WHO SPECIFICATIONS AND EVALUATIONS

FOR PUBLIC HEALTH PESTICIDES

d-ALLETHRIN[1]

(*RS*)-3-allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*)-*cis, trans*-chrysanthemate

2002

WORLD HEALTH ORGANIZATION
Geneva

[1] d-Allethrin is the name given by the manufacturer, in the absence of an ISO common name

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d-ALLETHRIN

Disclaimer[1]

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.

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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.

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

PART ONE

SPECIFICATIONS

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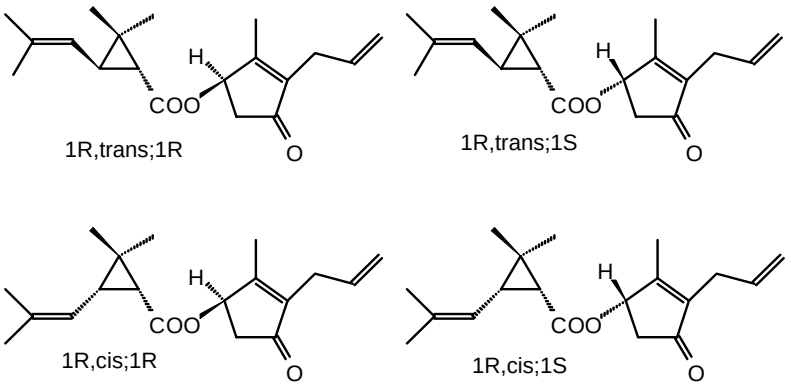
d-ALLETHRIN

d-ALLETHRIN INFORMATION
d-ALLETHRIN TECHNICAL MATERIAL

WHO SPECIFICATIONS AND EVALUATIONS FOR
PUBLIC HEALTH PESTICIDES

d-ALLETHRIN

INFORMATION

Common name	No ISO common name for *d*-allethrin. Footnote 1
Chemical name	**CAS**: none **IUPAC**: (*RS*)-3-allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*)-*cis, trans*-chrysanthemate
CAS Registry number	No CAS number available for *d*-allethrin. Footnote 2
CIPAC number	742
Structural formula	 *d*-allethrin consists of [1R,trans;1R] + [1R,trans;1S] +[1R,cis;1R] + [1R,cis;1S] in an approximate ratio of 4:4:1:1
Molecular formula	$C_{19}H_{26}O_3$
Relative molecular mass	302.41

[1] Allethrin is the ISO common name for the racemic mixture of 8 stereoisomers.

[2] CAS number for racemic allethrin: 584-79-2 (unstated stereochemistry and also used for bioallethrin).

d-ALLETHRIN TECHNICAL MATERIAL

WHO Specification WHO/742/TC (2002)

*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 (*742/2002*). 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 (*742/2002*) as PART TWO forms an integral part of this publication.*

1 Description

The material shall consist essentially of *d*-allethrin with related manufacturing impurities. It shall be a yellowish-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 ***d*-Allethrin content** (CIPAC 741/TC/M/-) (Note 2)

The *d*-allethrin content shall be declared (not less than 900 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

2.3 **Isomer composition** (Note 2)

The *trans*-isomer content of the *d*-allethrin shall be declared (not less than 75% and not more than 85%) and, when determined, the average measured *trans*-isomer content shall not be lower than the declared minimum value nor higher than the declared maximum value.

The *1R*-isomer content of the *d*-allethrin shall be declared (not less than 95%) and, when determined, the average measured *1R*-isomer content shall not be lower than the declared minimum content.

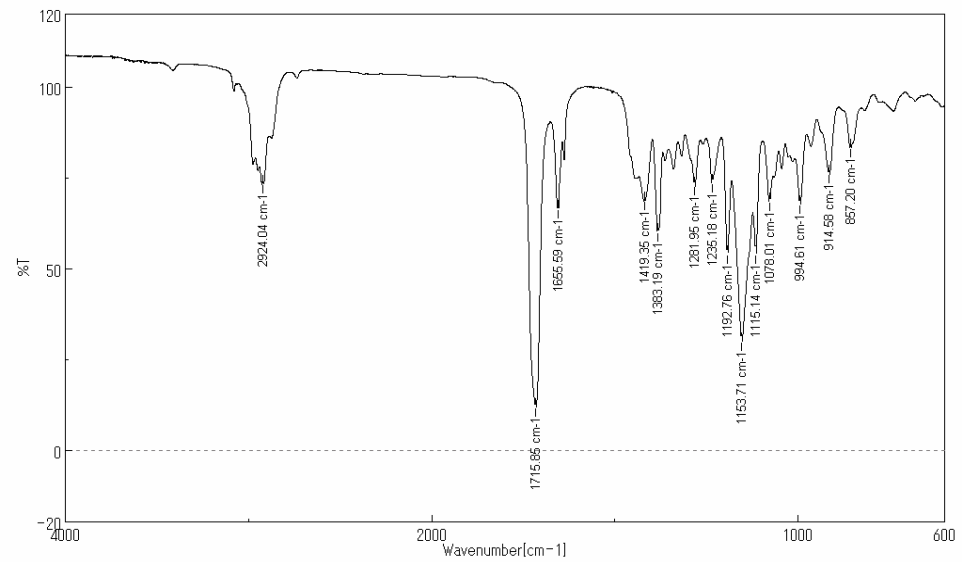
3 Relevant impurities

3.1 **Chrysanthemic anhydride** (Note 3) CAS: (2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylic anhydride. CAS No. 14297-82-6)

Maximum: 10 g/kg.

Note 1 Identity tests based on GC retention time (see Note 2) or IR spectrum provide evidence of identity as allethrin enantiomers but determination of the isomer composition (see Note 2) provides the definitive identity test for *d*-allethrin.

IR spectrum of *d*-allethrin (identifies the presence of allethrin enantiomers)



Note 2 Methods for the determination of *d*-allethrin content and isomer composition were adopted by CIPAC in 2003 but are not yet published. Prior to publication in CIPAC Handbook L, 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.

Note 3 Determination of chrysanthemic anhydride content.

Scope of method

The method is intended for the determination of chrysanthemic anhydride in d-allethrin TC. It is a relatively non-specific technique but has been shown to be satisfactory for the intended purpose. It is not intended for the determination of chrysanthemic anhydride in d-allethrin formulations.

Outline of method

Chrysanthemic anhydride in d-allethrin TC is reacted with excess morpholine. The amounts of morpholine added to, and remaining after, the reaction are determined with 0.1 mol/l HCl-methanol solution. The amount of morpholine consumed in the reaction, determined as hydrochloric acid equivalent, is used to calculate the content of chrysanthemic anhydride.

Reagents

Hydrochloric acid, concentrated

Methanol

Ethanol

Morpholine

Methyl red

Methyl yellow

Methylene blue

Sodium carbonate, volumetric analysis grade

Hydrochloric acid-methanol solution (approximately 0.1 mol/l). Dilute concentrated hydrochloric acid (9.5 ml) to 1000 ml with methanol.

Morpholine-methanol solution (approximately 0.1 mol/l). *Weigh or dispense morpholine (about 8.7 g or 8.7 ml)* and dilute to 1000 ml with methanol.

Methyl red indicator solution. Dissolve methyl red (0.1 g) in ethanol (100 ml) and filter if necessary.

Methyl yellow-methylene blue indicator solution. Dissolve methyl yellow (1 g) and methylene blue (0.1 g) in methanol (125 ml).

Procedure

Standardization of 0.1 mol/l hydrochloric acid-methanol solution. Weigh accurately sodium carbonate (0.15 g), previously heated to between 500ºC and 650ºC for 40 to 50 min and allowed to cool in a desiccator. Dissolve in water (30 ml), add methyl red indicator solution (3 drops) and titrate the solution with 0.1 mol/l hydrochloric acid-methanol until the colour of the solution changes to persistent orange to orange-red. Calculate the normality factor (f) using the following equation.

$$f = \frac{a}{V \times 5.299}$$

where a = amount (mg) of sodium carbonate, corrected for purity;

V = volume (ml) of 0.1 mol/l hydrochloric acid-methanol solution;

5.299 = mass of sodium carbonate equivalent to 0.1 mole of hydrochloric acid (105.989 ÷ 2 x 0.1).

Determination. Weigh accurately 2.0 g of sample into a conical flask (100 ml). Add 25 ml morpholine-methanol solution and dissolve the sample completely. Add methyl yellow-methylene blue indicator solution (3 to 4 drops) and titrate with 0.1 mol/l hydrochloric acid-methanol until the colour of the solution changes from green to red. Perform a blank determination in the same manner, adding exactly the same volume of morpholine solution.

Calculation

$$\text{Chrysanthemic anhydride (g/kg)} = \frac{31.846 \times (B - A) \times f \times 1000}{W}$$

where A = the volume of 0.1 mol/l hydrochloric acid-methanol solution used to titrate the sample solution;

B = the volume of 0.1 mol/l hydrochloric acid-methanol solution used to titrate the blank solution;

f = the normality factor for the 0.1 mol/l hydrochloric acid-methanol solution;

W = the amount (mg) of the test sample;

31.846 = mass of chrysanthemic anhydride equivalent to 0.1 mole of hydrochloric acid (318.46 x 0.1).

PART TWO

EVALUATION REPORT(S)

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d-ALLETHRIN

2002 Evaluation report based on submission of data from Sumitomo Chemical Company Ltd, incorporating footnotes added in 2003 and 2004. (TC)

WHO SPECIFICATIONS AND EVALUATIONS FOR

PUBLIC HEALTH PESTICIDES

***d*-ALLETHRIN**

EVALUATION REPORT WHO/742/2002

Explanation

d-Allethrin was evaluated by the WHO/IPCS in 1989 (IPCS, 1989a). It was reviewed by US EPA in 1975 and by the Health and Safety Executive in UK prior to 1985.

The draft specification and the supporting data were provided by Sumitomo Chemical Company Ltd., Japan, in 2001.

The patent for *d*-allethrin has expired.

Uses

d-Allethrin is a synthetic pyrethroid with fast knock down activity against household pest insects. It is used in public health against mosquitoes, houseflies and cockroaches[1].

Identity

ISO common name

None (footnote 2)

Chemical name

IUPAC: (*RS*)-3-allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*)-*cis, trans*-chrysanthemate

CA: None (footnote 3)

CAS Registry number

None (footnote 4)

CIPAC number

742

Synonyms

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[1] 2003 footnote. The proposer stated that *d*-allethrin is also registered for use on garden plants.

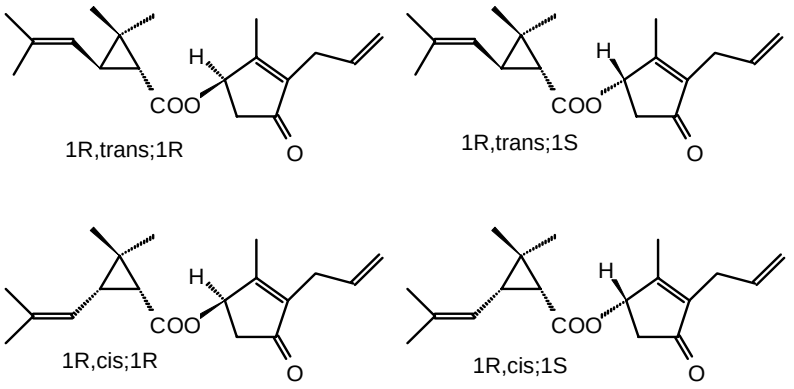
[2] Allethrin is the ISO common name for the racemic mixture of 8 stereoisomers; *d*-allethrin is the name given by the Sumitomo Chemical Company to the specific ratio of isomers defined by the WHO specification.

[3] Proposed CAS name: 2-methyl-4-oxo-3-(2-propenyl)-2-cyclopent-1-yl 2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylate.

[4] The CAS number for allethrin is 584-79-2.

Pynamin Forte

Structural formula



d-allethrin consists of [1R,trans;1R] + [1R,trans;1S] +[1R,cis;1R] + [1R,cis;1S] in an approximate ratio of 4:4:1:1

Notes on the isomer composition of some related active ingredients:
allethrin is a racemic mixture of the 8 stereoisomers;
bioallethrin consists of [1R,trans:1R] and [1R,trans;1S] isomers, approx ratio 1:1;
esbiothrin consists of [1R,trans:1R] and [1R,trans;1S] isomers, approx ratio 1:3;
S-bioallethrin (esbiol) is the [1R,trans;1S] isomer.

Molecular formula

$C_{19}H_{26}O_3$

Relative molecular mass

302.41

Identity tests

(1) isomer composition (enantio-specific)[1];
(2) GC retention time in the analytical method, capillary GC with FID (not enantio-specific);
(3) IR spectrum (not enantio-specific).

[1] 2003 footnote. The isomer composition is determined by enantio-selective HPLC and not, strictly, enantio-specific HPLC.

Physico-chemical properties of pure *d*-allethrin

Table 1. Physico-chemical properties of pure *d*-allethrin

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure:	see vapour pressure for technical material	-	-
Melting point and temperature of decomposition:	Melting point: not applicable Decomposition temperature: not available	-	Not applicable
Solubility in water:	5.00 ± 0.11 mg/l at 25 °C and pH 5.9 to 6.0 Note[1]	99.5	EPA Guideline CG-1500 (Saito *et al*., 1989a)
Octanol / water partition coefficient:	log P_{OW} = 4.95 (4.89 to 4.97) at 25 °C and pH 5.8 to 6.0. Initial concentration in octanol = 738 to 3000 mg/l.	99.5	OECD 107 (Saito *et al*., 1989b)
Hydrolysis characteristics: *d-trans*-allethrin[2]	No measurable hydrolysis after 31 days at 25 °C and pH 5. Estimated half-life approx 500 days at 25 °C and pH 7. Half life: 4.3 days at 25 °C and pH 9.	Radiochemical purity: 99.3	EPA Guideline 161-1 (Estigoy *et al.*, 1990)
Photolysis[3] characteristics: *d-trans*-allethrin	Photodegradation in water under natural sunlight: Half life: 49 experiment hours or 19 sunlight hours at 25.5°C and pH 5	Radiochemical purity: 99.3	EPA Guideline 161-2 (Chari *et al.*, 1990)
Dissociation characteristics:	Not applicable		Not applicable

[1] Water solubility: observed values, 4.81-5.24 mg/l (n=18).

[2] Hydrolysis rates were measured at 0.5 mg/l in 1% aqueous acetonitrile in sterile dark conditions for 1 month at pH 5 and pH 7 and for 16 days at pH 9. Hydrolysis products were identified after pH 9 hydrolyis, allethrolone and two isomeric bicyclic ketones.

[3] Photolysis rates were measured at 0.5 mg/l in 1% aqueous acetonitrile in sterile buffer at pH 5 and 25.5°C. Quartz tubes of solution were exposed to sunlight at 37.45°N (Richmond, California) for 5 days in January. Photolysis products were identified as allethrolone, dihydroxyallethrolone and carbon dioxide. *Cis-trans* isomerization was not observed under the conditions.

Chemical composition and properties of *d*-allethrin technical material (TC)

Table 2. Chemical composition and properties of *d*-allethrin TC

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data.	Confidential information supplied and held on file by WHO. Mass balances were 98.7 to 99.5% and percentages of unknowns were 0.5 to 1.3%.
Declared minimum *d*-allethrin content:	900 g/kg.
Relevant impurities ≥ 1 g/kg and maximum limits for them:	Chrysanthemic anhydride = 10g/kg.
Relevant impurities **<** 1 g/kg and maximum limits for them:	None.
Stabilizers or other additives and maximum limits for them:	None.
Boiling temperature range[1] test guideline: 40 CFR 158	Boiling point (Pynamin forte): 281.5°C at 760 mm Hg. Observed values 282.2, 281.1, 282.2°C at 765.58 mm Hg. At approximately 199°C, the test material changed from a pale yellow to a dark yellow colour and, at 232°C, it turned brown and began to smoke. (Hoffman, 1989).
Vapour pressure[2] test guideline: 40 CFR 158	Pynamin forte: 1.65×10^{-4} Pa at 21.6 °C. Observed values: 1.45×10^{-4}, 1.91×10^{-4}, 1.60×10^{-4} Pa at 3 gas flow rates. (Semann *et al*., 1989).

[1] Boiling point measurements were made in a Siwoloboff boiling point apparatus. Purity of the material was not stated. The bath liquid was heated at about 3°C/min until 10°C below the expected boiling point, when the rate was reduced to 1°C/min.

[2] Vapour pressure was measured by a gas-saturation method. Dry nitrogen gas streams were passed through gas-saturation tubes at 21.6°C and then through traps in dry ice/ethanol for approx 5 days at flow rates of 4.4, 5.2 and 7.6 ml/min. The contents of the traps were measured by HPLC.

Hazard summary

Notes.

(i) The proposer provided written confirmation that the toxicological and ecotoxicological data included in the summary below were derived from *d*-allethrin 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 3. Toxicology profile of *d*-allethrin technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Duration and conditions	Result	Purity	Ref.
Rats, male and female	oral	EPA Guideline 81-1	LD_{50} = (male) 2150, (female) 900 mg/kg bw	92.4%	Hiromori *et al*., 1989a
Rabbits, male and female	dermal	EPA Guideline 81-2	LD_{50} = (male) 2660, (female) 4390 mg/kg bw	92.4%	Hiromori *et al*., 1989b
Rats, male and female	inhalation	EPA Guideline 81-3	LC_{50} = (male) >3875, (female) >3875 mg/m^3	92.4%	Kawaguchi *et al*., 1989
Rabbits, male and female	skin irritation	EPA Guideline 81-5	Not irritant	92.4%	Nakanishi *et al*., 1988
Rabbits, male and female	eye irritation	EPA Guideline 81-4	Minimal irritant	92.4%	Nakanishi *et al*., 1988
Guinea pigs	skin sensitization	Buehler method, EPA Guideline 81-6	Not sensitizing[1]	92.4%	Nakanishi *et al*., 1989

[1] 2003 footnote. The concentration of chrysanthemic anhydride in the test material was 6 g/kg.

Table 4. Toxicology profile of *d*-allethrin technical material based on repeated administration (subacute to chronic)

Species	Test	Duration and conditions	Result	Purity	Reference
Rats, male and female	inhalation	3 months EPA Guideline 82-4	NOEL = both sexes: 50.0 mg/m³	92.3%	Kawaguchi *et al*., 1993
Rats, male and female	feeding, toxicity	3 months	NOEL = 750 ppm diet, equivalent to: male: 49.6, female: 59.2 mg/kg/day	94.5%	Kadota, 1977 IPCS, 1989, p40
Mice, male and female	feeding, toxicity	5 weeks	NOEL = both sexes: 100 ppm , equivalent to: male: 14, female: 16 mg/kg/day	93.4%	Edwards *et al*., 1986
Dogs, male and female	feeding, toxicity	4 weeks	NOEL = both sexes: 10 mg/kg/day	93.1%	Dalgard *et al*., 1987
Dogs, male and female	feeding, toxicity	1 year EPA Guideline 83-1	NOEL = both sexes: 6 mg/kg/day	Not reported	Dalgard *et al*., 1989
Rats, male and female	feeding, carcinogenicity	123 weeks	NOEL = 125 ppm in diet, equivalent to: male: 5.9 mg/kg/day, female: 6.6 mg/kg/day. Carcinogenicity: negative	91.4%, 92.2%	Arai *et al*., 1985 IPCS, 1989, p45
Mice, male and female	feeding, carcinogenicity	81 weeks EPA Guideline 83-2	NOEL = male: 600 ppm, female: 600 ppm. Carcinogenicity: negative	93.1%	Mayfield *et al*., 1989e
Rats, male and female	feeding, 2 generation reproduction	EPA Guideline 83-4	Reproduction NOEL = 6000 ppm. Adult and fetus NOEL = 200 ppm	93.4%	Hoberman, 1989a
Rats, male and female	feeding, teratogenicity and embryotoxicity	EPA Guideline 83-3	Maternal NOEL = 30 mg/kg. Developmental NOEL = 100 mg/kg	93.4%	Hoberman, 1989b
Rabbits, male and female	feeding, teratogenicity and embryotoxicity	EPA Guideline 83-3	Maternal NOAEL = 100 mg/kg Developmental NOAEL = >100 mg/kg	93.4%	Hoberman, 1989c

Table 5. Mutagenicity profile of *d*-allethrin 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	93.4%	Kogiso *et al*., 1989a
Rat hepatocytes	DNA damage and repair	In vitro	Negative	93.4%, 91.9%	Kogiso *et al*., 1989b
Chinese hamster ovary cells	Mammalian chromosomal aberration test	In vitro	Negative	93.4%, 91.9%	Kogiso *et al*., 1989c

Table 6. Ecotoxicology profile of *d*-allethrin and related technical materials.

Species	Test	Duration and conditions	Result	Purity	Reference
Bobwhite	Acute dietary toxicity	8 days	LC_{50} : >5620 ppm	*d*-allethrin 93.4%	Fink and Beavers, 1978a
Mallard	Acute dietary toxicity	8 days	LC_{50} : >5620 ppm	*d*-allethrin 93.4%	Fink and Beavers, 1978b
Coho salmon	Acute flow-through toxicity	96 hr at 12°C	LC_{50} (96 hr): 9.40 μg/L	*d*-trans-allethrin 90%	Mauck *et al.*, 1976.
Steelhead trout	Acute flow-through toxicity	96 hr at 12°C	LC_{50} (96 hr): 9.70 μg/L	*d*-trans-allethrin 90%	Mauck *et al.*, 1976.
Channel catfish	Acute flow-through toxicity	96 hr at 12°C	LC_{50} (96 hr): 27.0 μg/L	*d*-trans-allethrin 90%	Mauck *et al.*, 1976.
Yellow perch	Acute flow-through toxicity	96 hr at 12°C	LC_{50} (96 hr): 9.90 μg/L	*d*-trans-allethrin 90%	Mauck *et al.*, 1976.
Fathead minnow	Acute flow-through toxicity	96 hr at 12°C	LC_{50} (96 hr): 53 μg/L	S-bioallethrin 98%	Mauck *et al.*, 1976.
Channel catfish	Acute flow-through toxicity	96 hr at 12°C	LC_{50} (96 hr): 14.6 μg/L	S-bioallethrin 98%	Mauck *et al.*, 1976.
Daphnia pulex	Static	3 hours	LC_{50} : 25 mg/L	bioallethrin, purity not stated	IPCS, 1989, p36
Honey-bee	Contact toxicity		LD_{50} 3.4 μg/bee	allethrin, purity not stated	IPCS, 1989, p37
Honey-bee	Oral toxicity		LD_{50} 4.6-9.1 μg/bee	allethrin, purity not stated	IPCS, 1989, p37

d-Allethrin was evaluated by the WHO/IPCS in 1989, with the following conclusions(IPCS, 1989, p54).

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 for fish and honey-bees, they are only likely to cause a problem in the case of spillage or misuse.

The WHO hazard classification of *d*-allethrin is: slightly hazardous.

Formulations

The main formulation types available are MC (mosquito coils) and MV (vaporizing mats).

These formulations are registered and sold in many countries throughout the world.

Methods of analysis and testing

The validation of the analytical method for the active ingredient (including identity tests) is in progress under the auspices of CIPAC. The *d*-allethrin is determined by capillary GC with FID. The method was submitted to JMPS in 2002 (Furuta, 2002)[1].

Analytical methods for isomer composition are available (Fujita, 2002a). The optical isomer ratios are determined by HPLC using a chiral stationary phase, while the geometric isomer ratio is determined by GLC on a non-chiral stationary phase. The methods have been validated by Sumitomo Chemical Co Ltd. The isomer composition determined by these methods provides the critical identity test for *d*-allethrin[2].

The analytical method for the determination of the relevant impurity, chrysanthemic anhydride, in *d*-allethrin TC is available (Fujita, 2002b) but it has not yet been peer-validated. The method relies on the back-titration of residual morpholine after standard addition to the sample.[3]

An additional (non-stereospecific) identity test relies on matching the IR spectrum of the test sample with the IR spectrum for *d*-allethrin.

Test methods for determination of physico-chemical properties of technical active ingredient were OECD and EPA, while those for the formulations were in accordance with the WHO guideline specifications for household insecticide products.

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[1] 2003 footnote. The analytical method for determination of d-allethrin content was successfully validated and adopted by CIPAC in June, 2003.

[2] 2003 footnote. The identity test for determination of *trans*- and 1*R* isomer ratios was successfully peer validated and adopted by CIPAC in June, 2003.

[3] 2003 footnote. The analytical method for determination of chrysanthemic anhydride in d-allethrin TC was successfully peer validated and is appended to the specification.

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as *d*-allethrin.

Appraisal

The data submitted were in accordance with the requirements of the FAO Manual (5th edition) and supported the draft specifications.

No common name is available for *d*-allethrin; *d*-allethrin is the name given by the manufacturer.

The technical material, *d*-allethrin is a mixture of [1R,trans;1R] + [1R,trans;1S] + [1R,cis;1R] [1R,cis:1S] allethrin in an approximate ratio of 4:4:1:1.

The CIPAC number for *d*-allethrin is 742. Allethrin and bioallethrin have CIPAC numbers 267 and 203, respectively.

A CAS name and a number are available for allethrin, but not for *d*-allethrin.

d-Allethrin is out of patent.

d-Allethrin is slightly volatile at room temperature (vapour pressure 0.165 mPa at 25°C) with a boiling point of 281.5°C. It has low water solubility (5 mg/l at 25°C) and the octanol-water partition coefficient (log P_{OW} = 4.95 at 25°C) makes *d*-allethrin a fat-soluble compound. It is stable to hydrolysis under neutral or slightly acidic conditions, but hydrolyses readily under basic conditions. Photolysis in water degrades *d*-trans-allethrin quickly; cis-allethrin is not detected as a significant product.

The hydrolysis study used *d*-trans-allethrin, which comprises 80% of *d*-allethrin active ingredient, so the results should be generally transferable to *d*-allethrin. The photolysis study also used *d*-trans-allethrin.

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on all impurities present at or above 1 g/kg. Analyses of 5 batches of *d*-allethrin produced in 2000 and 2001 accounted for 98.7 to 99.5% of the material, including 2.0 to 2.2% of higher molecular weight unknowns.

Chrysanthemic anhydride was identified by the proposer as a relevant impurity because it has a potential for skin sensitization. The opinion of WHO/PCS was that chrysanthemic anhydride should be considered a relevant impurity, on a precautionary basis, but that further information is required to define the risks involved and to support the limit proposed. Following a post-meeting consideration of all data available on the hazards presented by chrysanthemic anhydride and the associated risks, agreement was reached between WHO/PCS and the proposer that the maximum level of chrysanthemic anhydride in

d-allethrin TC should be 10 g/kg[1,2]. The highest level of chrysanthemic anhydride in the 5-batch analyses was 7 g/kg. The concentration of chrysanthemic anhydride in *d*-allethrin TC is measured by a back-titration method. This method may be unsuitable for the determination of chrysanthemic anhydride in d-allethrin formulations but specifications for such formulations were not proposed to the meeting. Given the low level of active ingredient in the MV (vaporizing mats) and MC (mosquito coil) formulations and very low probability of substantial dermal contamination of users, WHO/PCS concluded that chrysanthemic anhydride should not be considered a relevant impurity in these formulations. Therefore, if specifications for these formulations are proposed in future, it would not be necessary to develop a more sensitive and specific method for the determination of chrysanthemic anhydride in such products.

The impurity profile data submitted to WHO were declared by the Australian National Registration Authority for Agricultural and Veterinary Chemicals (NRA) to be identical to those submitted for registration in Australia (Sethi, 2002).

Toxicology studies on *d*-allethrin generally showed low mammalian toxicity. The IPCS evaluation in 1989 concluded that, under recommended conditions of use, the exposure of the general population to allethrins is negligible and is unlikely to present a hazard. Also, with the usual precautions, the use of allethrins is unlikely to present a hazard to those occupationally exposed to them. The WHO hazard classification of *d*-allethrin is: slightly hazardous.

The attention of the Meeting was drawn to the recent restriction on household uses of synthetic pyrethroids in The Netherlands because of reports of neuronal effects following the exposure of neonatal mice (Schreuder, 2002).

d-Allethrin is of low toxicity to birds. Toxicity testing showed that S-bioallethrin is toxic to fish and allethrin is toxic to honey-bees. It is reasonable to conclude that *d*-allethrin is also toxic to fish and honey-bees. The IPCS evaluation in 1989 concluded that 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 IPCS evaluation of 1989 was relevant to the uses at that time. It is reasonable to conclude that *d*-allethrin is hazardous to fish and honey-bees, while the risk will depend on their exposure.

The analytical method for active ingredient (capillary GC with FID) is in process of validation by CIPAC[3]. This method also serves as a non-stereospecific identity test. An IR spectrum is available as an additional non-stereospecific identity test.

An analytical method for isomer composition is available. The optical isomer ratios are determined by HPLC using a chiral stationary phase, while the geometric isomer ratio is determined by GLC on a non-chiral stationary phase. It

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[1] 2003 footnote. In tests using the Buehler method, the LOAEL for chrysanthemic anhydride in d-allethrin was 100 g/kg.

[2] 2004 footnote. The limit of 10 g/kg is in accordance with the classification and labelling of skin sensitizers provided by the Globally Harmonized System of Classification and Labelling of Chemicals (United Nations, New York and Geneva, 2003, 443 pages).

[3] 2003 footnote. The analytical method for determination of d-allethrin content was successfully validated and adopted by CIPAC in June, 2003.

has been company validated[1]. The method for isomer composition is recommended as the primary identity test.

No special requirements for containers and packages have been identified.

The proposed specification for *d*-allethrin TC requires the determination of *d*-allethrin content and measurements of total trans-isomer and total 1R-isomer contents in the active ingredient to distinguish *d*-trans-allethrin from other mixtures of allethrin isomers. A limit of 10 g/kg in the TC was proposed for chrysanthemic anhydride[2].

The existence of an FAO specification for *d*-trans-allethrin TC (303/2/S/3) should be noted.

Recommendations

The meeting recommended that the draft specification for *d*-allethrin TC proposed by Sumitomo Chemical Company Ltd, with amendments, should be adopted by WHO, subject to acceptable validation of analytical methods for the active ingredient and relevant impurity[3].

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[1] 2003 footnote. The analytical method for determination of isomer composition by HPLC using a chiral stationary phase was successfully peer validated and adopted by CIPAC in June, 2003.

[2] 2003 footnote. The analytical method for determination of chrysanthemic anhydride in *d*-allethrin TC was successfully peer validated and is appended to the specification. The method is not specific to chrysanthemic anhydride (other anhydrides may interfere) and it has limited sensitivity. However, it is fit for the intended purpose and is simpler and likely to be more robust than more specific and/or sensitive methods.

[3] 2003 footnote. The analytical method for determination of *d*-allethrin content was successfully validated and adopted by CIPAC in June, 2003. Methods for determination of the isomer ratio (identity test) and of the content of the chrysanthemic anhydride (relevant impurity) were also successfully peer validated in 2003. Validation and adoption of the methods enabled the specification to be published in 2003.

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