WHO SPECIFICATIONS AND EVALUATIONS

FOR PUBLIC HEALTH PESTICIDES

ESBIOTHRIN [1/]

(*RS*)-3-allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*,3*R*)-2,2-dimethyl -3-(2-methylprop-1-enyl) cyclopropanecarboxylate

WORLD HEALTH ORGANIZATION

GENEVA

[1/] Esbiothrin is the name given by the manufacturer to a mixture of two stereoisomers, [1*R,trans;R*] and [1*R,trans;S*], of allethrin in an approximate ratio of 1:3.

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WHO specifications are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements.

Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

Furthermore, pesticides which are manufactured to comply with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable to their manufacture, sale, transportation, storage, handling, preparation and/or use.

WHO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may be arise as a result of, or in connection with, the manufacture, sale, transportation, storage, handling, preparation and/or use of pesticides which are found, or are claimed, to have been manufactured to comply with these specifications.

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[1] This disclaimer applies to all specifications published by WHO.

INTRODUCTION

WHO establishes and publishes specifications* for technical material and related formulations of public health pesticides with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 2002, the development of WHO specifications has followed the **New Procedure**, described in the 1st edition of Manual for Development and Use of FAO and WHO Specifications for Pesticides (2002). This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by WHO and the experts of the "FAO/WHO Joint Meeting on Pesticide Specifications" (JMPS).

WHO Specifications now only apply to products for which the technical materials have been evaluated. Consequently, from the year 2002 onwards the publication of WHO specifications under the **New Procedure** has changed. Every specification consists now of two parts, namely the specifications and the evaluation report(s):

Part One: The Specification of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the 1st edition of the "FAO/WHO Manual on Pesticide Specifications."

Part Two: The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by WHO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the "FAO/WHO Manual on Pesticide Specifications" and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

WHO specifications developed under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. WHO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version. Dates of publication of the earlier versions, if any, are identified in a footnote. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

* Footnote: The publications are available on the Internet under (http://www.who.int/whopes).

PART ONE

SPECIFICATIONS

ESBIOTHRIN

ESBIOTHRIN

INFORMATION

ISO common name: Allethrin is the ISO common name for a racemic mixture of 4 pairs of diastereoisomers. Esbiothrin is the name given by the manufacturer to a mixture of two stereoisomers, [1*R,trans;R*] and [1*R,trans;S*], of allethrin in an approximate ratio of 1:3.

Synonyms: None.

Chemical name:

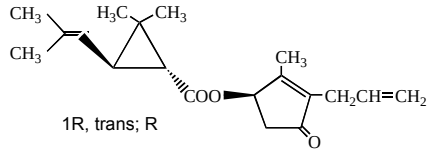
IUPAC: (*RS*)-3-allyl-2-methyl-4-oxocyclopent-2-enyl (1*R, 3R*)-2,2-dimethyl -3-(2-methylprop-1-enyl)cyclopropanecarboxylate.

CA: None. CAS name for allethrin is: 2-methyl-4-oxo-3-(2-propenyl)-2-cyclopent-1-yl 2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylate.

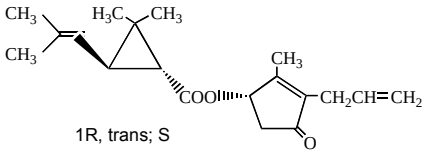
CAS No: 260359-57-5

CIPAC No: 751

Structural formula:



1R, trans; R



1R, trans; S

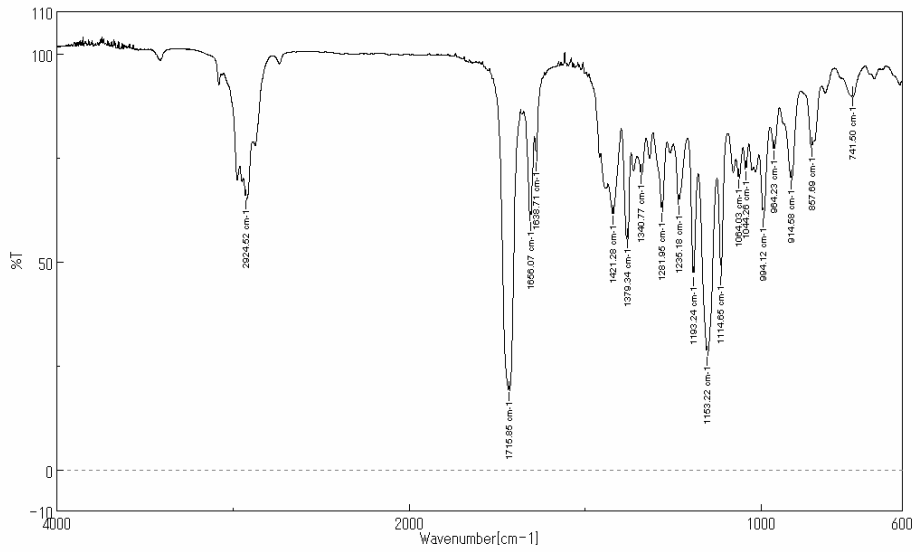
esbiothrin consists of [1*R*,*trans*;*R*]+[1*R,trans;S*] in an approximate ratio of 1:3.

Molecular formula: $C_{19}H_{26}O_3$

Relative molecular mass:

302.41

Identity tests: Retention time by capillary GC-FID (analytical method for active ingredient content); chiral HPLC retention time and peak pattern (analysis method for isomer ratio); IR spectrum (see below).



IR spectrum of esbiothrin.

ESBIOTHRIN TECHNICAL MATERIAL (TC)

WHO Specification 751/TC (October 2004*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (751/2003). It should be applicable to relevant products of this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for the products of other manufacturers. The evaluation report (751/2003) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist essentially of esbiothrin, with related manufacturing impurities. It shall be a yellow to brown oil, substantially odourless and free from extraneous materials or added modifying agents.

2 Active ingredient

2.1 **Identity tests** (Note 1)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Esbiothrin content** (Note 2)

The esbiothrin content shall be declared (not less than 930 g/kg) and, when determined, the mean measured content shall not be lower than the declared minimum content.

2.3 **Isomer composition** (Note 2)

The *trans*-isomer content in the active ingredient in the material shall be declared (not less than 98.5%) and, when determined, the mean measured *trans*-isomer content in the active ingredient shall not be lower than the declared minimum value.

The 1*R*-isomer content at the acid moiety in the active ingredient in the material shall be declared (not less than 98%) and, when determined, the mean measured 1*R*-isomer content in the active ingredient shall not be lower than the declared minimum content.

The *S*-isomer content at the alcohol moiety in the active ingredient in the material shall be declared (not less than 75% and not more than 80%) and,

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.who.int/whopes/quality/en/.

when determined, the mean measured *S*-isomer content in the active ingredient shall not be lower than the declared minimum content.

Note 1 GC retention time and IR spectrum may be used to confirm the identity as allethrin isomers but the HPLC peak pattern (clause 2.3) is required to confirm the identity as esbiothrin.

Note 2 Methods for the identification and determination of esbiothrin content were adopted by CIPAC in 2003 but are not yet published in a Handbook. Prior to such publication, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org or from the Secretary, Dr László Bura, Central Service for Plant Protection and Soil Conservation, Budaörsi út 141-145, 1118 Budapest, Hungary.

PART TWO

EVALUATION REPORTS

ESBIOTHRIN

ESBIOTHRIN

EVALUATION REPORT 751/2003

Explanation

Esbiothrin was evaluated by the WHO/IPCS in 1989 (Environmental Health Criteria 87). It was reviewed by the US EPA in 1982. It is currently under evaluation by WHOPES. Patent protection for esbiothrin has expired.

The draft specification and the supporting data were provided by Sumitomo Chemical Company Ltd., Japan, in 2002.

Uses

Esbiothrin is a synthetic pyrethroid with fast knock-down activity against household pest insects. It is used in public health against mosquitoes, houseflies and cockroaches.

Identity

ISO common name: Allethrin is the ISO common name for a racemic mixture of 4 pairs of diastereoisomers. Esbiothrin is the name given by the manufacturer to a mixture of two stereoisomers, [1*R,trans;R*] and [1*R,trans;S*], of allethrin in an approximate ratio of 1:3.

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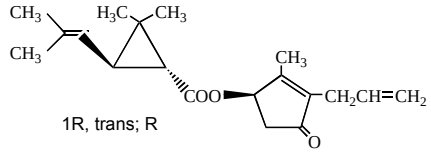
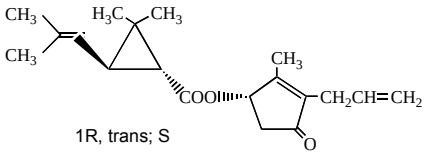


1R, trans; R



1R, trans; S

esbiothrin consists of [1R,trans;R]+[1*R,trans;S*] approximate ratio of 1:3.

Molecular formula: $C_{19}H_{26}O_3$

Relative molecular mass:

302.41

Identity tests: Retention time by capillary GC-FID (analytical method for active ingredient content); chiral HPLC retention time and peak pattern (analysis method for isomer ratio); IR spectrum

Notes on the isomer composition of related pesticides:

- allethrin consists of a racemic mixture of 8 stereoisomers;
- bioallethrin consists of [1*R*,*trans;*1*R*] and [1*R*,*trans;*1*S*] isomers in an approximate ratio of 1:1;
- esbiothrin consists of [1*R*,*trans;*1*R*] and [1*R*,*trans;*1*S*] isomers in an approximate ratio of 1:3;
- *S*-bioallethrin consists of the [1*R*,*trans;*1*S*] isomer.

Physical and chemical properties of esbiothrin

Table 1. Physico-chemical properties of pure esbiothrin.

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure:	0.044 Pa at 25°C, determined on bioallethrin	≥ 99%	Gas saturation method. Roussel Uclaf, 1992
Melting point and temperature of decomposition:	Melting point: not applicable Decomposition temperature: not available	-	-
Solubility in water:	4.6 mg/l at 25°C, determined on bioallethrin	≥ 99%	Undersaturation/over-saturation method. Roussel Uclaf, 1992
Octanol / water partition coefficient:	Log Kow = 4.68 at 25°C, determined on bioallethrin	≥ 99%	Flask shake method, Roussel Uclaf, 1992
Hydrolysis characteristics: bioallethrin	No measurable hydrolysis after 31 days at 25°C and pH 5. Half-life approximately 500 days at 25°C and pH 7. Half-life 4.3 days at 25°C and pH 9.	radiochem-ical purity:99.3	EPA Guideline 161-1. Estigoy, 1990

Parameter	Value(s) and conditions	Purity %	Method reference
Photolysis characteristics: bioallethrin	Photodegradation in water under natural sunlight. Half-life: 49 experiment hours or 19 sunlight hours at 25.5°C and pH 5	Not reported	EPA Guideline 161-3. Chari,1990.
Dissociation characteristics:	Does not dissociate.	-	-

Table 2. Chemical composition and properties of esbiothrin technical material (TC).

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data.	Confidential information supplied and held on file by FAO. Mass balances were 97.1-97.3%.
Declared minimum esbiothrin content:	930g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them:	None
Relevant impurities < 1 g/kg and maximum limits for them:	None
Stabilizers or other additives and maximum limits for them:	None
Melting or boiling temperature range	Boiling point: 165-170°C at 0.15 mm Hg

Hazard summary

Notes.

(i) The proposer provided written confirmation that the toxicological and ecotoxicological data included in the summary below were derived from esbiothrin having impurity profiles similar to those referred to in the table above.

(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table 1. Toxicology profile of esbiothrin technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Duration and conditions	Result	Purity	Ref.
Rat, male & female	Oral	EPA Guideline 81-1	LD_{50} = 432.3 mg/kg bw (male) LD_{50} = 378.0 mg/kg bw (female)	Not reported	Audegond *et al.*, 1979
Rabbit, male & female	Dermal	EPA Guideline 81-2	LD_{50} = >2000 mg/kg bw (male) >2000 mg/kg bw (female)	Not reported	Kaysen & Sales, 1984 [main study] Kaysen & Sales, 1989 [amendment]
Rat, male & female	Inhalation	EPA Guideline 81-3	LC_{50} = (male) 2.63, (female) 2.63 mg/L	Not reported	Hardy *et al*., 1984
Rabbit, male & female	Skin irritation	EPA Guideline 81-5	Slightly irritating (not irritant under EU criteria)	94.6%	Audegond *et al*., 1984a
Rabbit, male & female	Eye irritation	EPA Guideline 81-4	Slightly irritating (not irritant under EU criteria)	Not reported (1^{st} study) 94.6% (2^{nd} study)	Audegond *et al.*, 1984b(1^{st} study) Kuhn, 1990 [2nd study]

Species	Test	Duration and conditions	Result	Purity	Ref.
Guinea pig	Skin sensitization	Buehler method, EPA Guideline 81-6	Not sensitizing	95.7%	Glaza, 1989

Table 2. Toxicology profile of esbiothrin technical material based on repeated administration (sub-acute to chronic).

Species	Test	Duration and conditions	Result	Purity	Reference
Rat, male & female	feeding, toxicity	8 weeks	No particular clinical signs were observed and no treatment-related mortality was noted for the doses of 500, 1500, 3000, 6000 and 12000 ppm.	Not reported	Courcy di Rosa, 1986a
Mouse, male & female	feeding, toxicity	8 weeks	No particular clinical signs were observed and no treatment-related mortality was noted for the doses of 100, 1000, 2000, 4000 and 8000 ppm.	Not reported	Courcy di Rosa, 1986b
Dog, male & female	feeding, toxicity	28days	No clinical signs were observed in 50, 200, 800 and 3200 ppm groups. At the top dose (6400 ppm), one male showed clinical signs and died. General appearance and behaviour of females were not affected at 6400 ppm. No other deaths occurred.	Not reported	Petra, 1987a
Rabbit, male & female	Dermal, toxicity	EPA 82-2 3 weeks	NOEL = >1000 mg/kg bw/day.	94.5%	Henwood, 1990
Mouse, male & female	feeding, carcinogenicity	EPA 83-5 102 weeks	NOEL = 41.9 mg/kg/day (male), 49.7 mg/kg/day (female). Carcinogenicity: negative.	93.8%	Simmonard, 1990a
Rat, male & female	feeding, carcinogenicity	EPA 83-5 104 weeks	NOEL = 27.0 mg/kg/day (male), 38.1 mg/kg/day (female). Carcinogenicity: negative.	93.8%	Simmonard, 1990b
Dog, male & female	Feeding toxicity	EPA 83-1 1 year	NOAEL = 13.7 mg/kg/day (male), 16.1 mg/kg/day (female).	93.8%	Petra, 1987b
Rats, male & female	feeding, 2 generation reproduction	EPA Guideline 83-4	Reproduction NOEL = 1800 ppm, Overall NOEL = 600 ppm.	Not reported	Savary, 1989 Savary, 1990
Rats, male & female	feeding, teratogenicity and embryotoxicity	EPA Guideline 83-3	Maternal NOAEL = 25 mg/kg/day, Developmental NOAEL = 125 mg/kg/day (highest dose tested).	95.2%	Lochry, 1990
Rabbits, male & female	feeding, teratogenicity and embryotoxicity	EPA Guideline 83-3	Maternal NOAEL = 100 mg/kg/day, Developmental NOAEL = 300 mg/kg/day.	95.2%	Hoberman, 1990

Table 3. Mutagenicity profile of esbiothrin technical material, based on *in vitro* and *in vivo* tests.

Species	Test	Conditions	Result	Purity	Reference
Salmonella typhimurium, *Escherichia coli*	Gene mutation	Ames test, *in vitro*	Negative	Not reported	Chantot & Vannier, 1984
Mouse lymphoma cell	Mutagenic potential	*In vitro*	Negative	Not reported	Richold *et al*., 1984
Rat hepatocytes	Unscheduled DNA synthesis	*In vitro*	Negative	95.7%	Curren, 1988
Mouse	Micronucleus assay	*In vivo*	Negative	Not reported	Vannier & Fournex, 1984

Table 4. Ecotoxicology profile of esbiothrin technical material.

Species	Test	Duration and conditions	Result	Purity	Reference
Rainbow trout	Acute flow-through toxicity	EPA 72-1	LC_{50} (96 hr): 13 ppb	Not reported	Handley *et al*., 1993a
Daphnia magna	Acute flow-through toxicity	EPA 72-2	EC_{50} (48 hr): 8.9 ppb	Not reported	Handley *et al*., 1993b
Apis mellifera (honey bee)	Acute contact and acute oral toxicity	Acetone solutions applied topically or diluted in 20% aqueous sucrose for feeding (allethrin)	Contact LD_{50} = 3.4 µg/bee Oral LD_{50} = 4.6-9.1 µg/bee	>95%	Stevenson, 1978

Esbiothrin was evaluated by the WHO/IPCS (IPCS, 1989), with the following conclusions.

General population: under recommended conditions of use, the exposure of the general population to allethrins is negligible and is unlikely to present a hazard.

Occupational exposure: with reasonable work practices, hygiene measures, and safety precautions, the use of allethrins is unlikely to present a hazard to those occupationally exposed to them.

Environment: under recommended conditions of use and application rates, it is unlikely that allethrins or their degradation products will attain significant levels in the environment. In spite of the high toxicity of these compounds to fish and honey bees, they are only likely to cause a problem in the case of spillage or misuse.

The WHO hazard classification of esbiothrin is moderately hazardous (WHO, 1998).

Formulations

The main formulation type available is MV (vaporizing mats), which is registered and sold in many countries throughout the world. A draft specification for MV was not submitted for consideration by the meeting.

Methods of analysis and testing

The analytical method for the active ingredient (including identity tests) was adopted by CIPAC in 2003. The esbiothrin content is determined by capillary GC with FID

detection. Esbiothrin is distinguished from other mixtures of allethrin stereoisomers by means of the isomer ratio determined by HPLC with a chiral column.

Test methods for determination of physico-chemical properties of technical esbiothrin were OECD and EPA.

Containers and packaging

No special requirements for containers and packaging were identified.

Expression of the active ingredient

The active ingredient is expressed as esbiothrin, as defined by the WHO specification.

Appraisal

Esbiothrin is an active ingredient that had not previously been the subject of a WHO specification.

Esbiothrin is designated as the esterification product of *d-trans* chrysanthemic acid with *d* + *dl*-allethrolone. Esbiothrin is therefore comprised of >98.5 % *trans*-isomer with respect to the chrysanthemic acid moiety, 98% of the 1*R*-isomer and 75-80% of the 1*S*-isomer with respect to the alcohol moiety. It therefore contains the [1*R*,3*R*;1*R*] and [1*R*,3*R*;1*S*] isomers in an approximate ratio of 1:3.

Esbiothrin is related to other active ingredients containing the allethrin isomers: allethrin, bioallethrin, esbiothrin and *S*-bioallethrin are active ingredients with increasing degree of enantiopurity in the acid- and alcohol moieties.

Allethrin consists of a racemic mixture of 8 isomers, and a typical allethrin in the market consist of 8 isomers in ratio of [1R, *trans*, 1R]:[1R, *trans*, 1S]:[1S, *trans*, 1R]:[1S, *trans*, 1S]: [1R, *cis*, 1R]:[1R, *cis*, 1S]:[1S, *cis*, 1R]:[1S, *cis*, 1S] = 4:4:4:4:1:1:1:1. Bioallethrin is composed of a 1:1 mixture of the [1*R*,*trans;*1*R*] and [1*R,trans;*1*S* isomers] isomers, finally esbiothrin is composed of a 1:3 mixture of the [1*R,trans;*1*R*] and [1*R,trans;*1*S*] isomers, respectively, and *S*-bioallethrin is the single [1*R,trans;*1*S*] stereoisomer.

Some data on physico-chemical properties were elaborated using bioallethrin instead of esbiothrin. Nevertheless, the Meeting considered these data (solubility, octanol-water partition coefficient) to be acceptable, as they were expected to be very similar for bioallethrin and esbiothrin. Esbiothrin, represented by bioallethrin, shows a low solubility in water but is highly soluble in organic solvents like hexane, ethanol, acetone, toluene etc. It has a high octanol-water partition coefficient and a low volatility. Due to the sensitivity of esbiothrin to light and significant hydrolysis rates at elevated pH, or biologically, there is a low risk of accumulation in soil and biota.

Confidential information on the manufacturing process and on all impurities present at or above 1 g/kg was provided to the Meeting, together with limits for impurities in

TC. Limits for impurities were supported by 5 batch analysis data, in which unaccounted material was in the range of 21-29 g/kg. The unaccountable material was therefore slightly higher than the 20 g/kg limit considered as typical in the FAO/WHO manual (FAO/WHO, 2002) but the Meeting accepted that further characterization of the TC may be impracticable. As the alcohol moiety incorporates C=C double bonds in the ring and in propenyl chain, a small proportion of higher molecular weight material can be produced during synthesis. No relevant impurities were present, with maxima of either ≥1 g/kg or <1 g/kg. The minimum active ingredient content in esbiothrin TC is 930 g/kg. Information on the manufacturing process and impurity profiles submitted to WHO was found to be similar to that submitted in support of registration of esbiothrin in Switzerland.

Esbiothrin in the TC and formulations is determined by a capillary GC-FID method adopted by CIPAC in 2003. Because other mixtures of allethrin stereoisomers are available, the GC method does not enable esbiothrin to be distinguished clearly from related active ingredients. A chiral HPLC method, which allows the determination of the stereoisomer ratios and therefore enables clear identification of esbiothrin, was also adopted by CIPAC in 2003, as an identity test. Although the identity test requires the use of expensive chiral columns, the Meeting noted that it was the only practical method available.

Esbiothrin was shown to have low mammalian toxicity either by oral or dermal exposure, it was a slight irritant to rabbit skin and eye but was not a sensitizer in the Buehler test. Given the low acute toxicity, the Meeting did not consider the lack of purity data in certain studies to be a serious data gap.

Esbiothrin showed no evidence of mutagenic responses in bacterial, micronucleus or sister chromatid exchange tests and no evidence of carcinogenicity in long-term feeding studies.

In a 2-generation reproduction study in rats, and in studies of embryotoxicity teratogenicity in rats and rabbits, no reproductive effects, embryotoxicity or teratogenicity were observed at any dose level.

As with pyrethrins and other synthetic pyrethroids, esbiothrin is highly toxic to *Daphnia,* fish and honey bees. Esbiothrin is used only in public health applications, against mosquitoes and houseflies. Hence human exposure will be mainly through inhalation fumes/mists emitting from vaporising mats when heated. Since esbiothrin is not used in agriculture, it is unlikely that dietary exposure will be of significance and there should be no significant implications for the environment.

On the basis of the 1-year dog study, NOAELs of 13.7 and 16.1 mg/kg bw/day for males and females, respectively, were established by Petra (1987b).

Esbiothrin was evaluated by the IPCS in 1989 and reviewed by the US EPA in 1982. The IPCS classified esbiothrin as moderately hazardous.

Recommendations

The Meeting recommended that the draft specification for esbiothrin TC, proposed by Sumitomo Chemical Company Limited, should be adopted by WHO.

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