

**FAO SPECIFICATIONS AND EVALUATIONS
FOR AGRICULTURAL PESTICIDES**

CYFLUTHRIN

(RS)- α -cyano-4-fluoro-3-phenoxybenzyl
(1RS,3RS;1RS,3SR)-3-(2,2-dichlorovinyl)-2,2-
dimethylcyclopropanecarboxylate

2004



Food and Agriculture Organization
of the United Nations

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DISCLAIMER¹

FAO 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.

FAO 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, FAO 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.

FAO is not responsible, and does not accept any liability, for the testing of pesticides for compliance with the specifications, nor for any methods recommended and/or used for testing compliance. As a result, FAO does not in any way warrant or represent that any pesticide claimed to comply with a FAO specification actually does so.

¹ This disclaimer applies to all specifications published by FAO.

INTRODUCTION

FAO establishes and publishes specifications* for technical material and related formulations of agricultural 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.

Since 1999, the development of FAO specifications has followed the **New Procedure**, first described in the 5th edition of the “Manual on the development and use of FAO specifications for plant protection products” (FAO Plant Production and Protection Paper No. 149) and, subsequently, in the 1st edition of the “Manual for Development and Use of FAO and WHO Specifications for Pesticides” (FAO Plant Production and Protection Paper No. 173, 2002). This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the experts of the “FAO/WHO Joint Meeting on Pesticide Specifications” (JMPS).

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently, from the year 2000 onwards, the publication of FAO specifications under the **New Procedure** was changed. Every specification now consists 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 FAO 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.

FAO 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. FAO 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 those 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 Internet under (<http://www.fao.org/pest-and-pesticide-management/en/>) or as hardcopy from the Plant Protection Information Officer.

PART ONE

SPECIFICATIONS

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CYFLUTHRIN

INFORMATION

ISO common names:

Cyfluthrin (draft E-ISO, BSI, BAN)

Cyfluthrine (draft (f) F-ISO)

Synonyms:

Baythroid, Solfac, Baygon, Tempo, Bay FCR 1272, FCR 1272, OMS 2012

Chemical names:

IUPAC (RS)- α -cyano-4-fluoro-3-phenoxybenzyl (1RS,3RS;1RS,3SR)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

CA Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-cyano(4-fluoro-3-phenoxyphenyl)methyl ester

CAS Nos:

68359-37-5 (unstated stereochemistry)

86560-92-1 (diastereoisomer I)

86560-93-2 (diastereoisomer II)

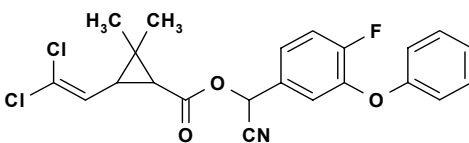
86560-94-3 (diastereoisomer III)

86560-95-4 (diastereoisomer IV)

CIPAC No:

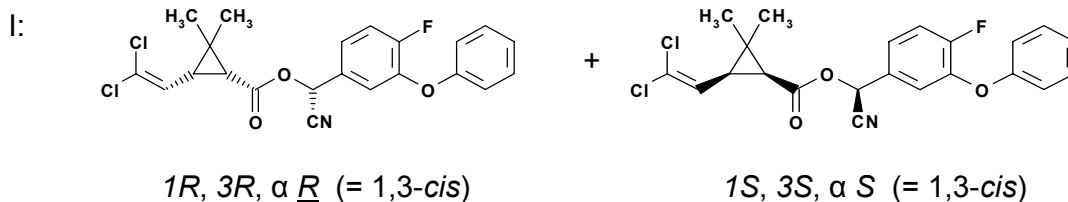
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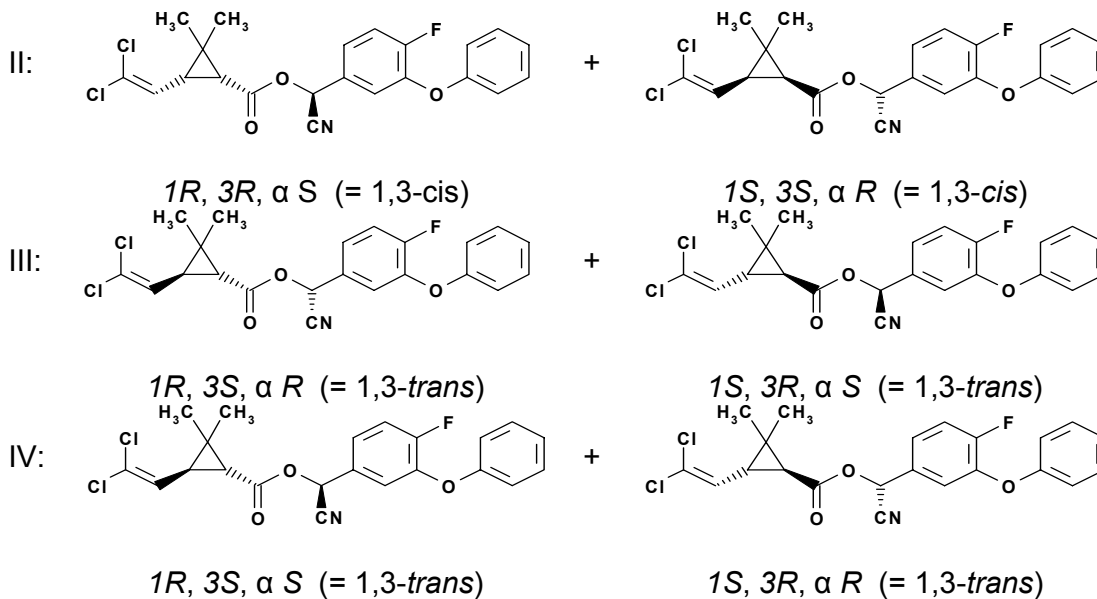
Structural formulae:



unstated stereochemistry

Cyfluthrin is a mixture of 4 diastereoisomeric pairs of enantiomers, I, II, III and IV, corresponding to designations of cis I, cis II, trans I and trans II, respectively, in CIPAC methods:





Molecular formula:



Relative molecular mass:

434.3 g/mol

Identity tests (CIPAC 385/TC/M/2.1 - 385/TC/M/2.4):

HPLC retention times (normal phase, external standardization); TLC R_f values (coated silica, against reference standard); IR spectrum; ¹H-NMR spectrum (200 MHz).

CYFLUTHRIN

TECHNICAL MATERIAL

FAO/WHO Specification 385/TC (November 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 (385/2003). 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 (385/2003) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist of cyfluthrin, together with related manufacturing impurities, and shall be an amber to brown, highly viscous oil which may be partly crystallized, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 Identity tests (CIPAC 385/TC/M/2, CIPAC Handbook H, p 107, 1998) (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 Cyfluthrin content (CIPAC 385/TC/M/3, CIPAC Handbook H, p 108, 1998) (Note 1)

The cyfluthrin content shall be declared (not less than 920 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

2.3 Isomeric composition (CIPAC 385/TC/M/3.1, CIPAC Handbook H, p 108, 1998) (Note 1)

The cyfluthrin shall contain the four diastereoisomers in the following proportions:

- 23-27% diastereoisomer I;
- 17-21% diastereoisomer II;
- 32-36% diastereoisomer III;
- 21-25% diastereoisomer IV.

3 Physical properties

3.1 Alkalinity (MT 31, CIPAC Handbook F, p 96, 1994)

Maximum alkalinity: 1.0 g/kg calculated as NaOH.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: <http://www.fao.org/pest-and-pesticide-management/en/>

Note 1 Before sampling for analysis by 385/TC/ methods, heat the technical material to 80°C, to melt/dissolve any crystalline active ingredient present and produce a completely homogeneous liquid. Complete identification of cyfluthrin requires confirmation that the diastereoisomers are present in the appropriate ratio (clause 2.3).

CYFLUTHRIN

EMULSION, OIL IN WATER

FAO Specification 385/EW (November 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 reports (385/2003). 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 reports (385/2003) as PART TWO forms an integral part of this publication.

1 Description

The formulation shall consist of an emulsion of technical cyfluthrin, complying with the requirements of FAO/WHO specification 385/TC (2003), in an aqueous phase together with suitable formulants in form of a white emulsion. After gentle agitation, the formulation shall be homogeneous (Note 1) and suitable for dilution in water.

2 Active ingredient

2.1 Identity tests (CIPAC 385/TC/M/2, CIPAC Handbook H, p 107, 1998, 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 Cyfluthrin content (CIPAC 385/EW/M/3, CIPAC Handbook H, p 117, 1998)

The cyfluthrin content shall be declared (g/kg or g/l at $20 \pm 2^\circ\text{C}$, Note 3) and, when determined, the average content measured shall not differ from that declared by more than the tolerance given below.

Declared content in g/kg or g/l at $20 \pm 2^\circ\text{C}$	Tolerance
Up to 25	$\pm 15\%$ of the declared content
Above 25 up to 100	$\pm 10\%$ of the declared content
Note: in each range the upper limit is included.	

3 Physical properties

3.1 pH range (MT 75.3, CIPAC Handbook J, p 131, 2000)

pH range: 2.5 to 3.5 (undiluted).

3.2 Pourability (MT 148.1, CIPAC Handbook J, p 133, 2000)

Maximum "residue": 0.5%.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: <http://www.fao.org/pest-and-pesticide-management/en/>

3.3 Emulsion stability and re-emulsification (MT 36.1.1, CIPAC Handbook F, p 108, 1995) (Note 4)

The formulation, when diluted at $30 \pm 2^\circ\text{C}$ (Note 5) with CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of stability, MT 36.1
0 h	Initial emulsification complete
0.5 h	"Cream", maximum: 0 ml
2.0 h	"Cream", maximum: 0 ml "Free oil", maximum: 0 ml
24 h	Re-emulsification complete
24.5 h	"Cream", maximum: 0 ml "Free oil", maximum: 0 ml
Note: tests after 24 h are required only where results at 2 h are in doubt	

3.4 Persistent foam (MT 47.2, CIPAC Handbook F, p 152, 1995) (Note 6)

Maximum: 0 ml after 1 min.

4 Storage stability

4.1 Stability at 0°C (MT 39.3, CIPAC Handbook J, p 126, 2000)

After storage at $0 \pm 2^\circ\text{C}$ for 7 days, no separation of particulate or oily matter shall be visible after gentle agitation.

4.2 Stability at elevated temperature (MT 46.3, CIPAC Handbook J, p 128, 2000)

After storage $54 \pm 2^\circ\text{C}$ for 14 days, the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 7) and the formulation shall continue to comply with the clauses for:

- pH range (4.2);
- emulsion stability and re-emulsification (4.4).

Note 1 All physical and chemical tests listed in this specification are to be performed with a laboratory sample taken after the recommended homogenization procedure.

Before sampling to verify the formulation quality, the commercial container must be inspected carefully. On standing, emulsions may develop a concentration gradient which could even result in the appearance of a clear liquid on the top (sedimentation of the emulsion) or on the bottom (creaming up of the emulsion). Therefore, before sampling, the formulation must be homogenized according to the instructions given by the manufacturer or, in the absence of such instructions, by gentle shaking of the commercial container (for example, by inverting the closed container several times). Large containers must be opened and stirred adequately.

Note 2 Complete identification of cyfluthrin requires confirmation that the diastereoisomers are present in the appropriate ratio (refer to specification 385/TC, 2003, clause 2.3).

Note 3 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 4 This test will normally be carried out only after the stability at elevated temperatures test (5.2).

Note 5 The formulation should be tested at the highest and lowest rates of use recommended by the supplier.

Note 6 The test should be carried out at the highest application concentration.

Note 7 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

EVALUATION REPORT(S)

CYFLUTHRIN

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2003 EVALUATION REPORT based on submission of data from Bayer, Germany (TC, WP, EW).	11

CYFLUTHRIN

EVALUATION REPORT 385/2003

Explanation

The data for cyfluthrin were evaluated for the review of existing FAO and WHO specifications.

Cyfluthrin is not under patent.

Existing specifications for cyfluthrin were adopted in 1995 by FAO (TC, WP, EC, UL, EW), as full specifications under the old procedure (FAO, 1996) and in 1999 by WHO as full (TC, WP) or interim (EW) specifications under the old procedure (WHO 1999). An evaluation of cyfluthrin and its formulations was conducted by WHOPEP and reported in 1998 (WHO, 1998).

Cyfluthrin has recently been notified to the EU, under code N117, according to Directive 98/8/EC (Biocidal Products Directive).

In 1997, cyfluthrin was included in FAO/WHO evaluations of toxicology and residues of certain veterinary drugs in animals and foods (JECFA, 1997a and 1997b).

Cyfluthrin was evaluated by EPA in the USA, to establish pesticide tolerances (USEPA, 2001). Cyfluthrin and its formulations were also evaluated by the California EPA, in 1998, for environmental fate assessment.

The draft specifications and supporting data for cyfluthrin were provided by Bayer Crop Science AG, in 2002.

Uses

Cyfluthrin is a synthetic pyrethroid insecticide which is effective against a wide variety of agricultural and public health pests, particularly Lepidoptera, Coleoptera, Hemiptera and Diptera (Hammann & Fuchs, 1981). Its mode of action is characterized by interference with nervous transmission, due to inhibition of membrane sodium channel systems in the target organism. Cyfluthrin is mainly a contact insecticide, it is not systemic and does not penetrate into plant tissue. Application methods include residual sprays, fogging and impregnation.

Identity

ISO common names:

Cyfluthrin (draft E-ISO, BSI, BAN)

Cyfluthrine ((f) draft F-ISO)

Synonyms:

Baythroid, Solfac, Baygon, Tempo, Bay FCR 1272, FCR 1272,

OMS 2012

Chemical names:

IUPAC, (RS)- α -cyano-4-fluoro-3-phenoxybenzyl (1RS,3RS;1RS,3SR)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

CA, Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-cyano(4-fluoro-3-phenoxyphenyl)methyl ester

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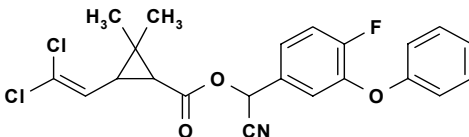
86560-94-3 (diastereoisomer III)

86560-95-4 (diastereoisomer IV)

CIPAC No:

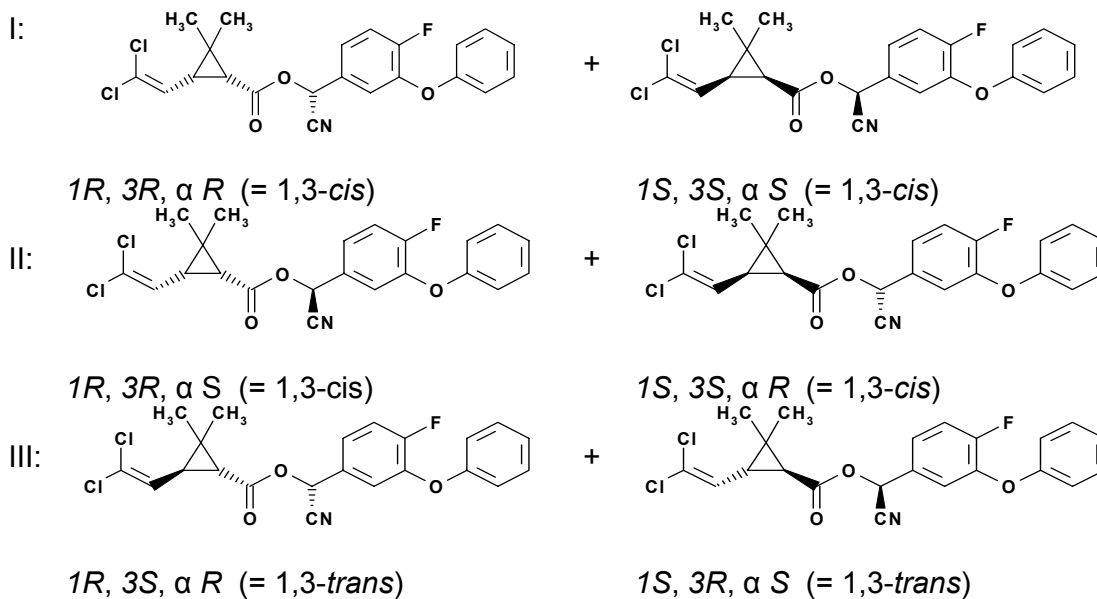
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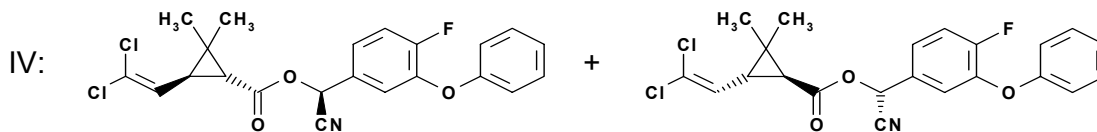
Structural formulae:



unstated stereochemistry

Cyfluthrin is a mixture of 4 diastereoisomeric pairs of enantiomers, I, II, III and IV, corresponding to designations of cis I, cis II, trans I and trans II, respectively, in CIPAC methods:





1R, 3S, α S (= 1,3-trans)

1S, 3R, α R (= 1,3-trans)

Molecular formula:



Relative molecular mass:

434.3

Identity tests (CIPAC 385/TC/M/2.1 - 385/TC/M/2.4):

HPLC retention time (normal phase, external standardization; TLC Rf value (coated silica, against reference standard); IR spectrum; ¹H-NMR spectrum (200 MHz).

Physico-chemical properties

Table 1. Physico-chemical properties of pure cyfluthrin.

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure	(vapour pressure in Pa at 20°C) Diastereoisomer I: 9.6×10^{-7} Diastereoisomer II: 1.4×10^{-8} Diastereoisomer III: 2.1×10^{-8} Diastereoisomer IV: 8.5×10^{-8} (vapour pressure in Pa at 25°C) Diastereoisomer I: 2.1×10^{-6} Diastereoisomer II: 3.4×10^{-7} Diastereoisomer III: 4.7×10^{-7} Diastereoisomer IV: 2.0×10^{-7}	98.8 97.4 97.8 98.9 98.8 97.4 97.8 98.9	OECD 104, by extrapolation
Melting point and temperature of decomposition	Melting point: Diastereoisomer I: 64.40°C Diastereoisomer II: 80.71°C Diastereoisomer III: 65.04°C Diastereoisomer IV: 106.19°C Boiling point: not measurable. Decomposition temperature: >220°C. DTA measurement: exothermic decomposition in the range 250-380°C. TGA measurement: weight loss at temperatures above 160°C	98.7 99.2 98.1 99.8	EEC A1, DSC
Solubility in water	The material used was a defined mixture of the 4 diastereoisomeric enantiomer pairs. (solubility in µg/l at pH 3/pH 7) Diastereoisomer I: 2.5/2.2 Diastereoisomer II: 2.1/1.9 Diastereoisomer III: 3.2/2.2 Diastereoisomer IV: 4.3/2.9. Solubility only slightly influenced by pH.	96.6 total (i.e. 25.1, 18.8, 31.6 and 21.1% of I, II, III and IV, respectively)	EEC A6 OECD 105

Parameter	Value(s) and conditions	Purity %	Method reference
Octanol / water partition coefficient	The material used was a defined mixture of the 4 diastereoisomeric enantiomer pairs. (log Pow at 20°C): Diastereoisomer I: 6.00, Diastereoisomer II: 5.94, Diastereoisomer III: 6.04, Diastereoisomer IV: 5.91	99.0 total (i.e. 23.7, 17.1, 34.8 and 23.4% of I, II, III, IV, respectively)	EEC A8 OECD 107
Hydrolysis characteristics	The material used was a defined mixture of the 4 diastereoisomeric enantiomer pairs. (DT ₅₀ at pH 4, 7 and 9 at 20°C) Diastereoisomer I: >1 year, 270 days, 42 hours. Diastereoisomer II: >1 year, 270 days, 42 hours. Diastereoisomer III: >1 year, 160 days, 33 hours. Diastereoisomer IV: >1 year, 160 days, 33 hours.	99.0 total (i.e. 23.6, 17.9, 31.6 and 21.1% of I, II, III and IV, respectively)	OECD 111
Photolysis characteristics	The material used was a defined mixture of the 4 diastereoisomeric enantiomer pairs. DT ₅₀ 12.2 days in water. DT ₅₀ 25.7 hours in air.	99.0 total	EPA 161-2 ECETOC
Dissociation characteristics	Cyfluthrin does not show basic or acidic properties in water.	-	-
Density	(g/cm ³ at 20°C) Diastereoisomer I: 1.46 Diastereoisomer II: 1.373 Diastereoisomer III: 1.316 Diastereoisomer IV: 1.356.	99.2 99.3 99.8 98.9	EC A3

An assessment of the environmental fate of cyfluthrin (USEPA, 1992), concluded that cyfluthrin is sensitive to breakdown by sunlight. On the surface of soils, its half-life was 48-72 hours. It had a half-lives of 56 and 63 days in German loam and sandy loam soils, respectively, and had similar persistence in soils under anaerobic conditions. Cyfluthrin was shown to be very immobile in soils and was not considered to pose a threat of ground water contamination. Similarly, cyfluthrin was shown to be broken down quickly in surface waters. Because it is of low water solubility and is less dense than water, it can float as a surface film, where it is subject to rapid breakdown by sunlight (1 day). It was shown to be stable to hydrolysis in water at acidic pH but quickly hydrolyzed under basic conditions.

Table 2. Chemical composition and physico-chemical properties of cyfluthrin technical material (TC).

Manufacturing process, maximum limits for impurities, 5 batch analysis data	Confidential information was supplied and held on file by FAO and WHO. Mass balances were 97.8-98.7%.
Declared minimum cyfluthrin content	920 g/kg
Isomer ratio of TC	23-27% diastereoisomer I, 17-21% diastereoisomer II, 32-36% diastereoisomer III, 21-25% diastereoisomer IV.
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 temperature range	64-106°C.
Boiling temperature range	>220°C (decomposition).
Density	1.281 g/cm ³ at 20°C.

Hazard summary

Notes.

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from cyfluthrin 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 cyfluthrin technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Duration and conditions	Result [(isomer/form)]
Rat, male	Oral	In water/Cremophor EL(*), 5 rats, doses 13-20 mg/kg bw.	LD ₅₀ = 16 mg/kg bw
Rat, male	Oral	In polyethylene glycol 400 (**), doses 10-2500 mg/kg bw, 15 rats, recovery period 14 days	LD ₅₀ = 590 mg/kg bw
Rat, female	Oral	In polyethylene glycol 400 (**), doses 10-2500 mg/kg bw, 15 rats, recovery period 14 days	LD ₅₀ = 1189 mg/kg bw
Rat, male	Oral	In acetone/oil	LD ₅₀ = 254 mg/kg bw
Rat, male, female	Dermal	24 h, undiluted TC, 25 rats, doses 2500 and 5000 mg/kg bw	LD ₅₀ = >5000 mg/kg bw
Rat, male, female	Dermal	24 h, distilled water/Cremophor EL	LD ₅₀ = >5000 mg/kg bw
Rat, male, female	Dermal	24 h, physiological NaCl	LD ₅₀ = >5000 mg/kg bw
Rat, male	Inhalation	4 h, in dimethyl sulfoxide/polyethylene glycol 400	LC ₅₀ = 575 mg/m ³
Rat, female	Inhalation	4 h, in dimethyl sulfoxide/polyethylene glycol 400	LC ₅₀ = 490 mg/m ³
New Zealand White rabbits	Skin irritation	Intact or abraded skin, according to guidelines recommended by US Department of Agriculture	No manifestations of irritation.
New Zealand White rabbits	Eye irritation	5 min and 24 h	Moderate to severe reddening and mild to moderate swelling of the conjunctiva.
Pirbright White guinea-pigs, male	Skin sensitization	Magnusson-Kligman maximization test	No evidence of skin-sensitizing potential

The acute oral toxicity of cyfluthrin was clearly related to the formulation. In rats dosed orally with cyfluthrin in water/Cremophor EL, absorption of cyfluthrin was rapid, with a maximum blood concentration being reached in 1 hour. In rats dosed orally with cyfluthrin in polyethyleneglycol 400, absorption of cyfluthrin was slower and less, being undetectable in the blood at 4 hours and reaching a peak

concentration in the blood at 6 hours. Compared with the rats dosed using water/Cremophor EL, the stomach contents of rats dosed using polyethyleneglycol contained more cyfluthrin. Case reports (WHO/PCS, 2004) in humans have shown that local skin irritation can arise from exposure to cyfluthrin formulations.

Table 4. Toxicology profile of cyfluthrin technical material based on repeated administration (sub-acute to chronic).

Species	Test	Duration and conditions	Result
Wistar rat, male, female	Oral gavage	28 days, groups of 20 male and 20 female rats, doses of 0, 5, 20 or 80 mg/kg bw, once a day	NOAEL = 20 mg/kg bw/day
Wistar rat, male, female	Oral, feeding, toxicity	3 months, groups of 30 male and 30 female rats, doses of 0, 30, 100 or 300 ppm <i>via</i> the feed	NOAEL = 300 ppm, corresponding to 30 mg/kg bw/day
Wistar rat, male, female	Oral, feeding, carcinogenicity	2 years, groups of 50 male and 50 female rats, doses of 0, 50, 150 or 450 ppm <i>via</i> the feed	NOAEL = Male: 50 ppm, corresponding to 2.02 mg/kg bw/day Female: 50 ppm, corresponding to 2.71 mg/kg bw/day, The range of tumours found was normal for rats of the age and strain used. Cyfluthrin had no oncogenic potential.
Albino rabbit, male, female	Dermal	15 days, 5 days/week (6 h per day), groups of 6 male and 6 female rats, doses of 0, 50 and 250 mg/kg bw	NOAEL = 250 mg/kg bw
Wistar rat, male, female	Inhalation	3 weeks (15 x 6 h), groups of 10 male and 10 female rats. 1 st study: 0, 2.3, 11.5, 69.5 mg/m ³ 2 nd study: 0, 0.4, 1.4, 10.5 mg/m ³	NOAEL = 0.4 mg/m ³
Wistar rat, male, female	Inhalation	4 weeks (6 h/day, 5 days/week), groups of 10 male and 10 female rats, 0, 0.44, 6.0, 46.6 mg/m ³	NOAEL = 0.44 mg/m ³ air, corresponding to a nominal dose of 0.16 mg/kg bw/day
Wistar rat, male, female	Inhalation	13 weeks (63 x 6 h), groups of 10 male and 10 female rats, 0, 0.09, 0.71, 4.52 mg/m ³	NOAEL = 0.09 mg/m ³ air
Wistar rat, male, female	Feeding, 3 generation reproduction	Groups of 10 male and 20 female rats, 0, 50, 150, 450 ppm <i>via</i> the feed, throughout the entire experimental period (mating period, gestation and rearing)	NOAEL = 3.74 mg/kg bw/day (males), 5.14 mg/kg bw/day (females) (based on: growth retardation and decreased liver and kidney weights of parental rats; growth retardation of pups; deficiencies in lactation; reduced viability of pups; and reduced number of pups per litter; of rats fed at 150 ppm). No effect on reproduction at lower doses but treatment-related effects were seen at high doses..

Species	Test	Duration and conditions	Result
FB30 rats, female	Gavage, teratogenicity and embryotoxicity	From 6 th to 15 th day of gestation, in daily oral doses of 0, 3, 10 and 30 mg/kg bw. Formulation agent polyethylene glycol 400	NOAEL = 3 mg/kg bw/day for maternal toxicity 30 mg/kg bw for foetotoxicity based on: behavioural effects in dams at 10 mg/kg bw/day; and absence of foetotoxic effects at 10 and 30 mg/kg bw/day. No teratogenic effects observed.
Wistar rats, female	Gavage, teratogenicity and embryotoxicity	From 6 th to 15 th day of gestation, in daily oral doses of 0, 1, 3, 10 mg/kg bw. Formulation agent water/Cremophor EL	No effects on fertility, mating, or gestational parameters; no foetotoxicity or teratogenicity
Wistar rat, male, female	sub-chronic delayed neurotoxicity	5 months, groups of 15 male and 15 female rats, daily gavage in doses known to induce manifest signs of intoxication (60 and 80 mg/kg bw per day)	No signs of delayed neurotoxicity were observed at the clinical or histological levels.

Table 5. Mutagenicity profile of cyfluthrin technical material, based on *in vitro* and *in vivo* tests.

Species	Test	Conditions	Result
<i>Salmonella typhimurium</i> (TA 100, TA 98, TA1535, TA 1537)	Salmonella microsome test, <i>in vitro</i>	Concentrations: 0, 20, 100, 500, 2500, 12500, 24000 µg/plate, with and without S-9 mix	Negative
<i>Salmonella typhimurium</i> (TA 100, TA 98, TA1535, TA 1537)	Salmonella microsome test, <i>in vitro</i>	Concentrations: 0, 10, 50, 100, 500, 1000, 5000, 10000, 20000 µg/plate, with and without S-9 mix	Negative
<i>Escherichia coli</i> (B/r WP2 try hcr)	Plate test for back mutation, <i>in vitro</i>	0, 5, 10, 100, 500, 1000, 5000 µg/plate, with and without S-9 mix	Negative
<i>Saccharomyces cerevisiae</i> (D7)	Reverse mutation induction assay, <i>in vitro</i>	0, 625, 1250, 2500, 5000, 10000 µg/plate, with and without S-9 mix	Negative
Male NMRI mouse	Dominant lethal test, <i>in vivo</i>	30 or 60 mg/kg bw per os	Negative
Male and female NMRI mouse bone marrow cells	Micronucleus test, <i>in vivo</i>	2 x 75, or 2 x 15 mg/kg bw per os	Negative

Table 6. Ecotoxicology profile of cyfluthrin technical material.

Species	Test	Duration and conditions	Result
<i>Daphnia magna</i> (water flea)	Acute toxicity	24 and 48 h, pH 8.04, O ₂ saturation value 99.9%, temperature 19.8°C, ai concentration 0.0001-1.0 mg/l	EC ₅₀ = >0.056 mg/l (24h); 0.0027 mg/l (48h)
<i>Daphnia magna</i> (water flea)	Acute toxicity	48 h, EPA OPP 72-2	EC ₅₀ = 0.16 µg/l
<i>Oncorhynchus mykiss</i> (rainbow trout)	Short-term toxicity, flow-through	96h; temperature 10.8-13.0°C; pH 7.1-7.9; dissolved oxygen 4.7-10.1 mg/l; photoperiod 16 hours light daily; stock solution of 0.1mg cyfluthrin/ml dimethyl formamide, added to 19 l glass jars to produce 0.47-10.0 ppb	LC ₅₀ = 0.47µg/l (96h)

Species	Test	Duration and conditions	Result
<i>Scenedesmus subspicatus</i> (green alga)	Effect on growth, static water	96h (test times 0, 24, 48, 72, 96h); temperature 22.9-23.8°C; pH 7.85-10.21; cyfluthrin at 0.01-10.0 mg/l	IC ₅₀ = >10 mg/l NOEC = 0.1 mg/l
Earthworm	Acute toxicity	7 and 14 days; pH 6.4-6.9; soil water content 24.4-33.7%; cyfluthrin at 10, 100 and 1000 mg/kg dry soil	LC ₅₀ = >1000 mg/kg dry soil
<i>Apis mellifera</i> (honey bee)	Acute oral toxicity	24h; cyfluthrin at 0.01 to 0.1 µg/bee	LD ₅₀ = 0.051 µg/bee
Bobwhite quail	Acute toxicity	14 days; 31.2 -2000 mg/kg bw administered to groups of 5 male and 5 female birds. No mortality or morbidity observed	LD ₅₀ = >2000 mg/kg bw NOEL = 2000 mg/kg bw

Cyfluthrin was evaluated in 1987 by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) (FAO/WHO, 1988), which established an ADI of 0-0.02 mg/kg body weight. In 1997, the FAO/WHO Joint Expert Committee on Food Additives (JECFA) reviewed the data on cyfluthrin as part of a toxicological evaluation of certain veterinary drugs residues in food (JECFA, 1997b). The committee re-evaluated the data considered by the JMPR in 1988, together with several new studies, and concluded that the critical end-points were observed in the long-term rat feeding study. The NOEL was 50 ppm in feed, equal to 2 mg/kg body weight per day, on the basis of depression of body weight gain. Using this NOEL and a safety factor of 100, the Committee established an ADI for cyfluthrin of 0-0.02 mg/kg body weight, which was identical to that established by the JMPR in 1987.

Some occupational or accidental exposure poisoning cases have been reported, with symptoms including burning, itching and tingling sensations on skin, especially mucous areas (lips, prepuce). Washing was not an effective treatment. The effects have generally been greater with exposure to the WP than with the EW. The irritation was probably due to local, rather than systemic, effects (Flucke, 1979)

The IPCS hazard classification of cyfluthrin is Class II (Moderately Hazardous) (IPCS, 2002)

Formulations

The main formulation types available are EC, EW, UL and WP. EC and EW formulations are used both as agricultural and public health pesticides, whereas UL and WP are used for public health purposes.

These formulations are registered and sold in over 60 countries throughout the world.

Methods of analysis and testing

Analytical methods for determination of cyfluthrin content and identity have been adopted and published by CIPAC (CIPAC, 1998). Identification is by means of HPLC retention time; TLC R_f values and spot colour development with *o*-toluidine; and IR and proton-NMR (200 MHz) spectra. Two CIPAC methods are available for the determination of cyfluthrin content: reversed-phase and normal-phase HPLC, both involving detection by UV-absorption at 235 nm and external standardization. The reversed-phase method is intended only for the determination of total cyfluthrin, whereas the normal-phase method determines both the total cyfluthrin content and

the ratio of the diastereoisomers (both characteristics are defined by clauses in the specifications).

The methods for determination of impurities were based on HPLC (CIPAC normal phase method) and GC (Bayer Method 2201-0281803-99). Water content (Karl Fischer) was determined according using CIPAC MT 30.5.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, USEPA or EEC, as indicated in Table 1, while those for the formulations were CIPAC methods, as indicated in the specifications.

The physical properties, the methods for testing them and the limits proposed for the cyfluthrin TC, EW and WP comply with the requirements of Manual on Development and Use of FAO and WHO Specifications of Pesticides (FAO/WHO, 2002).

Containers and packaging

Cyfluthrin should be packed in containers of HDPE or, in the case of metal drums, cans or packs, containers which have a tightly fitting inner lining of HDPE.

Expression of the active ingredient

The active ingredient is expressed as cyfluthrin, comprising 4 diastereoisomeric pairs of enantiomers in the ratios defined by the specification.

Appraisal

Cyfluthrin is a synthetic pyrethroid insecticide. The molecule contains three chiral centres and therefore exists in 8 enantiomeric forms, giving four pairs of diastereoisomers. Selective enrichment of diastereoisomers can produce effectively different active ingredients, such as beta-cyfluthrin, but the subject of the present evaluation is essentially the racemate, known simply as cyfluthrin, in which the four diastereoisomeric pairs are present in somewhat similar (but not equal) ratios. The ratios are defined by the specification.

Existing specifications for cyfluthrin were adopted in 1995 by FAO (TC, WP, EC, UL, EW), as full specifications under the old procedure (FAO, 1996) and in 1999 by WHO as full (TC, WP) or interim (EW) specifications under the old procedure (WHO 1999). An evaluation of cyfluthrin and its formulations was conducted by WHOPES and reported in 1998 (WHO, 1998).

In common with many other synthetic pyrethroids, cyfluthrin is of low volatility and has very low water solubility. A pH dependence water solubility was observed though small. It is fairly rapidly hydrolysed in alkaline conditions, with a half-life in the range 33-42 hours (depending on the diastereoisomer) at pH 9 and 20°C, but it is relatively stable in neutral or acidic conditions. Cyfluthrin is subject to photolysis, with half-lives of about 12 days in water and 26 hours in air and, because it can float as a surface film on natural water, its degradation in natural sunlight may also be rapid. On the surface of soils, cyfluthrin has a half-life of 2-3 days, whereas in aerobic or anaerobic soils, its half-life was about 2 months. It is not mobile in soil.

Commercially confidential information on the manufacturing process and on all impurities present at or above 1 g/kg was provided by the proposer, together with limits for impurities in the TC. Limits for impurities were supported by 5 batch analysis. Mass balances were 97.8-98.7%. The guideline maximum provided in the Manual (FAO/WHO, 2002) for the unaccountable fraction is 2% but the Meeting

agreed to accept the data on the basis that errors in measuring the large number of minor impurities probably contributed to the low accountability.

The manufacturer stated that the confidential data presented to the Meeting were essentially identical to those submitted for registration in European countries and the USA. A comparison was made between the data submitted to FAO/WHO and those submitted to for registration in India. The toxicological data submitted were the same. However, the confidential data submitted to FAO/WHO revealed three additional impurities, compared with the data submitted to India. The manufacturer stated that, as part of a programme of refinement of production, quality control and analysis, new 5 batch data had been produced (in which the three additional impurities had been identified) and manufacturing limits for certain other impurities had been revised.

The Meeting agreed that none of the impurities should be considered relevant.

Draft specifications were submitted broadly in accordance with the requirements of the Manual (FAO/WHO, 2002) but the Meeting questioned certain clauses.

The manufacturer proposed that water should be considered a relevant impurity in the TC and WP. The Meeting accepted that, in the case of the WP, water should be limited, to minimize the potential for fusion of the powder particles during storage of the formulation. The manufacturer proposed a limit of 10 g/kg for water in the TC, to minimize the potential for hydrolysis. However, cyfluthrin has extremely low affinity for water, hydrolysis is slow except under alkaline conditions, and, in principle, 10 g/kg water could hydrolyze 240 g/kg cyfluthrin. The Meeting accepted that, for company purposes, the manufacturer may continue to specify the water content but it agreed that water should not be considered as a relevant impurity in the TC, for the purposes of FAO and WHO specifications.

The draft specification for TC included a clause for diastereoisomer composition (which is, in effect, an identity test for cyfluthrin) but this was not included in the formulation specifications. The manufacturer accepted the principle of the requirement but stated that it would have major implications for registrations throughout the world. The normal phase HPLC method for analysis of WP and EW formulations permits determination of the diastereoisomer ratio and the requirement is implicit in clauses for description and identity. The Meeting agreed that a note to the identity clause, drawing attention to the need for determination of the diastereoisomer composition, would be sufficient.

The draft TC specification also included a clause with limits for acidity and alkalinity. Cyfluthrin is readily hydrolyzed under alkaline conditions, so a limit for alkalinity is justified. However, cyfluthrin is stable under acid conditions (the pH range specified for the EW is 2.5-3.5, rather strongly acidic) and the Meeting and manufacturer agreed that a sub-clause for acidity was not necessary.

The clause for pourability of the EW provided a limit based on the rinsed residue but the Manual (FAO/WHO, 2002) specifies only pourability. Rinsing is as much a function of the container as of the formulation, and therefore rinsing test results are not meaningful, so the Meeting and manufacturer agreed that the limit should reflect pourability only.

The clause for wet sieve testing in the draft specification for WP included limits for formulation retention on 40 and 100 μm sieves, in addition to the usual 75 μm test sieve. The manufacturer explained that additional characterization of particulates

had proven necessary for cyfluthrin WP, to ensure that filters and nozzles would not be blocked, and the Meeting accepted the additional sub-clauses.

The analytical methods for identification and determination of cyfluthrin are full CIPAC methods and have been validated for analysis of TC, WP and EW. Test methods for determination of the physico-chemical properties of cyfluthrin were OECD, USEPA and EU, while those for characterization of the formulations were CIPAC methods.

The hazards associated with cyfluthrin have been well characterized. The acute oral LD₅₀ for rats varied from 16 to 1189 mg/kg body weight, depending on the vehicle used, showing that the formulating agent has a strong influence on the acute oral toxicity. Cyfluthrin is toxic by inhalation but acute toxicity by the dermal route is low. Cyfluthrin did not induce skin irritation in rabbits but case reports in humans have shown that local skin irritation can arise from exposure to cyfluthrin formulations. Cyfluthrin caused eye irritation in rabbits. It did not induce dermal sensitization in guinea pigs.

The chronic toxicity of cyfluthrin by dermal route was low, higher by the oral route, and high by the inhalation route. Cyfluthrin showed no potential for carcinogenicity. In a 3-generation study and in two developmental toxicity studies in rats, no effects on reproductive functions were observed and cyfluthrin showed no evidence of teratogenicity or embryotoxicity. Studies on mutagenicity in microbes, with or without metabolic activation, were consistently negative. Cyfluthrin did not induce micronuclei or dominant lethal mutations in mice.

As may be expected for a pyrethroid, cyfluthrin is toxic to fish, aquatic arthropods and honey bees. It is of low toxicity to birds and earthworms.

The WHO hazard classification of cyfluthrin is moderately hazardous.

Toxicological evaluations by the FAO/WHO JMPR and the FAO/WHO JECFA established an ADI for cyfluthrin of 0-0.02 mg/kg body weight, based on the depression of body weight gain in a long-term feeding study on rats. The USEPA concluded that there is reasonable certainty that no harm will result to the general population and to the infants and children from exposure to cyfluthrin residues.

The Meeting noted that, although the EW specification (as amended) is applicable to both agricultural and public health formulations, users must adhere to label recommendations and not use the products interchangeably.

Recommendations

The meeting recommended that:

- (i) the existing FAO specifications for cyfluthrin TC, WP, EW, EC and UL should be withdrawn;
- (ii) the existing WHO specifications for TC, WP and EW should be withdrawn;
- (iii) the proposed specifications for TC and EW (with amendments discussed in the above appraisal and with the cyfluthrin content of the EW restricted to 50 g/kg in the case of WHO) should be adopted by FAO and WHO;
- (iv) the proposed specification for WP (with amendments discussed in the above appraisal and with the cyfluthrin content restricted to 100 g/kg) should be adopted

by WHO;

- (v) The manufacturer should be invited to draft additional specifications for cyfluthrin formulations, if required, for consideration by the 2005 meeting.

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