WHO SPECIFICATIONS AND EVALUATIONS

FOR PUBLIC HEALTH PESTICIDES

d,d,trans-CYPHENOTHRIN [1/]

(*S*)-alpha-cyano-3-phenoxybenzyl (1*R, 3R*)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylate

World Health Organization

[1/] *d,d,trans*-cyphenothrin is the name given by the manufacturer, in the absence of an ISO common name. Cyphenothrin is the ISO common name for a mixture of 4 pairs of diastereoisomers. The name *d,d,trans*-cyphenothrin refers to the mixture, comprised mainly of the stereoisomer (*S*)-alpha-cyano-3-phenoxybenzyl (1*R, 3R*)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropane-carboxylate together with small proportions of the other stereoisomers, which is defined by the WHO specification.

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***d,d,trans*-CYPHENOTHRIN**

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.

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.

Additionally, WHO wishes to alert users to the fact that improper storage, handling, preparation and/or use of pesticides can result in either a lowering or complete loss of safety and/or efficacy.

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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 follows the **New Procedure**, described in the Manual for Development and Use of FAO and WHO Specifications for Pesticides. 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 above-mentioned manual.

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 above-mentioned manual 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 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. 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/quality/en/).

PART ONE

SPECIFICATIONS

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d,d,trans-CYPHENOTHRIN

d,d,trans-CYPHENOTHRIN

INFORMATION

ISO common name: Cyphenothrin is the ISO common name for a mixture of 4 pairs of diastereoisomers, designated as (±)-α-cyano-3-phenoxybenzyl (±)-*cis-trans*-chrysanthemate. The name *d,d,trans*-cyphenothrin* refers to an enantio-enriched mixture, comprised mainly of the single stereoisomer (*S*)-alpha-cyano-3-phenoxybenzyl (1*R, 3R*)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylate, with only small proportions of the other stereoisomers, as defined by the WHO specification.

Synonyms: None

Chemical name:

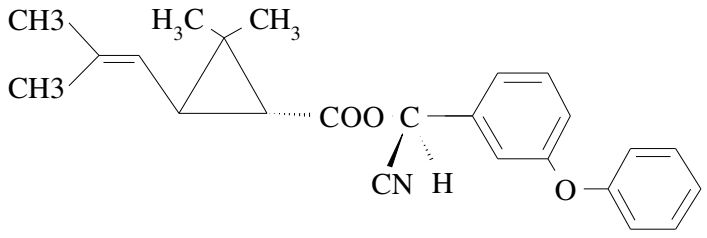
IUPAC: None. IUPAC name for the main stereoisomer present is: (*S*)-α-cyano-3-phenoxybenzyl (1*R, 3R*)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylate.

CA: None. CAS name for cyphenothrin is: cyano(3-phenoxyphenyl)methyl 2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylate.

CAS No: None. CAS number for cyphenothrin is: 39515-40-7

CIPAC No: 761 for *d,d,trans*-cyphenothrin
804 for cyphenothrin

Structural formula:



Molecular formula: $C_{24}H_{25}NO_3$

Relative molecular mass:

375.47

Identity tests: GC retention time (cyphenothrin); IR spectrum (cyphenothrin); enantio-selective HPLC peak pattern (*d,d,trans*-cyphenothrin).

* *d,d,trans*-cyphenothrin is the name given by the manufacturer, in the absence of an ISO common name.

WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

d,d,trans-CYPHENOTHRIN TECHNICAL MATERIAL (TC)

WHO Specification 761/TC (August 2017*)

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 reports (761/2003, 761/2017). 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 specification. The specification may not be appropriate for the products of other manufacturers. The evaluation reports (761/2003, 761/2017), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of *d,d,trans*-cyphenothrin, together with related manufacturing impurities. It shall be a yellow to yellowish-brown oil or a yellow waxy solid, essentially odourless and free from visible extraneous matter and modifying agents, except the stabilizer (Note 1).

2 Active ingredient

2.1 **Identity tests** (804/TC/(M)/2, CIPAC Handbook M, p.45, 2009, Note 2)

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,d,trans*-cyphenothrin content** (804/TC/(M)/3, CIPAC Handbook M, p.47, 2009)

The *d,d,trans*-cyphenothrin 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** (804/TC/(M)/2, CIPAC Handbook M, p.45, 2009)

The *trans*-isomer content in the *d,d,trans*-cyphenothrin shall be declared (not less than 97%) and, when determined, the mean measured value shall not be lower than the declared minimum *trans*-isomer content.

The 1*R*-isomer content at the acid moiety in the *d,d,trans*-cyphenothrin shall be declared (not less than 95%) and, when determined, the mean measured value shall not be lower than the declared minimum 1*R*-isomer content.

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* 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/.

The *S*-isomer content at the alcohol moiety in the *d,d,trans*-cyphenothrin in the material shall be declared (not less than 92%) and, when determined, the mean measured value shall not be lower than the declared minimum *S*-isomer content.

Note 1 The stabilizer, 2,6-di-*tert*-butyl-*p*-cresol, is added within the concentration range 10-20 g/kg.

Note 2 GC retention time may be used to confirm the identity as cyphenothrin but the enantio-selective HPLC peak pattern (clause 2.3) is required to confirm the identity as *d,d,trans*-cyphenothrin.

WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

d,d,trans-CYPHENOTHRIN EMULSIFIABLE CONCENTRATE (EC)

WHO Specification 761/EC (August 2017*)

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 reports (761/2003, 761/2017). 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 reports (761/2003, 761/2017), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of technical *d,d,trans*-cyphenothrin, complying with the requirements of WHO specification 761/TC (August 2017), dissolved in suitable solvents, together with any other necessary formulants. It shall be in the form of a stable homogeneous liquid, free from visible suspended matter and sediment, to be applied as an emulsion after dilution in water.

2 Active ingredient

2.1 Identity tests (804/TC/(M)/2, CIPAC Handbook M, p.50, 2009, 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,d,trans*-cyphenothrin content (804/EC/(M)/3, CIPAC Handbook M, p.50, 2009)

The *d,d,trans*-cyphenothrin content shall be declared (g/l at 20 ± 2°C, Note 2) and, when determined, the average content measured shall not differ from that declared by more than the following tolerance:

Declared content in g/kg or g/l at 20 ± 2°C	Tolerance
Above 25 up to 100 Note: the upper limit is included in the range.	± 10% of the declared content

2.3 Isomer composition (804/EC/(M)/2, CIPAC Handbook M, p.50, 2009)

The *trans*-isomer content in the *d,d,trans*-cyphenothrin shall be declared (not less than 97%) and, when determined, the mean measured value shall not be lower than the declared minimum *trans*-isomer content.

* 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/.

The 1*R*-isomer content at the acid moiety in the *d,d,trans*-cyphenothrin shall be declared (not less than 95%) and, when determined, the mean measured value shall not be lower than the declared minimum 1*R*-isomer content.

The *S*-isomer content at the alcohol moiety in the *d,d,trans*-cyphenothrin in the material shall be declared (not less than 92%) and, when determined, the mean measured value shall not be lower than the declared minimum *S*-isomer content.

3 Relevant impurities

3.1 **Water** (MT 30.5, CIPAC Handbook J, p.120, 2000)

Maximum: 2 g/kg.

4 Physical properties

4.1 **pH range** (MT 75.3, CIPAC Handbook J, p.131, 2000)

pH range: 4.0 to 7.0.

4.2 **Emulsion stability and re-emulsification** (MT 36.3, CIPAC Handbook K, p.137, 2003)

The formulation, when diluted at 30 ± 2°C (Note 3) with CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of stability, MT 36.3
0 h	Initial emulsification complete
0.5 h	'Cream' and/or 'Free oil', maximum: 2 ml
2 h	'Cream', maximum: 4 ml 'Free oil': maximum: 2 ml
24 h	Re-emulsification complete
24.5 h Note: tests after 24 h are required only where results at 2 h are in doubt.	'Cream', maximum: 4 ml 'Free oil', maximum: 2 ml

4.3 **Persistent foam** (MT 47.1, CIPAC Handbook O, p.177, 2017) (Note 4)

Maximum: 60 ml after 1 min.

5 Storage stability

5.1 **Stability at 0ºC** (MT 39.3, CIPAC Handbook J, p.126, 2000)

After storage at 0 ± 2ºC for 7 days, the volume of solid and/or liquid which separate shall be not more than 0.3 ml.

5.2 **Stability at elevated temperature** (MT 46.3, CIPAC Handbook J, p.128, 2000)

After storage at 54 ± 2ºC for 14 days, the determined average active ingredient content must not be less than 95% relative to the determined average content found before storage (Note 5) and the formulation shall continue to comply with the clauses for:

- pH range (4.1);
- emulsion and re-emulsification (4.2).

Note 1 GC retention time may be used to confirm the identity as cyphenothrin but the enantio-selective HPLC peak pattern (clause 2.3) is required to confirm the identity as *d,d,trans*-cyphenothrin.

Note 2 If the buyer requires both g/kg and g/l at 20°C, then in case of dispute the analytical results shall be calculated as g/kg.

Note 3 As outlined in CIPAC MT 36.3, the test concentrations should be based on those in the recommended directions for use supplied with the product. Where several concentrations are recommended, the highest and lowest concentrations within the scope of the method should be used.

Note 4 The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier.

Note 5 Samples of the formulation taken before and after the storage stability test should be analyzed concurrently after the test in order to reduce the analytical error.

PART TWO

WHO EVALUATION REPORTS

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d,d,trans-CYPHENOTHRIN

d,d,trans-CYPHENOTHRIN

FAO/WHO EVALUATION REPORT 761/2017

Recommendations

The Meeting recommended the following:

The revised specification for *d,d,trans*-cyphenothrin EC, as proposed by Sumitomo Chemical Co, Ltd. and as amended, should be adopted by WHO.

Appraisal

The Meeting considered the draft revised specification with a supporting report, submitted by Sumitomo Chemical Co, Ltd., in support of the revision of the WHO specification for *d,d,trans*-cyphenothrin EC.

The company requested the Meeting to revise the specification limit for persistent foam from maximum 3 ml after 1 minute to maximum 60 ml after 1 minute. The previous limit of 3 ml after 1 minute was erroneously set in the past and is unrealistic for usual EC formulations and particularly for low dilution rates. The data provided by the manufacturer on three recent batches of *d,d,trans*-cyphenothrin EC formulation supported this revision and it was agreed by the Meeting.

The company proposed to remove the clauses for water content and pH range. The Meeting discussed the impact of residual water and pH on stability of active ingredient in the EC formulation. Based on physical-chemical properties and stability data (evaluation report 761/2003), the Meeting concluded that the pH and water content are still required to guarantee the stability of active ingredient in the formulation.

The company also proposed to widen the specification limits for emulsion stability and re-emulsification explaining that, even if equivalent nonionic surfactants (same chemical name, same CAS number) are used, volumes of cream or free oil created in the emulsion stability test may vary. A wider tolerance is therefore required for this property to maintain the flexibility in the sources of supply of surfactants. The limits proposed by the company are consistent with data provided and the Meeting accepted the need to change the limits for emulsion stability.

CIPAC has started to adopt 25 ± 5°C as standard test temperature range for physical-chemical tests, and the test temperature specified in the FAO/WHO Manual "4.5.45 Emulsion stability and re-emulsification" is 25 ± 5°C. However, the Meeting concluded that the test temperature specified in the current MT 36.3, i.e. 30 ± 2°C, should be adopted in the specification.

The study report provided by the manufacturer on three recent batches of *d,d,trans*-cyphenothrin EC formulation confirmed also that the existing limits for *d,d,trans*-cyphenothrin content, isomer composition, water content, pH, stability at 0°C and at elevated temperature correctly reflect the properties of the EC formulation.

The Meeting proposed also, in the TC and EC specifications, to refer to the CIPAC methods as published in Handbook M for identity tests, *d,d,trans*-cyphenothrin content and isomer composition.

ANNEX 1. REFERENCES

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
	Fumio Nishioka & Yumiko Kozuki	2017	Physico-chemical properties of *d,d,trans*-cyhenothrin emulsifiable concentrate. Sumitomo Chemical Co., Ltd. April 2017. Unpublished.
	Fumio Nishioka & Yumiko Kozuki	2017	Additional information and data about *d,d,trans*-cyphenothrin emulsifiable concentrate. June 2017. Unpublished.

WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

d,d,trans-CYPHENOTHRIN

FAO/WHO EVALUATION REPORT 761/2003

Explanation

The data for *d,d,trans*-cyphenothrin were evaluated in support of new WHO specifications.

d,d,trans-Cyphenothrin is not under patent.

d,d,trans-Cyphenothrin has not been evaluated by the FAO/WHO JMPR or WHO/IPCS. It is currently under review by the US EPA.

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

Uses

d,d,trans-Cyphenothrin is synthetic pyrethroid, acting by contact poisoning. It is used in public health against flies, mosquitoes, cockroaches, etc. (Matsuo, 1980).

Identity

ISO common name: Cyphenothrin is the ISO common name for a racemic mixture of 4 pairs of diastereoisomers, designated as (±)-α-cyano-3-phenoxybenzyl (±)-*cis-trans*- chrysanthemate. The name *d,d,trans*-cyphenothrin refers to an enantio-enriched mixture, comprised mainly of the single stereoisomer (*S*)-α-cyano-3-phenoxybenzyl (1*R, 3R*)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylate, with only small proportions of the other stereoisomers, as defined by the WHO specification.

Synonyms: None

Chemical name:

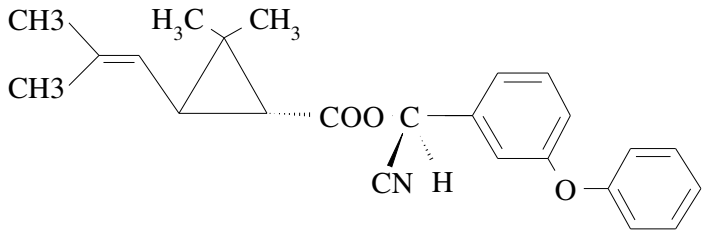
IUPAC: None. IUPAC name for the main stereoisomer present is: (*S*)-alpha-cyano-3-phenoxybenzyl (1*R, 3R*)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylate.

CA: None. CAS name for cyphenothrin is: cyano(3-phenoxyphenyl)methyl 2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylate.

CAS No: None. CAS number for cyphenothrin is: 39515-40-7

CIPAC No: 761

Structural formula:



Molecular formula: $C_{24}H_{25}NO_3$

Relative molecular mass:

375.47

Identity tests: GC retention time (cyphenothrin); IR spectrum (cyphenothrin); enantio-selective HPLC peak pattern (*d,d,trans*-cyphenothrin).

Physical and chemical properties of *d,d,trans*-cyphenothrin

Table 1. Physico-chemical properties of pure *d,d,trans*-cyphenothrin.

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure:	<7.52 x 10^{-10} Pa at 20, 35 and 45°C	100.2	EPA Guideline 63-9
Melting point and temperature of decomposition:	Melting point: 43.8 °C Decomposition temperature: Not available	Not stated	EPA Guideline 63-5,
Solubility in water:	<10 x 10^{-9} g/l at 25°C at pH 7	100.2	EPA Guideline 63-8
Octanol / water partition coefficient:	log P_{OW} >6 at 25°C at pH 5.2	100.2	EPA Guideline 63-11
Hydrolysis characteristics:	Not available	-	-
Photolysis characteristics:	Not available	-	-
Dissociation characteristics:	Does not dissociate	-	-

Table 2. Chemical composition and properties of *d,d,trans*-cyphenothrin technical material (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 98.0-98.5%.
Declared minimum *d,d,trans*-cyphenothrin content:	930 g/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:	BHT: 20 g/kg
Melting or boiling temperature range	Boiling point: 154°C at 0.1 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 *d,d,trans*-cyphenothrin 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,d,trans*-cyphenothrin technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Duration and conditions	Result
Rat M/F	Oral	EPA Guideline 81-1	LD_{50} 188 mg/kg bw (male); 220 mg/kg bw (female)
Rat M/F	Dermal*	EPA Guideline 81-2	LD_{50} > 5000 mg/kg bw (male and female)
Rat M/F	Inhalation*	EPA Guideline 81-3	LC_{50} >1850 mg/m^3 (male and female)
Rabbit	Skin irritation*	EPA Guideline 81-5	negative
Rabbit	Eye irritation*	EPA Guideline 81-4	negative
Guinea pig	Skin sensitization*	Buehler method	negative

* The toxicity of *d,d,trans*-cyphenothrin is not expected to differ significantly from that of cyphenothrin (Wilkinson 1996; Kaneko 1984).

Table 4. Toxicology profile of *d,d,trans*-cyphenothrin technical material, based on repeated administration (sub-acute to chronic).

Species	Test	Duration and conditions	Result
Rat M/F	Feeding toxicity*	180-day study, Guideline of Japanese Ministry of Agriculture, Forestry and Fisheries	NOAEL = 300 ppm 16.8 mg/kg bw/day (male) 19.6 mg/kg bw/day (female)
Mouse M/F	Feeding toxicity*	90-day study, EPA Guideline 82-1	NOAEL = 500 mg/m^3 (male, female)
Dog M/F	Feeding, toxicity*	90-day study, EPA Guideline 82-1	NOAEL = 3 mg/kg/day (male, female)
Rat M/F	Inhalation*	28-day study	NOEL= 7.76 mg/m^3 (male, female)
Rat M/F	Feeding, carcinogenicity*	Sumitomo report No. EET-0084. 2-year study, EPA Guideline 83-2	Carcinogenicity: no statistically significant increased incidence of neoplasms associated with treatment compared with the control group. NOEL = 1000 ppm (48 mg/kg/day) (male); 300 ppm (18 mg/kg/day) (female),

Species	Test	Duration and conditions	Result
Mouse M/F	Feeding, carcinogenicity*	Sumitomo report No. EET-0084. 2-year study, EPA Guideline 83-2	Carcinogenicity: no statistically significant increased incidence of neoplasms associated with treatment compared with the control group. NOEL > 1000 ppm (male, female)
Dog M/F	Oral*	[1-year study] EPA Guideline 83-1	NOEL = 3 mg/kg/day
Rat M/F	Feeding, 2-generation reproduction*	Sumitomo report No. EET-0067. EPA Guideline 83-4 Fed S-2703F in diet continuously throughout two successive generations at 0, 100, 300, 1000 ppm; 24 rats/sex/dose both F1 and F2.	No dose related mortalities observed. Statistically significant lower body weight gains observed in F1 high dose females. No additional statistically significant differences found in other adult parameters. No significant differences in any clinical observations in the F1 and F2 pups. Generally gross necropsy and histomorphologic findings of adults and offspring were few and were not considered treatment related. Adult NOEL = 300 ppm (based on decreased body weight gain at 1000 ppm); Developmental NOEL = 1000 ppm (based on no treatment related effects).
Rat M/F	Feeding, teratogenicity and embryotoxicity*	Sumitomo report No. EET-0026. Subcutaneous treatment with S-2703 Forte (cyphenothrin) at 0, 50, 150, 500 mg/kg/day on days 7 to 17 of gestation; 38 female rats/dose.	Significant decrease in maternal weight gain in highest dose group. Maternal NOEL = 150 mg/kg/day (based on decreased weight gain at 500 mg/kg/day). No physiological or developmental effects on fetuses at any dose level. Developmental NOEL = 150 mg/kg/day (based on viability of F1 offspring on 4^{th} day). No teratogenic effects attributable to cyphenothrin observed.

Species	Test	Duration and conditions	Result
Rabbit M/F	Feeding, teratogenicity and embryotoxicity*	Sumitomo report No. EET-0036. Subcutaneous treatment with S-2703 Forte (cyphenothrin) at 0, 50, 125 mg/kg/day on days 6-18 of gestation and 250 mg/kg/day on days 6-10 of gestation; 15 New Zealand White female rabbits/dose.	Significant decrease in maternal weight gain in the two highest dose groups. Maternal NOEL = 50 mg/kg/day (based on decreased body weight at 125 and 250 mg/kg/day). No physiological or developmental effects on fetuses at any dose level. Developmental NOEL = 250 mg/kg/day (based on no effects). No teratogenic effects attributable to cyphenothrin observed.

* The toxicity of *d,d,trans*-cyphenothrin is not expected to differ significantly from that of cyphenothrin (Wilkinson 1996; Kaneko 1984).

Table 5. Mutagenicity profile of *d,d,trans*-cyphenothrin technical material, based on *in vitro* and *in vivo* tests.

Species	Test	Conditions	Result
Salmonella typhimurium and *Escherischia coli*	Bacterial reverse mutation*	EPA Guideline 84-2	negative
Mouse bone marrow erythrocytes	Micronucleus test*	EPA Guideline 84-2	negative
Chinese hamster ovary cells	Sister chromatid exchange assay*	EPA Guideline 84-2	negative

* The toxicity of *d,d,trans*-cyphenothrin is not expected to differ significantly from that of cyphenothrin (Wilkinson 1996; Kaneko 1984).

Table 6. Ecotoxicology profile of *d,d,trans*-cyphenothrin technical material.

Species	Test	Duration and conditions	Result
Bobwhite quail	Acute dietary toxicity*	EPA Guideline 71-2	LC_{50} >5620 ppm
Rainbow trout	Acute flow-through toxicity	EPA Guideline 72-1; 96 hr	LC_{50} = 0.38 µg/l
Daphnia magna	Acute flow-through toxicity	EPA Guideline 72-2; 48 hr	LC_{50} = 1.2 µg/l

* The toxicity of *d,d,trans*-cyphenothrin is not expected to differ significantly from that of cyphenothrin (Kent 1996).

Neither WHO/PCS nor FAO/WHO JMPR have evaluated *d,d,trans*-cyphenothrin. The IPCS hazard classification of cyphenothrin (1*R*-isomers) is Class II, moderately hazardous (WHO, 2002).

Formulations

The main formulation types available are EC, OL, for use in public health applications. The EC formulation is registered and sold in Japan, Jordan, Argentina, UAE and other countries.

Methods of analysis and testing

The analytical method for determination of *d,d,trans*-cyphenothrin content (including identity tests) is based on packed column GC with FID and internal standardization with di(2-ethylhexyl) phthalate (Asada 1995). A CIPAC collaborative study of the method with capillary column GC is in progress, the results of the full study are expected to be presented in 2005*. The method for determination of identity as *d,d,trans*-cyphenothrin is based on enantio-specific HPLC. (Asada 1995).

Test methods to determine the physical and chemical properties of the technical active ingredient were OECD and USEPA, while those for the formulations were according to the FAO/WHO Manual (FAO/WHO 2002).

Containers and packaging

No special requirements for containers and packing have been identified.

Expression of the active ingredient

The active ingredient is expressed as *d,d,trans*-cyphenothrin, as defined by the WHO specification.

Appraisal

The active ingredient, *d,d,trans*-cyphenothrin, has not previously been the subject of a WHO specification.

The ISO name, cyphenothrin, denotes the mixture of the racemic chrysanthemic acid bound to the racemic cyanhydrin, an α-cyanoalcohol. Cyphenothrin has 3 chiral centres and is therefore comprised of 4 racemic pairs of diastereoisomers, with a total of 8 stereoisomers. The name, *d,d,trans*-cyphenothrin, is the name given by the manufacturer to the esterification product of the 1*R-trans* acid moiety and the *S* form of the cyanhydrin. The prefix “d,d,trans-” reflects the former designation (d, for dextro-rotary) of the configurations of the chiral centres of the chrysanthemic acid moiety and the cyanhydrin. together with the trans configuration for the the chrysanthemic acid, the form with the highest insecticidal activity (Matsuo *et al*. 1980). The mixture, characterized by the WHO specification as *d,d,trans*-cyphenothrin, contains 97% trans-isomer, 95% of the 1*R* isomer and 92% of the *S*-isomer in the alcohol moiety. The total content of *d,d,trans*-cyphenothrin can be determined by capillary column GC, whereas the stereoisomer ratios are determined using enantio-selective liquid chromatography, by which all minor and major stereoisomers present can be separated and quantified. The capillary GC method is in process of validation under the auspices of CIPAC, whereas the enantio-selective HPLC method for isomer ratio is in process of peer validation.

d,d,trans-Cyphenothrin is almost insoluble in water but highly soluble in organic solvents, such as hexane, ethanol, acetone, toluene etc. It is of low volatility. It is

* Analytical methods for identification and quantification of d,d,trans-cyphenothrin in the TC and EC were adopted by CIPAC in 2005 (CIPAC 2005a and 2005b).

stable under normal storage conditions but is readily hydrolyzed in water at higher pH and is sensitive to light (Roberts and Hutson 1999). It has a low potential for bioaccumulation due to hydrolysis, photolysis and metabolism in water, soil and in biota (Roberts and Hutson 1999).

Commercially 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 the TC. Limits for impurities were supported by 5 batch analysis data, in which unaccountable material represented 15 to 20 g/kg (mass balances were 98.0 to 98.5%). The declared minimum active ingredient content was 930 g/kg. The proposer stated that no relevant impurities are present in the technical material, either > 1 g/kg maximum or less than 1 g/kg maximum, and the meeting agreed. The proposer stated that 2,6-di-*tert*-butyl-*p*-cresol (BHT, "butylated hydroxytoluene") is added as a stabilizer, at 20 g/kg, after the final step of the synthesis, to reduce the sensitivity of the TC to degradation by oxygen and light. The meeting accepted that the stabilizer should be present at the concentration recommended by the proposer but decided that these should form a Note to the specification and should not be part of the specification itself.

The impurity data submitted in support of the WHO specification were not derived from TCs produced by the same process as the corresponding data submitted for registration of cyphenothrin by the Swiss Office of Public Health in 1985. The results and manufacturing specifications were nevertheless similar in most respects (cyphenothrin content, amounts of by-products and unaccountable material) and the meeting agreed that there was no significant difference.

The data for toxicology of *d,d,trans*-cyphenothrin partly rely on studies conducted with cyphenothrin. The data package submitted for registration of *d,d,trans*-cyphenothrin in Switzerland included an article on the comparative metabolism of stereoisomers of cyphenothrin in rats (Wilkinson 1996; Kaneko *et al*. 1984). Taking this into account, the meeting agreed that data generated with cyphenothrin were acceptable for the purposes of evaluating *d,d,trans*-cyphenothrin. The active ingredient generally shows low mammalian toxicity and is not a sensitizer in the Buehler and is not irritating to the rabbit eye and skin. There was no evidence of carcinogenicity in the rat or mouse. There was no evidence of mutagenic responses in bacterial, micronucleus or sister chromatid exchange tests. In a 2-generation reproduction study in the rat, no reproductive effects were observed at any dose level. There was no evidence of teratogenicity or developmental effects in rats or rabbits, although there was a decrease in maternal weight gain and a consequential decrease in rat offspring viability at the high dose tested.

d,d,trans-Cyphenothrin is very toxic to *Daphnia magna* and fish but it has a low toxicity to bobwhite quails.

d,d,trans-Cyphenothrin is only used in public health applications (mainly as emulsifiable concentrates or oil miscible liquids), against mosquitoes, houseflies, cockroaches and main formulations are emulsifiable concentrates and oils. With no uses of *d,d,trans*-cyphenothrin in agriculture, it is unlikely that dietary exposure will be of significance.

On the basis of the one-year dog study, a NOEL of 16.8 to 19.6 mg/kg bw/d is established by the Swiss Office of Public Health. The *d,d,trans*-cyphenothrin TC was classified as moderately toxic (Class 3) in Switzerland and, although it has not been classified by the International Programme on Chemical Safety (IPCS), this organization has classified the closely related cyphenothrin (1*R*-isomers) as Class II, moderately hazardous.

Recommendations

The meeting recommended that the draft specifications for *d,d,trans*-cyphenothrin TC and EC, proposed by Sumitomo Chemical Company Limited and amended as described in the appraisal above, should be adopted by WHO, subject to acceptable validation of the analytical and identity test methods*.

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