bean or rice plants with half-lives of less than one day under greenhouse conditions. The residue levels in both plants were 0.04-0.28 mg/kg for *trans*-phenothrin and 0.10-0.30 mg/kg for *cis*-phenothrin after 30 days, compared with approximately 10 mg/kg immediately after treatment. Both isomers primarily underwent ozonolysis at the isobutenyl double bond, probably via the photochemical reactions indicated previously (Fig. 2). The resultant ozonides (6) were detected soon after treatment but they were rapidly decomposed to the corresponding aldehyde (7) and carboxylic acid (8) (3-phenoxy-benzyl-2,2-dimethyl-3-carboxy-cyclopropanecarboxylate) derivatives. Cleavage of the ester linkage also occurred, together with hydroxylation at the 2'-position (10) or 4'-position (9) of the alcohol moiety. Conjugation of the acids and alcohols with sugars was also observed, and the formation of polar products was more extensive in rice than in bean plants. There was little translocation of *trans*- or *cis*-phenothrin or of its degradation products to the untreated parts of the plants. Limited uptake of radiolabelled products into bean plants took place from light clay, sandy loam soil, and from sand treated with <sup>14</sup>C-methylene-labelled *trans*- or *cis*-phenothrin.

The degradation of <sup>14</sup>C-labelled [1*R*,*trans*]- or [1*R*,*cis*]-phenothrin in two soils was investigated by Nambu et al. (1980). Both isomers decomposed rapidly under upland conditions, with initial half-lives of 1-2 days, but under flooded conditions the degradation was much slower, with initial half-lives of 2-4 weeks and 1-2 months for the *trans* and *cis* isomers, respectively. Analysis of the soil extracts revealed unchanged parent isomers, (16), 3-(4'-hydroxyphenoxy)benzoic acid (17), (12), 3-(4'-hydroxyphenoxy)benzyl alcohol (14), (9), and 3-hydroxybenzyl-2,2-dimethyl-3-(2,2-dimethylvinyl)-cyclopropanecarboxylate (11). These degradation products were not persistent and underwent further degradation in soil, under both upland and flooded conditions, to yield large amounts of <sup>14</sup>CO<sub>2</sub> and unextractably bound residues. More <sup>14</sup>C carbon dioxide was formed in soils under upland conditions than under flooded conditions and more was formed from *trans*-phenothrin than from the *cis* isomer. Bound <sup>14</sup>C residues were associated mainly with the humic acid and fulvic acid fractions of soil organic matter. The fulvic acid fraction contained small amounts of the same degradation products as in the soil extracts.

#### 4.4 Degradation on Stored Foods

When  $^{14}\text{C}$ -[1R,*trans*]- or  $^{14}\text{C}$ -[1R,*cis*]-phenothrin was applied at 4 mg/kg to wheat grains of 11% moisture content and the crop was stored at 15 or 30°C in the dark for 12 months, most of the phenothrin remained intact. Major metabolites were formed by hydrolysis of the ester linkage and oxidation of 3-phenoxybenzyl alcohol to 3-phenoxybenzoic acid. The methyl ester of 3-phenoxybenzoic acid was also produced. After storage at 30°C for 12 months, these metabolites amounted to 13.9% in the case of the *trans* isomer and 6.3% in the case of the *cis* isomer (Nambu et al., 1981).

## 5. KINETICS AND METABOLISM

### Appraisal

The pathways by which phenothrin is metabolized in mammals are summarized in Fig. 3.

Comparative metabolism studies have shown that the metabolism of racemic phenothrin is similar to that of [1R,cis,trans]-phenothrin (*d*-phenothrin).

No information is available on the *in vivo* metabolism of the acid moieties of *trans*-[1R,trans]- or *cis*-[1R,cis]-phenothrin. However, the acid moiety liberated *in vivo* (chrysanthemic acid) is the same as that of resmethrin and tetramethrin and, therefore, its fate can be predicted from the resmethrin and tetramethrin data.

### 5.1 Metabolism in Mammals

#### Appraisal

After rats are treated with radiolabelled phenothrin, either by single or repeated oral exposure, or dermally, the radioactivity is rapidly (and almost totally) excreted into urine and faeces within 3 to 7 days. The major metabolic pathways of both *trans*- and *cis*-phenothrin in rats are oxidation at the 4-position of the alcohol moiety or the isobutenyl group of the acid moiety and cleavage of the ester linkage (see Fig. 3). Cleavage of the ester bond is more difficult in the *cis* isomer than in the *trans* isomer. Thus, ester-form metabolites oxidized in the various positions of the molecule are the major metabolites of the *cis* isomer and are excreted mostly in the faeces. However, ester-cleaved metabolites are the major products from the *trans* isomer and are mostly excreted in urine.

When [1R,trans]-phenothrin labelled with  $^{14}\text{C}$  at the methylene moiety was given as a single oral dose (200 mg/kg body weight) to Sprague Dawley male rats, the radiocarbon was rapidly eliminated, 57% and 43% being recovered within 3 days in urine and faeces, respectively (Miyamoto et al., 1974). There was no detectable radiocarbon in the expired air. Similarly, Sprague Dawley male rats given a single oral dose (10 mg/kg body weight) of  $^{14}\text{C}$ -[1R,trans]-phenothrin, excreted the radiocarbon rapidly in the urine (75%) and faeces (21%) (Kaneko et al., 1981).

In a study by Isobe et al. (1987), Sprague Dawley male and female rats were given a single oral administration of  $^{14}\text{C}$ -[1R,trans]-phenothrin in corn oil at 4 and 200 mg/kg body weight. Within 7 days the radiocarbon was almost completely eliminated in the urine and faeces. The % elimination was as follows:

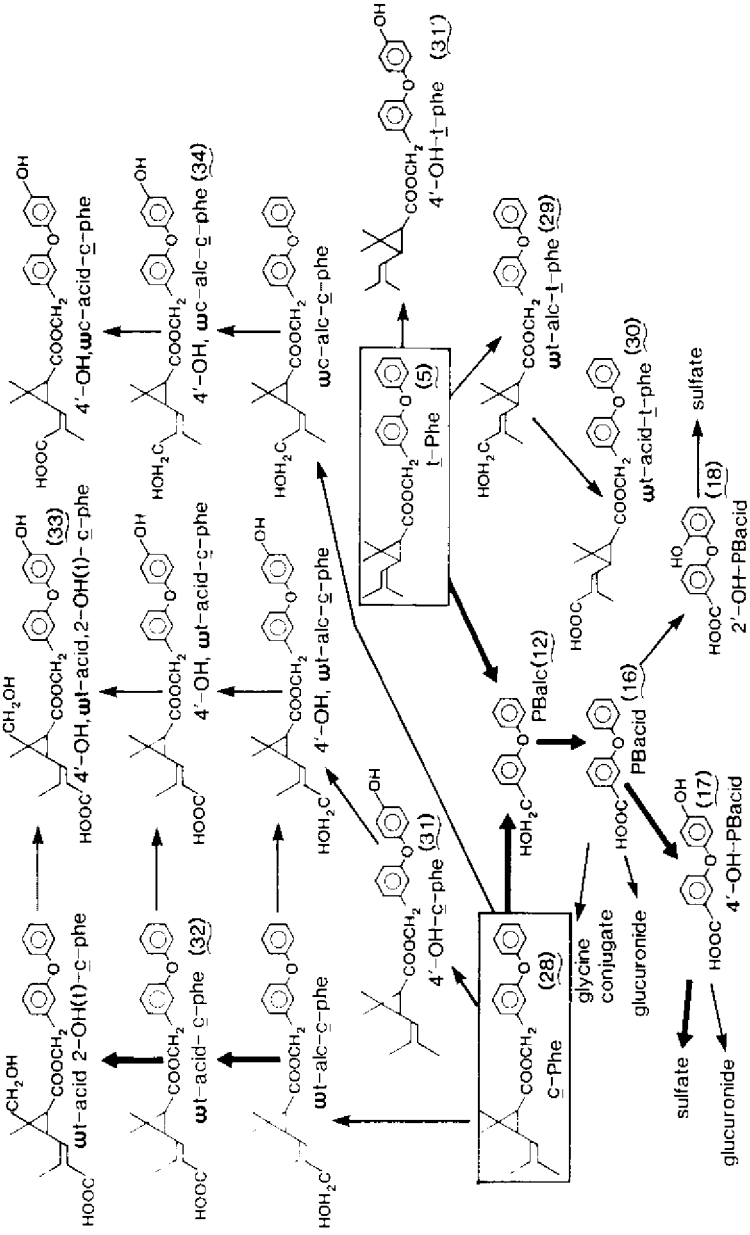


Fig. 3. Metabolic pathways of trans- and cis-phenothrin in mammals.

Dose (mg/kg)	Urine		Faeces	
	Males	Females	Males	Females
4	38	40	61	60
200	39	25	56	60

Sprague Dawley male rats eliminated 65% of the dosed radiocarbon in the faeces over 3 days after a single oral administration (200 mg/kg body weight) of  $^{14}\text{C}$ -[1R,*cis*]-phenothrin (28) (Suzuki et al., 1976), and 22 and 74% of the dose into urine and faeces, respectively, 7 days after a single oral dose of 10 mg/kg body weight (Kaneko et al., 1981).

When  $^{14}\text{C}$ -[1R,*cis*]-phenothrin in corn oil was administered once orally to Sprague Dawley male and female rats at 4 or 200 mg/kg body weight, the radiocarbon was excreted into the urine (11-18%) and faeces (81-87%) within 7 days. Similarly, when Sprague Dawley rats were treated repeatedly with  $^{14}\text{C}$ -[1R,*trans*] or  $^{14}\text{C}$ -[1R,*cis*] isomers at 4 mg/kg body weight per day for 14 days, the radiocarbon was rapidly and almost completely excreted: 75-70% in urine and 24-29% in faeces for the *trans* isomer, and 24% in urine and 72-73% in faeces for the *cis* isomer (Isobe et al., 1987).

The tissue residues in rats 7 days after a single oral dose of  $^{14}\text{C}$ -[1R,*cis*]- or  $^{14}\text{C}$ -[1R,*trans*]-phenothrin at 10 mg/kg body weight were generally very low although the fat showed somewhat higher residue levels (1-2.5 mg/kg) (Kaneko et al., 1981). Similarly, high  $^{14}\text{C}$  residue levels (up to 23 mg/kg) were found in the fat, 7 days after a single oral dose of the [1R,*cis*] isomer at 200 mg/kg body weight (Isobe et al., 1987).

The major metabolite of the *trans* isomer, when given as a single oral dose of 200 mg/kg to rats, was 3-(4'-hydroxyphenoxy)-benzoic acid (17) (4'-OH-PBacid, 54%). There were smaller amounts of 3-phenoxybenzoic acid (16) (PBacid, 9.5%) and its glycine conjugate (Miyamoto et al., 1974).

When [1R,*trans*]-phenothrin was given to rats at 4, 10, or 200 mg/kg body weight (oral single dose) or 4 mg/kg body weight (repetitive oral dose for 14 days), the sulfate conjugate of 4'-OH-PBacid was predominant, accounting for 28, 43, 28, and 55%, respectively, of the dose. In addition, PBacid (4, 10, 5, and 6%), its glycine conjugate (1,3,2, and 2%) and glucuronide (2,3,1, and 3%), and free 4'-OH-PBacid (2,11,3, and 3%) were found. The sulfate conjugate of 3-(2'-hydroxyphenoxy)benzoic acid (18) (2'-OH-PBacid) was also found as a minor metabolite (Kaneko et al., 1981; Isobe et al., 1987).

When rats were given  $^{14}\text{C}$ -[1R,*trans*]-phenothrin (10 mg/kg body weight), the unmetabolized compound and two ester-form metabolites were detected in their faeces in small amounts (0.4-1.2%), which had hydroxymethyl (29) (*wt-alc-t-phe*) or carboxyl group (30) *wt-acid-t-phe*) (see Fig. 2) at the position of the *trans* methyl group of chrysanthemic acid (Kaneko et al., 1981).

When Sprague Dawley rats were administered a single oral dose of [1R,*trans*]-phenothrin at 4 or 200 mg/kg body weight level or given an oral dose of 4 mg/kg body weight per day for 14 days, unmetabolized compound was found in the faeces (44-45, 44-60, and 14-16% of the dose, respectively). An ester-form metabolite, the 4'-hydroxy *w(t)*-acid derivative of *trans*-phenothrin, was also detected (0.4-0.6%) (Isobe et al., 1987).

When male Sprague Dawley rats were given *cis*-phenothrin (200 mg/kg body weight), three ester-form metabolites, which accounted for 14% of the dosed radioactivity, were found in the faeces. These were 4'-hydroxy-*cis*-phenothrin (31) (4'-OH-*c-phe*), an ester-form derivative with the *trans* methyl of the isobutenyl group being oxidized to carboxyl group (32) (*wt-acid-c-phe*), and a compound with the *geminal*-dimethyl groups oxidized (2-OH-) in addition to both of the above modifications (33) (4'-OH,*wt-acid*, 2-OH(*t*)-*c-phe*) (Suzuki et al., 1976).

In addition to this, the *cis* isomer gave rise to nine ester-form metabolites in the faeces varying in amounts from 2% (4'-OH, *wc-alc-c-phe* (34)) to 13% (4'-OH, *wt-acid*, 2-OH(*t*)-*c-phe* (33)) of the dosed radiocarbon after single oral administration. These ester-form metabolites were transformed by oxidation reactions at any of the following positions: 4'-position of the phenoxy group, the *trans* or *cis* methyl of the isobutenyl groups, and the *trans* methyl of the *geminal*-dimethyl group (Kaneko et al., 1981).

When Sprague Dawley rats were given a single oral dose of [1R,*cis*]-phenothrin at 4 or 200 mg/kg body weight level or an oral dose of [1R,*cis*]-phenothrin at 4 mg/kg body weight per day for 14 days, ester-form metabolites (1-9% of the dosed radioactivity) were found, in addition to unmetabolized compound (17-59% of the dose). The urine contained 4'-OH-PBacid as a sulfate conjugate (7-18%) and in the free form (0.3-1%), and PBacid as glycine or glucuronide conjugates and in the free form (0.3-1%) (Isobe et al., 1987).

Following the dermal treatment of male Sprague Dawley rats with dust or emulsifiable concentrates (E.C.) of either  $^{14}\text{C}$ -[1R,*trans*]- or  $^{14}\text{C}$ -[1R,*cis*]-phenothrin at 10 mg/kg body weight, the  $^{14}\text{C}$  absorption into the body was estimated to be 3-7% of the initial dose with dust and 8-17% with the E.C. After both dust and E.C. treatments, the radiocarbon excreta (as a percentage of the initial dose) recovered in the urine was 2.6-8.7% for the *trans* isomer, and 1.5-4.8% for the *cis* isomer, and in the faeces was 0.6-2.2% for the *trans* isomer, and 3.0-12.3% for the *cis* isomer. Since the same metabolites are formed following either oral exposure or dermal treatment, it appears that both phenothrin isomers undergo the same metabolism once in the systemic circulation,



regardless of the route of administration (Kaneko et al., 1981; Isobe et al., 1987).

Information concerning the comparative metabolism of racemic (1RS) phenothrin and its d-isomer (1R) was obtained through a study of CD rats and ddY mice given a single oral dose of either [1R,*trans*]-, [1S,*trans*]-, [1RS,*trans*]-, [1R,*cis*]-, [1S,*cis*]-, or [1RS,*cis*]-phenothrin. The radiocarbon derived from each isomer was almost completely eliminated from the rats and mice within six days after dosing. The *trans* isomers were mainly eliminated in the urine (rat, 85-88%; mice, 65-75%) and the *cis* isomers mainly in the faeces (rat, 57-71%; mice, 54-71%). The amounts of  $^{14}\text{C}$  in the urine and faeces of rats and mice treated with the [1R,*trans*] and [1R,*cis*] isomers did not differ significantly from those corresponding to the [1RS,*trans*] and [1RS,*cis*] isomers, respectively. The  $^{14}\text{C}$  tissue residues were very low, except in the fat. There were no striking differences in  $^{14}\text{C}$  levels among the three *trans* isomers and the three *cis* isomers. The  $^{14}\text{C}$  levels of the *cis* isomers in fat (maximum 3.5 mg/kg) were three to seven times higher than those of the *trans* isomers (less than 1 mg/kg). The major urinary and faecal metabolites were remarkably similar in both rats and mice. In both rats and mice, there were virtually no differences in the metabolic fate of the [1R,*trans*] and [1RS,*trans*] isomers or of the [1R,*cis*] and [1RS,*cis*] isomers (Izumi et al., 1984).

## 5.2 Enzymatic Systems for Biotransformation

In studies by Miyamoto et al. (1974), [1R,*trans*]-phenothrin (1 mmol/litre) was incubated with the 8000-g supernatant from a liver homogenate of rats, mice, guinea-pigs, rabbits, or dogs at 37°C for 60 min in the absence of NADPH. The supernatant from the guinea-pig was the most active in degrading [1R,*trans*]-phenothrin, followed by that of dog, rabbit, rat, and mouse. The major metabolite in all the mammalian species tested was 3-phenoxybenzyl alcohol (12) (PBalc). Smaller amounts of PBacid (16) and trace amounts of 4'-OH-PBacid (17) were also found. However, in the presence of NADPH, the amounts of PBacid and unidentified ether-soluble metabolites increased in all species except dog. In contrast to [1R,*trans*]-phenothrin, [1R,*cis*]-phenothrin was hardly metabolized at all by the rat liver preparation in the absence of NADPH. NADPH enhanced the degradation rate of the *cis* isomer, leading to the formation of unidentified metabolites, while ester-cleaved metabolites such as PBacid (16), PBalc (12) and 4'-OH-PBacid (17) were found in very small amounts. When [1R,*trans*]-, [1R,*cis*]-, [1S,*trans*]-, and [1S,*cis*]-phenothrin were incubated with rat liver microsomes at 37.5°C for 30-60 min to estimate  $K_m$  and  $V_{max}$  using a Lineweaver-Burk plot, the values for  $K_m$  (0.11-0.17 mmol/litre) were similar for the four isomers, whereas the values for  $V_{max}$  were different; both the *trans* isomers yielded values for  $V_{max}$  20-30 times larger than did the *cis* isomers (Miyamoto et al., 1974).

In studies by Suzuki & Miyamoto (1978), pyrethroid carboxyesterase(s) that hydrolyze esters of chrysanthemic acid were purified from rat liver microsomes by cholic acid solubilization, ammonium sulfate fractionation, heat treatment, and DEAE-Sephadex A-50 column chromatography. The 45-fold-purified enzyme (38% yield) probably consisted of a single protein with a relative molecular mass of approximately 74 000, a  $K_m$  of 0.21 mmol/litre for [1R,*trans*]-phenothrin, and an optimum pH of 7-9. It was susceptible to inhibition by organophosphate and carbamate insecticides and insensitive to PCMB (*p*-chloromercurybenzoic acid), and mercuric and cupric ions. The enzyme seemed to require neither coenzymes nor cofactors and hydrolysed the *trans* isomers of several synthetic pyrethroids (tetramethrin, resmethrin, phenothrin, and permethrin) well, at more or less similar rates. On the other hand, the *cis* isomers were hydrolysed at rates 5-10 times lower than their *trans* counterparts. The purified pyrethroid carboxyesterase was apparently identical in nature to malathion carboxyesterase and *p*-nitrophenyl acetate carboxyesterase.

## 6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Data on the acute toxicity of racemic and isomeric phenothrin for aquatic organisms are summarized in Table 4.

### 6.1 Aquatic Organisms

Racemic phenothrin yielded 96-h  $LC_{50}$  values of 17-200  $\mu\text{g}/\text{litre}$  for the fish species tested (Table 4). The (1S)-optical isomers were relatively non-toxic with  $LC_{50}$  values of 10 000  $\mu\text{g}/\text{litre}$ , whereas the (1R)-optical isomer and racemic phenothrin were of similar toxicity with  $LC_{50}$  values between 120 and 200  $\mu\text{g}/\text{litre}$  for the killifish (*Oryzias latipes*) (Miyamoto, 1976).

When d-phenothrin was applied to ponds at the rates of 28 or 56 g/ha to control mosquito larvae, mayfly naiads were most affected but no other arthropods (damselfly, dragonfly naiads, ostracods, or diving beetle larvae) were seriously affected (Mulla et al., 1980).

### 6.2 Terrestrial Organisms

The available toxicity data for non-target terrestrial organisms are very limited.

Phenothrin has low toxicity (acute oral dosage) for bobwhite quail with an  $LD_{50}$  >2510 mg/kg body weight (Worthing & Walker, 1987). An 8-day feeding study with d-phenothrin on mallard duck and bobwhite quail indicated  $LD_{50}$  values of >5620 and >5000 mg/kg diet, respectively<sup>a</sup>.

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<sup>a</sup> Personal communication from J.L. Noles, Ecological Effects Branch, Hazard Evaluation Division, US Environmental Protection Agency, November 1987.

Table 4. The acute toxicity of racemic and isomeric phenothrin to non-target aquatic organisms

Species	Size	Parameter	Toxic concentration (µg/litre)	Stereo-isomeric composition	System <sup>a</sup>	Temperature (°C)	Reference <sup>b</sup>	
Fish	Killifish ( <i>Oryzias latipes</i> )	adult	48-h LC50	racemic	S	25	1	
		adult	48-h LC50	(+)-trans	S	25	1	
	Rainbow trout ( <i>Salmo gairdneri</i> )	adult	48-h LC50	170	(+)-cis	S	25	1
		adult	48-h LC50	10 000	(-)-trans	S	25	1
		adult	48-h LC50	10 000	(-)-cis	S	25	1
Bluegill ( <i>Lepomis macrochirus</i> )		96-h LC50	17	racemic			2	
		96-h LC50	18	racemic			2	
Arthropods <i>Daphnia pulex</i>		3-h LC50	50 000	racemic	S	25	1	
		3-h LC50	25 000-50 000	(+)-trans	S	25	1	
		3-h LC50	50 000	(+)-cis	S	25	1	
		3-h LC50	50 000	(-)-trans	S	25	1	
		3-h LC50	50 000	(-)-cis	S	25	1	

<sup>a</sup> S = static

<sup>b</sup> 1. Miyamoto (1976) 2. Worthing & Walker (1987)

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

The 1984 Joint FAO/WHO Meeting on Pesticide Residues concluded that the toxicological data for racemic phenothrin can be used to support that for d-phenothrin, owing to the similarity in metabolism and toxicity between the two compounds (FAO/WHO, 1985b).

### 7.1 Single and Short-Term Exposures

The acute toxicity in rats and mice is extremely low. The LD<sub>50</sub> values were >5000 mg/kg body weight when d-phenothrin was administered orally, subcutaneously, dermally, or by intraperitoneal injection to male and female Sprague Dawley rats (Segawa, 1979a) and ddY mice (Segawa, 1979b) (Table 5).

Table 5. The acute toxicity of racemic phenothrin and d-phenothrin to rats and mice<sup>a</sup>

Compound/ Route	LD <sub>50</sub> (mg/kg)			
	Rat		Mice	
	Male	Female	Male	Female
Phenothrin (racemic)				
Oral	> 5000	> 5000	> 5000	> 5000
Subcutaneous	> 5000	> 5000	> 5000	> 5000
Dermal	> 5000	> 5000	> 5000	> 5000
Intraperitoneal	> 5000	> 5000	> 5000	> 5000
Inhalation	> 1210 <sup>b</sup>	> 1210 <sup>b</sup>	> 1210 <sup>b</sup>	> 1210 <sup>b</sup>
d-Phenothrin				
Oral	> 10 000	> 10 000	> 10 000	> 10 000
Subcutaneous	> 10 000	> 10 000	> 10 000	> 10 000
Dermal	> 10 000	> 10 000	> 5000	> 5000
Intraperitoneal	> 10 000	> 10 000	> 10 000	> 10 000
Inhalation	> 3760 <sup>b</sup>	> 3760 <sup>b</sup>	> 1180 <sup>b</sup>	> 1180 <sup>b</sup>

<sup>a</sup> From: Segawa (1976; 1979a,b) and Khoda et al. (1977; 1979b; 1980)

<sup>b</sup> These are values for 4-h LC<sub>50</sub> (mg/m<sup>3</sup>)

There were no differences between the effects on male and female rats in acute toxicity studies carried out by Segawa (1976). Signs of poisoning appeared rapidly following the intravenous administration of phenothrin. These included fibrillation, tremor, slow respiration, salivation, lacrimation, ataxia, and paralysis. These signs, evident within 30 min to one hour following administration, diminished rapidly

to the point where, after 24 h, there were no signs of toxicity.

No differences in the oral toxicity between racemic phenothrin and d-phenothrin were detected by Segawa (1976; 1979a,b) (Table 5).

The intravenous LD<sub>50</sub> values for racemic phenothrin in ICR mice were 470 and 600 mg/kg for males and females, respectively, while those for d-phenothrin were 265 and 315 mg/kg (Hiromori et al., 1984).

Following a 4-h acute inhalation exposure (whole body), the LC<sub>50</sub> values were >1210 mg/m<sup>3</sup> for racemic phenothrin (particle size 5 µm) with both Sprague Dawley rats and ICR mice (Kohda et al. 1979b) and >3760 and 1180 mg/m<sup>3</sup> for d-phenothrin with Sprague Dawley rats and ICR mice, respectively (Kohda et al. 1977; 1979b) (see Table 5). At the higher concentration (3760 mg/m<sup>3</sup>), the mean particle size was considered to be 0.72 µm and the cumulative distribution of particles having a diameter between 0.46 and 1.09 µm was 88.9%, according to a particle-size distribution experiment (Kohda et al., 1980).

In studies by Kohda et al. (1979b), Sprague Dawley rats (15 of each sex) were exposed (whole body) by inhalation to racemic phenothrin at concentrations of 0, 43, or 220 mg/m<sup>3</sup> (4 h per day, 5 days per week) for 4 weeks. After this treatment, animals (10/sex per group) were sacrificed and the remaining rats were kept for 3 weeks without treatment. There were no adverse toxicological effects on the animals exposed to the highest dose. Under the same conditions (i.e. 220 mg/m<sup>3</sup> for 4 weeks), racemic phenothrin did not produce any adverse effects in male or female ICR mice. Similarly, d-phenothrin also produced no adverse toxicological effects in Sprague Dawley rats or ICR mice (both male and female) following whole body exposure at 210 mg/m<sup>3</sup> (particle size 5 µm) for 4 weeks (Kohda et al., 1979b).

The acute oral and intraperitoneal toxicity of phenothrin metabolites in rats and mice are shown in Table 6 and 7 (Kohda et al., 1979a; FAO/WHO, 1981).

Table 6. The acute oral toxicity of phenothrin metabolites

Chemical	No. <sup>a</sup>	Species	LD <sub>50</sub> (mg/kg)
3-Phenoxybenzyl alcohol	12	Rat	1330
3-Phenoxybenzaldehyde	13	Rat	600

<sup>a</sup> Chemical identification number used in Fig. 2

## 7.2 Long-Term Exposures and Carcinogenicity

### *Appraisal*

*There have been several long-term feeding studies with racemic phenothrin or d-phenothrin (dose levels ranging from 200 to 10 000 mg/kg diet) in rats and mice, the length of exposure ranging from 6 months to 2 years. A slight increase in liver weight and a*

Table 7. The acute intraperitoneal toxicity of several phenothrin metabolites in mice

Chemical	No. <sup>a</sup>	LD <sub>50</sub> (mg/kg)	
		Male	Female
3-Phenoxybenzyl alcohol	12	371	424
3-(4'-hydroxyphenoxy)benzyl alcohol	14	750-1000	750-1000
3-(2'-hydroxyphenoxy)benzyl alcohol	15	876	778
3-Phenoxybenzoic acid	16	154	169
3-(4'-hydroxyphenoxy)benzoic acid	17	783	745
3-(2'-hydroxyphenoxy)benzoic acid	18	859	912
3-Phenoxybenzaldehyde	13	415	416

<sup>a</sup> Chemical identification number used in Fig. 2

significant difference in some clinical/chemistry parameters from those of controls were observed at high doses. However, the no-observed-effect level (NOEL) values obtained in these studies were high (300-1000 mg/kg diet, corresponding to around 40-160 mg/kg body weight) and no tumorigenicity was observed. Two feeding studies with d-phenothrin (doses of 100-3000 mg/kg diet with exposure period 26 and 52 weeks) in dogs revealed similar results, the NOEL being 300 mg/kg diet (corresponding to around 7-8 mg/kg body weight per day). No tumorigenicity relating to phenothrin feeding was detected in these studies.

### 7.2.1 Rat

In a study by Murakami et al. (1981), [1R,cis]-phenothrin (d-phenothrin) was administered to Sprague Dawley rats (20 of each sex per group) at dose levels of 0, 1, 3, or 10 g/kg diet for 6 months. Ten rats of each sex per group were sacrificed after 3 months. d-Phenothrin had no significant effect on mortality, clinical signs, ophthalmology, urinalysis, or gross and histopathological findings. The serum albumin level was elevated after 3 months in males fed 10 g/kg and in females fed 3 or 10 g/kg, and after 6 months in males fed 3 or 10 g/kg. The albumin-globulin ratio was raised after 3 months in males fed 3 or 10 g/kg and in females fed 10 g/kg, and in both males and females fed 10 g/kg after 6 months. Absolute and relative liver weights in both males and females fed 3 or 10 g/kg were increased. Based on these data, it was concluded that the NOEL for d-phenothrin in this study was 1 g/kg diet for both sexes (55.4 mg/kg body weight per day for males and 63.3 mg/kg body weight per day for females).

In a standard oncogenicity study, Fisher-344 rats (50 of each sex per group) were fed d-phenothrin at dose levels of 0, 300, 1000 or 3000 mg/kg diet for at least 105 weeks in males and at least 118 weeks

in females. Additional rats (30 of each sex per group) were assigned to a chronic toxicity study with a 52-week interim sacrifice. There were no significant effects on clinical signs, mortality, food and water consumption, ophthalmology, blood biochemistry, haematology, or urinalysis. However, the body weight gain in females fed d-phenothrin at 3000 mg/kg was reduced, and the relative liver weight was increased in females fed 3000 mg/kg for 52 weeks and, at the end of the oncogenicity study, in males fed 3000 mg/kg. Microscopic examination revealed that the incidence of cystic dilatation of the sinuses of the mesenteric lymph nodes and of periacinar hepatocytic hypertrophy was higher in males fed 3000 mg/kg for at least 105 weeks. d-Phenothrin did not show any oncogenic activity to rats at up to 3000 mg/kg. Although at this dose an increase in the incidence of adenomas and carcinomas of the preputial gland was seen in males, the 1988 Joint FAO/WHO Meeting on Pesticide Residues (FAO/WHO, 1988b) considered it unlikely that this finding was of toxicological significance. The NOEL was 1000 mg/kg diet for both sexes (47 mg/kg body weight per day for males and 56 mg/kg body weight per day for females) (Martin et al., 1987).

When Sprague Dawley rats (50 of each sex per group) were fed a diet containing racemic phenothrin (0, 200, 600, 2000, and 6000 mg/kg diet) for 2 years, body weight and food consumption were slightly depressed at 6000 mg/kg in both males and females. Ophthalmological examinations, haematological studies, urinalyses, and clinical chemistry studies were performed at various intervals. At the end of the study all animals were sacrificed and examined for gross abnormalities, and extensive microscopic examinations were conducted on a variety of tissues and organs. There were no abnormal clinical or behavioral problems associated with phenothrin administration. The survival rate of all groups of treated rats was similar to that of controls. Males fed 6000 mg/kg showed a significant increase in serum glutamine-pyruvate aminotransferase activity. Ophthalmological examinations revealed some abnormalities, all of which appeared to be age related. Histopathological examination revealed no significant differences between the treated groups and the control group with respect to severity of lesions. No histopathological changes suggestive of oncogenicity resulting from phenothrin treatment were found (Hiromori et al., 1980).

### 7.2.2 *Mouse*

When Swiss White mice (50 of each sex per group) were fed racemic phenothrin for 18 months at dose levels of 0, 300, 1000, or 3000 mg/kg diet, there were no significant effects on mortality, clinical signs, haematologic values, clinical chemistry parameters, or gross pathological findings. Slight body weight depression occurred in males fed 3000 mg/kg, and increased liver weight was found at the highest dose level in both males and females. There was a statistically significant difference (compared with the controls) in lung amyloidosis in the 1000 and 3000 mg/kg dose groups, but no significant increase in tumours attributable to phenothrin ingestion (Murakami et al., 1980).



In studies by Amyes et al. (1987), B6C3F<sub>1</sub> hybrid mice (90 of each sex per group) were fed d-phenothrin in the diet at dose levels of 0, 300, 1000, or 3000 mg/kg. Fifty of each sex per group were allocated to a standard oncogenicity study lasting 104 weeks. The remaining mice were assigned to a chronic toxicity study, where 10 of each sex per group were sacrificed for interim study after 26 or 53 weeks and the remaining animals were examined after 78 weeks of treatment. There were no compound-related effects on clinical signs, mortality, ophthalmology, blood biochemistry, haematology, or urinalysis. However, body weight gains for males fed d-phenothrin at 3000 mg/kg were reduced and relative liver weights were increased in both sexes fed 3000 mg/kg and in males receiving 1000 mg/kg. Microscopic examination revealed that the incidence of periacinar hepatocyte hypertrophy with cytoplasmic eosinophilia was higher in males fed 3000 mg/kg. The incidence of liver tumors appeared higher in phenothrin-treated female mice than in control females, but the difference was not statistically significant. It was concluded, therefore, that administration of d-phenothrin to mice for 2 years at dietary levels of up to 3000 mg/kg diet did not significantly disturb the tumour burden or tumour profile of B6C3F<sub>1</sub> hybrid mice. The NOEL in this study was 300 mg/kg diet for males (40 mg/kg body weight per day) and 1000 mg/kg diet for females (164 mg/kg body weight per day).

### 7.2.3 Dog

When beagle dogs (six of each sex per group) were fed d-phenothrin at dose levels of 0, 100, 300, or 1000 mg/kg diet for 26 weeks, there were no compound-related abnormal findings in mortality, clinical signs, body weight, food consumption, ophthalmology, gross or microscopic pathology, haematology, or urinalysis studies. However, the alkaline phosphatase activity in males fed 300 mg/kg and males and females fed 1000 mg/kg was elevated and a slight increase in the mean relative liver weight in males fed 1000 mg/kg was noted. The NOEL in this study was 300 mg/kg (Pence et al., 1981).

In a study by Cox et al. (1987), beagle dogs (four of each sex per group) were fed d-phenothrin at dose levels of 0, 100, 300, 1000, or 3000 mg/kg diet for 52 weeks. There were no significant effects on clinical signs, body weight, food consumption, ophthalmology, or urinalysis. However, decreases in erythrocyte count, haemoglobin concentration, haematocrit, and total blood protein were noted in both male and female dogs fed 3000 mg/kg, whereas mean absolute and relative liver weights increased. Compound-related histopathological alterations were noted in the adrenal glands and liver. Focal degeneration of the adrenal cortex with cytoplasmic deposition of crystalline material was seen in one male dog fed 1000 mg/kg and four dogs fed 3000 mg/kg. The chemical nature or biological significance of this crystalline material was not recorded. Hepatocytes appeared to enlarge slightly in one male dog fed 1000 mg/kg and seven dogs fed 3000 mg/kg. The NOEL in this study was 300 mg/kg diet for males and 1000 mg/kg for females (8.24 and 26.77 mg/kg body weight per day for males and females, respectively).

### 7.3 Mutagenicity

The results obtained in *in vivo* and *in vitro* test systems indicate that d-phenothrin does not exhibit any mutagenic properties or cause chromosomal or DNA damage.

In a DNA-repair test with *Bacillus subtilis* (M45 rec<sup>-</sup> and H17 wild type strains) using dose levels of up to 5 mg/disk per plate, d-phenothrin did not inhibit the growth of any strain at any dose level, whereas the positive control, mitomycin C, showed a clear effect. The negative control gave a result similar to that of d-phenothrin (Kishida & Suzuki, 1981a).

A mutagenicity test with *Escherichia coli* (WP2 *uvr*) and *Salmonella typhimurium* (TA 1535, TA 1537, TA 1538, TA 98, and TA 100) using d-phenothrin at dose levels of up to 5 mg/plate with and without metabolizing enzyme system (S9 mix) yielded negative results, whereas a positive control gave a significant number of mutants (Kishida & Suzuki, 1981b).

In a host-mediated assay using *S. typhimurium* G46 (indicator bacteria), d-phenothrin in corn oil was given orally (twice with a 24-h interval) to groups of six male ICR mice at dose levels of 2500 or 5000 mg/kg body weight. Soon after the last administration, each mouse was injected intraperitoneally with the indicator cells. Three hours later, the bacterial mutation frequency in d-phenothrin-treated mice was no greater than that in the control group (Kishida & Suzuki, 1981c).

Suzuki et al. (1981) examined d-phenothrin for its ability to induce chromosomal aberrations *in vivo* using bone marrow cells. ICR mice were treated intraperitoneally with single doses of 2500, 5000, or 10 000 mg/kg body weight and sacrificed 6, 24, or 48 h after treatment. No chromosomal aberrations as a result of d-phenothrin treatment were detected.

In an *in vitro* chromosomal aberration test, Chinese hamster ovary cells (CHO-K1) were treated with d-phenothrin (dose levels:  $2 \times 10^{-5}$  to  $2 \times 10^{-4}$  mol/litre for 24 and 48 h in the absence of S9 mix;  $5 \times 10^{-5}$  to  $5 \times 10^{-4}$  mol/litre for 6 h in the presence of S9 mix). No significant increase in the number of cells with chromosomal aberrations was observed (Kogiso et al., 1986).

The ability of d-phenothrin to induce sister-chromatid exchanges (SCEs) was tested in cultured mouse embryonic cells *in vitro*. At doses of  $10^{-5}$ ,  $10^{-4}$ , and  $10^{-3}$  mol/litre (with and without S9 mix), d-phenothrin did not induce any increase in the frequency of SCEs (Suzuki & Miyamoto, 1981).

In a study of unscheduled DNA synthesis, HeLa S3 cells were treated with d-phenothrin at dose levels of 0, 0.25, 0.5, 1.0, 2.0, or 4.0 mg/ml in the presence of <sup>3</sup>H-thymidine (with and without S9 mix) for 3 h, and the incorporation of <sup>3</sup>H-thymidine into DNA was measured. There was no significant increase in the radioactivity of DNA from cells treated with d-phenothrin (Foster et al., 1984).

## 7.4 Reproduction, Embryotoxicity, and Teratogenicity

No teratogenicity or reproductive effects were observed when phenothrin was fed to rabbits or mice during the major organogenesis period of gestation or to rats in 3-generation reproduction studies.

### 7.4.1 *Embryotoxicity and teratogenicity*

In studies by Ladd et al. (1976), pregnant New Zealand White rabbits (17 per group) were administered racemic phenothrin orally at dose levels of 0, 3, 10, or 30 mg/kg body weight on days 6 to 18 of gestation. They were sacrificed on day 29 and the young obtained by caesarian section were examined. At 30 mg/kg, the body weight of females decreased during gestation, and there was a slight decrease in the number of live young and a slight reduction in fetal weight. Racemic phenothrin had no apparent teratogenic effect, as shown by a lack of gross internal or external somatic abnormalities and by normal fetal skeletal development following prenatal exposure.

Pregnant New Zealand White rabbits (15 per group) were orally administered d-phenothrin by intubation (0, 10, 100, or 1000 mg/kg body weight per day) on days 6 to 18 of gestation, and were sacrificed on day 29 or 30. Following caesarian section, 50% of the pups were maintained for 24 h to evaluate survival. No abnormalities were observed among the does (body weight, food consumption, clinical observations, and necropsy) or foetuses (implantation sites, corpora lutea, resorption sites, weight, condition, and viability). Data on foetal survival and from internal and external examinations for abnormalities showed no significant effects from administering d-phenothrin during gestation (Rutter, 1974).

In studies by Nakamoto et al. (1973), d-phenothrin was orally administered to pregnant ICR mice (17 or 18 per group) at dose levels of 0, 30, 300, or 3000 mg/kg body weight on days 7 to 12 of gestation (not covering the whole period of organogenesis). The dams were sacrificed on day 18 of gestation and the pups were obtained by caesarian section. Other mice (7 per group) were given d-phenothrin at dose levels of 0, 300, or 3000 mg/kg to evaluate postnatal effects. These mice were allowed to deliver naturally and the pups were kept for 29 days. At these levels, d-phenothrin showed no adverse effects, as indicated by maternal growth, fetal mortality and external and internal examination of fetuses for teratogenic or embryotoxic effects.

### 7.4.2 *Reproduction studies*

In a standard 3-generation (2 litters per generation) reproduction study, groups of rats (8 male and 16 female Charles River albino rats per group) were fed racemic phenothrin at dose levels of 0, 200, 600, or 2000 mg/kg diet. Various reproductive indices (i.e. mating index, fecundity index, male fertility index, female fertility index, and incidence of parturition) were measured. The adult rats showed no

significant mortality or complications during the study, and the reproductive parameters revealed no significant dose-related adverse effects attributable to phenothrin. Gross and microscopic findings indicated no adverse effect resulting from dietary phenothrin. It was concluded that phenothrin had no effect on reproduction (Takatsuka et al., 1980).

In a study by Tesh et al. (1987), d-phenothrin was fed to Charles River CD rats (30 of each sex per group) at dose levels of 0, 300, 1000, or 3000 mg/kg diet throughout two successive generations and up to the maturation of a third generation. At 300 and 1000 mg/kg, there was no adverse effect upon mortality, somatic growth, development, or reproductive performance. At 3000 mg/kg, mortality, body weight, and reproductive performance showed no significant response to treatment, and selected F<sub>2</sub> animals reared to maturity were in all respects comparable with control rats. However, F<sub>0</sub> and F<sub>1</sub> females and selected F<sub>2B</sub> male and female weanlings showed a slight but consistent increase in the relative liver weight. The NOEL in this study was 1000 mg/kg diet.

### 7.5 Neurotoxicity

Sprague Dawley rats exposed to d-phenothrin by inhalation at concentrations of up to 3760 mg/m<sup>3</sup> for 4 h showed no toxic signs as a result of exposure. Histopathologically, there were no compound-related alterations in the sciatic nerve (Kohda et al., 1977).

When d-phenothrin was given to Sprague Dawley rats orally for 5 consecutive days (5 g/kg body weight per day), one out of ten female rats died after four doses and signs of poisoning (piloerections and urinary incontinence) were noted in several of the animals. However, these signs disappeared rapidly at the end of the treatment and there were no other signs of poisoning such as leg weakness or ataxia. All animals were sacrificed 3 days after the final dose, and histopathological examination of the sciatic nerve revealed minute changes in axon and myelin, characterized by very slight axonal swelling, axonal disintegration, and/or demyelination. Since there were similar changes in the control animals, it was suggested that they were not due to the d-phenothrin. It was considered that the oral administration of very high doses of d-phenothrin does not lead to the neurotoxic effects observed with several other pyrethroid esters (Okuno et al., 1978).

### 7.6 Miscellaneous Effects

No d-phenothrin-attributable pharmacological effects were detected in various tests (e.g., spontaneous movement of isolated guinea-pig ileum, contraction of the rat phrenic nerve diaphragm preparation, cardiopulmonary physiology of anaesthetized cats, coordination and spontaneous movement of mice, and rectal temperature of rats) at doses of 100-300 µg/ml *in vitro*, 3 mg/kg intravenous, or 100-300 mg/kg intraperitoneal. A tentative arousal response was recorded in the

electroencephalogram of cats given d-phenothrin (4 mg/kg) intraperitoneally, as is commonly observed in animals given synthetic pyrethroids (Hara et al., 1974).

### 7.7 Mechanism of Toxicity - Mode of Action

Some synthetic pyrethroids given intravenously to rats cause either tremor (T-syndrome) or choreoathetosis with salivation (CS-syndrome) (Verschoyle & Aldridge, 1980). However, d-phenothrin (>600 mg/kg body weight) injected intravenously into the lateral tail vein caused neither T-syndrome nor CS-syndrome, due to its very low acute toxicity. From a study involving intracerebral dosing with [1R,*cis*]- or [1R,*trans*]-phenothrin in mice, both compounds were classified as Type I pyrethroids based on the occurrence of tremors (Lawrence & Casida, 1982) and on neurophysiological studies in cockroach cercal sensory nerves (Gammon et al., 1981).

## 8. EFFECTS ON HUMANS

Although d-phenothrin has been used for more than 10 years, no toxic effects and no cases of poisoning have been reported.

### 8.1 Clinical Studies

In a study by Hashimoto et al. (1980), d-phenothrin (talc powder formulation with Span 80 as a stabilizer) was applied to the head hair and pudenda hair of eight male human volunteers (three times at intervals of 3 days) at a dose of 32 mg/man per administration (0.44 to 0.67 mg/kg body weight per day). d-Phenothrin powder was washed off 1 h after application. There were no significant abnormalities due to d-phenothrin in terms of dermal irritation, clinical signs, or blood biochemical and haematological parameters. The blood levels of d-phenothrin were below the detection limit of 0.006 mg/kg.

## 9. PREVIOUS EVALUATION BY INTERNATIONAL BODIES

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) has discussed and evaluated d-phenothrin at its meetings in 1979, 1980, 1984, and 1988 (FAO/WHO, 1980, 1981, 1985a, 1988b).

Since 1988, an acceptable daily intake (ADI) of 0-0.07 mg/kg body weight has been established.

In the WHO Recommended Classification of Pesticides by Hazard, technical phenothrin is classified as unlikely to present an acute hazard in normal use (WHO, 1988).

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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  $\alpha$ -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  $\alpha$ -cyano group (allethrin, d-phenothrin, permethrin, tetramethrin, cismethrin, and bioresmethrin) (Type I: T-syndrome)*

The pyrethroids that do not contain an  $\alpha$ -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 intermittently, cause large depolarizing after-potentials, 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  $\alpha$ -cyano group on the 3-phenoxybenzyl alcohol (deltamethrin, cypermethrin, fenvalerate, and fenpropanate) (Type II: CS-syndrome)*

The pyrethroids with an  $\alpha$ -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-dependant 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  $\alpha$ -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]-*l*-butylbicyclophosphorothionate [ $^{35}$ 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, $\alpha$ ]-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]-dihydro-picrotoxin 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 benzodiaz-epine site of action (Lawrence et al., 1985).

The Type II pyrethroids (deltamethrin, 1R, *cis*-cypermethrin and [2S, $\alpha$ S]-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  $\alpha$ -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  $\alpha$ -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  $\alpha$ -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  $\alpha$ -cyano group on the phenoxybenzyl alcohol, indicates that it is this  $\alpha$ -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  $\alpha$ -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 advanced 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).

## RESUME, EVALUATION, CONCLUSIONS ET RECOMMANDATIONS

### 1. Résumé et évaluation

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

La phénothrine racémique a été synthétisée pour la première fois en 1969. Du point de vue chimique, il s'agit de l'ester de l'acide diméthyl-2,2 (diméthyl-2,2 vinyl)-3 cyclopropanecarboxylique et de l'alcool phénoxy-3 benzylique (PBalc). Il se présente sous la forme d'un mélange de quatre stéréoisomères : [1R,trans], [1R,cis], [1S,trans], [1S,cis]. La d-phénothrine est un mélange d'une partie d'isomère [1R,cis] pour quatre parties d'isomère [1R,trans], et elle est à l'heure actuelle le seul produit technique sur le marché. C'est l'isomère [1R,trans] qui est l'insecticide le plus actif; vient ensuite l'isomère [1R,cis].

La d-phénothrine de qualité technique se présente sous la forme d'un liquide jaune pâle à brun jaune et son degré de pureté est de 92,5 à 94,5%. Sa densité est de 1,058-1,061 à 25°C et sa tension de vapeur de 0,16 mPa à 20°C. Elle est difficilement soluble dans l'eau (2 mg par litre à 25°C) mais soluble dans les solvants organiques tels que l'acétone, le xylène et l'hexane. Elle est assez stable à l'air mais instable à la lumière, encore que sa photodégradation ne soit pas aussi rapide que celle des pyréthrinés naturelles. Elle est instable en milieu alcalin.

Le dosage des résidus peut s'effectuer par chromatographie en phase liquide à haute performance avec détecteur ultra-violet, la concentration minimale décelable étant de 0,05 mg par kg. Pour l'analyse du produit technique on utilise la chromatographie en phase gazeuse avec détection par ionisation de flamme.

#### 1.2 *Production et usage*

La d-phénothrine est utilisée depuis 1977. On estime que l'on utilise chaque année 70 à 80 tonnes de d-phénothrine dans le monde, essentiellement pour détruire les insectes incommodes dans les habitations, lutter contre les vecteurs de maladies et protéger les céréales ensilées; le produit est utilisé seul ou en association avec d'autres insecticides ou synergisants. Il est présenté sous forme d'huiles pour aérosols, de poudres ou de concentrés émulsionnables. La d-phénothrine est également utilisée pour détruire les poux de l'homme, auquel cas elle est présentée sous forme de poudre, de shampooing ou de lotion.

#### 1.3 *Exposition humaine*

Les aérosols classiques à usage domestique ne devraient pas conduire à des concentrations atmosphériques de d-phénothrine

supérieures à 0,5 mg/m<sup>3</sup>. Dans le blé ensilé, on peut trouver des résidus allant jusqu'à 4 mg/kg, mais ces teneurs tombent à 0,8 mg/kg dans la farine après mouture, et à 0,6 mg/kg après panification.

Pour détruire les poux, on applique la d-phénothrine sur la chevelure, par exemple en trois doses de 32 mg tous les trois jours. Il n'existe aucune donnée sur l'exposition professionnelle à la d-phénothrine.

L'exposition de la population dans son ensemble devrait être très faible, mais on manque de données précises sur ce point.

#### **1.4 Destinée dans l'environnement**

La phénothrine se dégrade facilement, sa demi-vie étant inférieure à un jour sur les végétaux et autres surfaces. La d-phénothrine ou ses produits de dégradation ne migrent que très peu vers les zones non traitées des végétaux. On a constaté que des haricots ne captaient que dans une faible mesure les produits radiomarqués provenant de sols traités par de la phénothrine marquée au carbone-14. Après traitement des sols avec de la [1R,trans]- ou de la [1R,cis]-phénothrine à raison de 1 mg/kg, on a constaté que les deux isomères se décomposaient rapidement, la demi-vie initiale étant de un à deux jours, mais que, en cas d'inondation, la dégradation était considérablement ralentie, la demi-vie initiale étant de deux à quatre semaines pour l'isomère trans et de un à deux mois pour l'isomère cis. On a observé que les isomères trans ou cis de la phénothrine se déplaçaient relativement peu (environ 2%) à travers des colonnes de terre, lorsque le lessivage commençait immédiatement ou deux semaines après le traitement.

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

#### **1.5 Cinétique et métabolisme**

Après avoir reçu une dose unique ou des doses répétées de phénothrine radiomarquée par voie orale ou percutanée, des rats ont rapidement et presque complètement excrété la fraction marquée dans leurs urines et leurs déjections en trois à sept jours. Les principales voies métaboliques des isomères cis et trans chez le rat consistent en une rupture de la liaison ester et l'oxydation en position 4' du reste alcool ou du groupement isobutényle du reste acide. Les métabolites résultant du clivage de l'ester (qui sont excrétés essentiellement dans les urines) constituent les principaux produits de dégradation de l'isomère trans alors que les métabolites restant sous forme d'ester (excrétés essentiellement dans les déjections) proviennent pour la plupart de l'isomère cis.

#### **1.6 Effets sur les êtres vivants dans leur milieu naturel**

La phénothrine a été expérimentée sur quelques groupes d'organismes non visés et dans chaque groupe sur quelques espèces

seulement. Chez les poissons, la  $CL_{50}$  à 96 heures de la phénothrine racémique et des stéréoisomères (1R) va de 17 à 200 microgrammes par litre. Une étude, portant sur des invertébrés aquatiques, a montré que chez *Daphnia pulex* la  $CL_{50}$  à 3 heures était de 25 à 50 mg/litre pour tous les isomères et la phénothrine racémique.

Une seule et unique étude au cours de laquelle de la phénothrine a été appliquée à des étangs n'a révélé aucun effet sur les arthropodes aquatiques.

La toxicité pour les oiseaux est faible, avec une  $DL_{50}$  aiguë par voie orale supérieure à 2500 mg/kg de poids corporel chez le colin de Virginie et une  $CL_{50}$  par voie alimentaire supérieure à 5000 mg/kg de nourriture chez ce volatile et chez le colvert.

Etant donné que la phénothrine se dégrade rapidement à la lumière solaire et qu'on l'utilise principalement pour traiter des céréales ensilées, l'exposition environnementale est vraisemblablement très faible. Dans ces conditions, des effets sur l'environnement sont tout-à-fait improbables.

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

La toxicité aiguë de la d-phénothrine est extrêmement faible, la  $DL_{50}$  étant supérieure à 5000 mg/kg de poids corporel chez le rat et la souris (par voie orale, sous-cutanée, dermique et intrapéritonéale) et la  $CL_{50}$  inhalatoire supérieure à 3760 mg/m<sup>3</sup> chez le rat. Le syndrome d'intoxication se caractérise par une hyperexcitabilité, une prostration, des tremblements, de l'ataxie et une paralysie. Sur la base de ces symptômes et d'après les résultats des études électrophysiologiques sur les nerfs sensoriels des cerques de la blatte, la phénothrine est classée parmi les pyréthroides du type I.

Exposés à de la d-phénothrine par inhalation à des concentrations allant jusqu'à 210 mg/m<sup>3</sup>, quatre heures par jour pendant quatre semaines, ou par voie orale cinq jours de suite à raison de 5000 mg/kg de poids corporel, des rats n'ont présenté aucun effet toxicologique indésirable.

Plusieurs études d'alimentation ont été effectuées sur des rats et des souris recevant de la d-phénothrine ou de la phénothrine racémique à des doses allant de 200 à 10 000 mg par kg de nourriture; la période d'exposition allait de six mois à deux ans. Ces études ont permis d'établir une dose sans effet observable allant de 300 à 1000 mg par kg de nourriture, ce qui correspond à peu près à 40-160 mg/kg de poids corporel et par jour. Chez des chiens à qui l'on avait administré de la d-phénothrine à des doses de 100 à 3000 mg/kg de nourriture avec des périodes d'exposition de 26 à 52 semaines, deux études ont permis d'obtenir une dose sans effet observable de 300 mg par kg de nourriture, soit 7 à 8 mg/kg de poids corporel et par jour.

Divers systèmes permettant d'étudier *in vivo* et *in vitro* les mutations géniques, les lésions et les réparations de l'ADN ainsi que les effets chromosomiques, ont permis de constater que la d-phénothrine n'avait pas d'effet mutagène.



Des études de deux ans ont également montré que la d-phénothrine n'était pas cancérogène pour le rat ni la souris à des doses allant jusqu'à 3000 mg par kg de nourriture. Aucune tératogénicité ni embryotoxicité n'a été observée chez des foetus de lapins et de souris dont les mères avaient reçu de la d-phénothrine à des doses allant jusqu'à 1000 et 3000 mg par kg de poids corporel, respectivement. Lors d'une étude de reproduction chez le rat, portant sur deux générations, on a établi que la dose sans effet observable était de 1000 mg par kg de nourriture.

Des rats exposés par inhalation à des doses très élevées de d-phénothrine (jusqu'à 3760 mg/m<sup>3</sup>) pendant quatre heures ou, quotidiennement, par voie orale, à une dose de 5000 mg par kg de poids corporel, cinq jours durant, n'ont présenté aucune dégénérescence myélinique ni désagrégation de l'axone au niveau du nerf sciatique.

### *1.8 Effets sur les êtres humains*

La d-phénothrine est utilisée depuis plus de 10 ans sans que l'on ait signalé d'intoxication humaine.

Rien n'indique que cette substance puisse avoir des effets nocifs sur l'homme pour peu qu'elle soit utilisée conformément aux recommandations.

## **2. Conclusions**

### *2.1 Population générale*

L'exposition de la population dans son ensemble à la d-phénothrine est vraisemblablement très faible et il n'y a probablement aucun risque à cet égard si le produit est utilisé conformément aux recommandations.

### *2.2 Exposition professionnelle*

Si elle est utilisée de manière convenable, moyennant un certain nombre de mesures d'hygiène et de sécurité, la d-phénothrine ne devrait pas présenter de risque pour les personnes qui lui sont exposées de par leur profession.

### *2.3 Environnement*

Du fait qu'elle se dégrade rapidement à la lumière solaire et qu'elle est principalement utilisée pour traiter les céréales ensilées, l'exposition environnementale à la phénothrine est vraisemblablement très faible. Dans ces conditions tout effet sur l'environnement est extrêmement improbable.

### 3. Recommandations

Les niveaux d'exposition résultant d'une utilisation conforme aux recommandations sont censés être extrêmement faibles, toutefois on pourrait envisager de confirmer cette hypothèse en étendant la surveillance à la d-phénothrine.

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