WHO SPECIFICATIONS AND EVALUATIONS

FOR PUBLIC HEALTH PESTICIDES

PERMETHRIN

(25:75 *cis:trans* isomer ratio)

3-phenoxybenzyl (1*RS*,*3RS*;1*RS*,3*SR*)-3-(2,2 dichlorovinyl)- 2,2-dimethyl-cyclopropane carboxylate

World Health Organization

TABLE OF CONTENTS

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.

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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 Specifications of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 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 under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. WHO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

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

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

PART ONE

SPECIFICATIONS

PERMETHRIN (25:75)

INFORMATION

ISO common name

permethrin (E-ISO), permethrine (F-ISO)

Chemical names

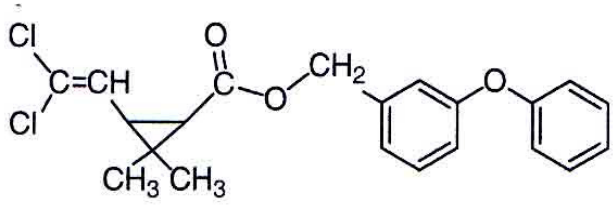
IUPAC: 3-phenoxybenzyl (1*RS*,*3RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclo-propanecarboxylate

CA: (3-Phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate

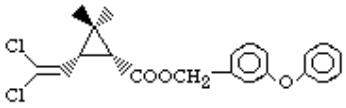
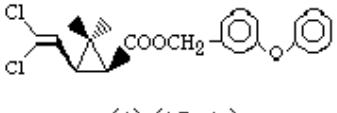
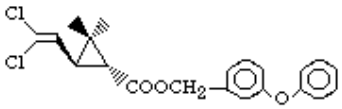
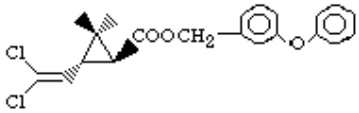
Synonyms

None

Structural formula



Two pairs of diastereomers (each consisting of a racemic pair of enantiomers; see below) are present in a ratio of approximately 25:75

Sl No	Name of isomer	Structure	Proportions
1	1R, *cis*	 (2) (1R,cis)	sum ≈ 25%
2	1S, *cis*	 (4) (1S,cis)	
3	1R, *trans*	 (1) (1R,trans)	sum ≈ 75%
4	1S, *trans*	 (3) (1S,trans)	

Molecular formula

$C_{21}H_{20}Cl_2O_3$

Relative molecular mass

391.3

CAS Registry number

52645-53-1

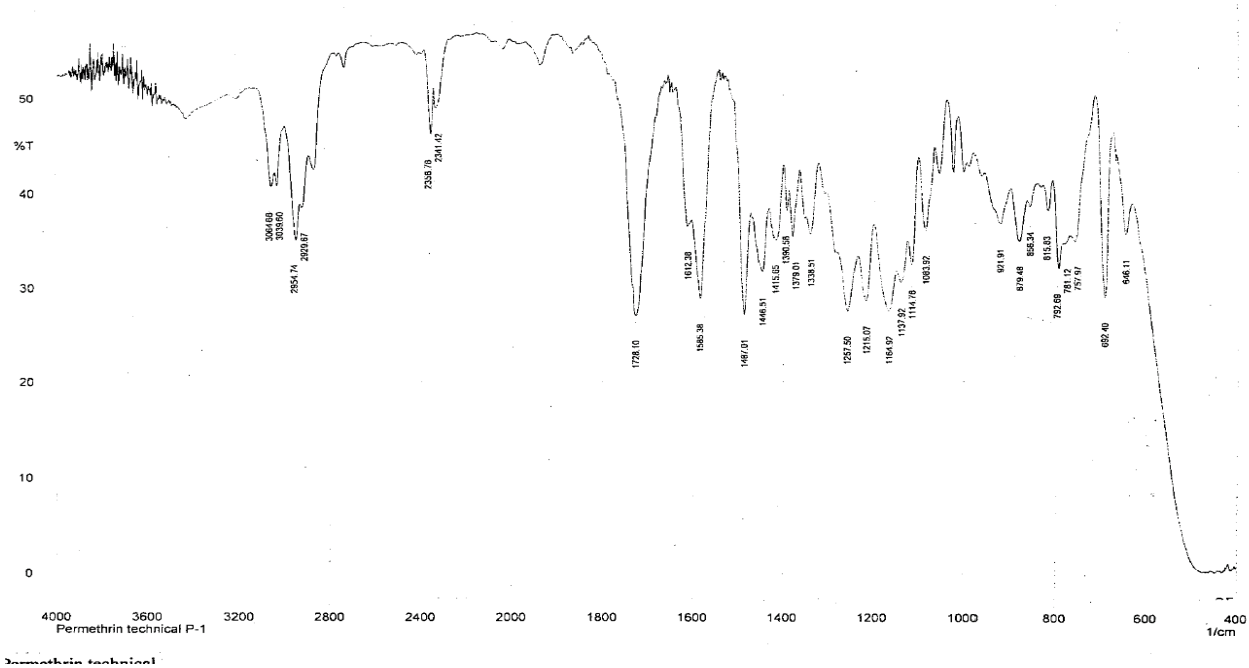
CIPAC number

331

Identity tests

GC retention times, IR spectrum.

Figure 1. IR spectrum of permethrin



25:75 *cis:trans* PERMETHRIN TECHNICAL MATERIAL

WHO specification 331/TC (April 2010*)

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 (331/2009). It should be applicable to TC produced by 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 TC produced by other manufacturers. The evaluation report (331/2009), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of permethrin together with related manufacturing impurities, and shall be a yellow-brown to brown viscous liquid, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (331/TC/M2/2, CIPAC Handbook M, p. 155, 2009)

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 **Permethrin content** (331/TC/M2/3, CIPAC Handbook M, p. 155, 2009)

The permethrin 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 **Permethrin isomer ratio** (331/TC/M2/3, CIPAC Handbook M, p. 155, 2009)

The [1*RS*,3*RS*]:[1*RS*,3*SR*] (*cis:trans*) permethrin isomer ratio shall be declared and, when determined, the average measured ratio shall be in the range 22.5-27.5:77.5-72.5.

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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/.

25:75 *cis:trans* PERMETHRIN EMULSIFIABLE CONCENTRATE

WHO specification 331/EC (September 2011*)

*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 (*331/2010*). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated source. The specification 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 who use TC from other sources. The evaluation report (*331/2010*), as PART TWO, form an integral part of this publication.*

1 Description

The material shall consist of technical permethrin, complying with the requirements of WHO specification 331/TC (April 2010), 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** (331/EC/M/2, 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 **Permethrin content** (331/EC/M/3, Note 1)

The permethrin content shall be declared (g/kg or g/L at 20°C ± 2°C, Note 2) and, when determined, the average content measured shall not differ from that declared by the following tolerances.

Declared content in g/kg or g/l at 20 ± 2°C	Tolerance
up to 25	± 15% of the declared content
above 25 up to 100	± 10% of the declared content
above 100 up to 250	± 6% of the declared content
above 250 up to 500	± 5% of the declared content
Note: In each range the upper limit is included	

2.3 **Permethrin isomer ratio** (331/EC/M/3, Note 1)

The [1*RS*,3*RS*]:[1*RS*,3*SR*] (*cis:trans*) permethrin isomer ratio shall be declared and, when determined, the average measured ratio shall be in the range 22.5-27.5:77.5-72.5.

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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/.

3 Physical properties

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

pH range: 3 to 6.5

3.2 **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
0 h	Initial emulsification complete
0.5 h	"Cream", maximum: 2 ml
2 h	"Cream", maximum: 2 ml "Free oil", maximum: 1 ml
24 h	Re-emulsification complete
24.5 h	"Cream", maximum: 2 ml "Free oil", maximum: 1 ml
Note: in applying MT 36.3, tests after 24 h are required only where results at 2 h are in doubt.	

3.3 **Persistent foam** (MT 47.2, CIPAC Handbook F, p.152, 1995) (Note 4)

Maximum: 50 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 ± 2°C for 7 days, the volume of solid and/or liquid which separate shall not be more than 0.3 ml.

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

After storage at 54 ± 2°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 5) and the product shall continue to comply with the clauses for:

- pH range (3.1).
- emulsion stability and re-emulsification (3.2).

Note 1 The methods extension for identification and determination of permethrin content in EC formulations were presented at the 2010 CIPAC Meeting and were adopted as full CIPAC methods in 2011. Prior to their publication in next Handbook, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org/cipacpub.htm.

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. The test is to be conducted in CIPAC standard water D.

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

EVALUATION REPORTS

PERMETHRIN (25:75)

PERMETHRIN

FAO/WHO EVALUATION REPORT 331/2010

Recommendations

The Meeting recommended that the specification for 25:75 *cis:trans* permethrin EC, proposed by Tagros Chemicals India Limited, as amended, should be adopted by WHO.

Appraisal

The WHO specification for permethrin 25:75 *cis-trans* ratio based on data submitted by Tagros was adopted at the 2009 JMPS Meeting. In the following year, the company submitted data for extension of the WHO specification to EC formulations for public health and this was considered at the JMPS Meeting in 2010.

Identity, content and diastereomer ratio clauses

The methods to confirm the identity of permethrin, primarily independent of *cis-trans* isomer ratio, are based on comparison of retention times of the chromatographic signals produced by the two diastereomers in capillary GC. The *cis* diastereomer (first eluting) is completely resolved from the second eluting *trans* diastereomer. Furthermore, mass spectrometry in combination with gas chromatography can be used as an identity test by comparing the EI mass spectra produced by these diastereomers and comparing them with those of an authentic standard. The methods are a part of the permethrin CIPAC method published in CIPAC Handbook M in 2009. The method is applicable to TC, LN and also to EC. The same method contains a procedure for the calculation of the diastereomer ratio in permethrin by comparing peak areas of the *cis* and *trans* permethrin signals.

The method extension for EC formulations was presented at the 2010 CIPAC Meeting in Slovenia and adopted as full CIPAC method in 2011.

Physical properties and storage stability

The clauses, limits and test methods proposed for physical properties of the EC were in accordance with the requirements of the FAO/WHO specification Manual with an exception: the necessity of a proposed pH range clause, which is not in the TC specification, was questioned by the Meeting. The manufacturer explained that permethrin is in fact not readily amenable to hydrolysis, but high pH may catalyse degradation, and this explanation was accepted by the Meeting. The other clauses were quite straightforward, but the Meeting noted the high but still acceptable amount of persistent foam (50 mL after one minute). Both the stability at 0°C and high temperature stability with their limits were found acceptable.

PERMETHRIN

FAO/WHO EVALUATION REPORT 331/2009

Recommendations

The Meeting recommended the following.

(i) The specification for 25:75 *cis:trans* permethrin TC, proposed by Tagros Chemicals India Limited, should be adopted by WHO.

Appraisal

The Meeting considered data and a draft specification (TC), submitted by Tagros Chemicals India Limited, for new WHO specification for permethrin TC with a *cis:trans* ratio of 25:75. Permethrin is no longer under patent and has been widely manufactured for many years with different *cis:trans* ratios. Technical grade permethrin is composed of 4 stereoisomers, due to the asymmetry at two carbon atoms in the cyclopropane ring, leading to 2 *cis* and 2 *trans* isomers. These designations refer to the respective positions of the substituents at the cyclopropane moiety. The racemic pairs of *cis* and *trans* isomers can be separated using non-chiral techniques but separation of the 2 *cis* or the 2 *trans* enantiomers would require a chiral separation technique and is not done on a routine basis.

Different manufacturing processes lead to different *cis:trans* ratios in technical grade permethrin but, generally, the nominal *cis:trans* ratio is either 25:75 or 40:60. The previously existing FAO (1991) and WHO (1999) specifications for permethrin encompassed both nominal ratios. The data submitted for the present review were in support of WHO specifications for the TC, which encompassed only permethrin with a nominal 25:75 *cis:trans* ratio.

Tagros Chemicals India Limited provided details of the manufacturing processes and 5-batch analysis data, relating to the 25:75 permethrin, together with manufacturing limits for purity and all impurities ≥1 g/kg. Mass balances in the 5-batch analytical data were good (99.6–99.8.%).

The minimum permethrin content of the permethrin TC was 920 g/kg. The data on this permethrin was stated by Tagros Chemicals India Limited to be similar to those submitted by the company for registration of permethrin as a biocide with Health and Safety Executive, UK (HSE). Written confirmation was provided by HSE that the data submitted for registration of permethrin 25:75 was the same as those submitted in support of the WHO specification.

The *cis:trans* isomer ratio of permethrin can influence certain hazard characteristics. For example, the acute oral LD_{50} of 80:20 *cis:trans* permethrin to rats (220 mg/kg bw) is lower than that of 20:80 *cis:trans* permethrin (6000 mg/kg bw) (JMPR 2002), although the acute RfD [2] and ADI [3] apply to all ratios of permethrin isomers. However, there is no evidence to suggest that any of the impurities influence the hazard characteristics and the Meeting agreed that none of the impurities in Tagros permethrin should be designated as relevant.

The analytical methods for determination of the active ingredient (including tests for identity and isomer ratio) are based on capillary GC-FID and internal standardization with triphenylphosphate, which were adopted by CIPAC in 2006, for analysis of permethrin TC and LN. The identity tests utilize IR spectroscopy, which is useful for distinguishing permethrin from other related pyrethroids but does not provide information on *cis:trans* ratio. The CIPAC method published in Handbook M provides both information on total permethrin content as well as on *cis:trans* ratio.

Impurities in permethrin were determined mainly by capillary GC with flame ionization detection. Sufficient validation data were elaborated to demonstrate that the methods used provided reliable results for establishing valid limits for impurities in the technical material.

Permethrin is a viscous liquid at room temperature; it does not dissociate in water and has low water solubility and volatility. It is stable to hydrolysis at pH 4-7 but is slowly hydrolysed at pH 9. Permethrin is stable at higher temperatures and, although photochemical degradation was observed in laboratory studies, this was stated by Tagros Chemicals India Limited to be of negligible significance in the field.

The Meeting considered the proposed FAO/WHO specification for 25:75 *cis:trans* permethrin TC, noting that the old (1991) FAO and (1999) WHO specifications applied to permethrin of both 25:75 and 40:60 ratios, respectively.

The Meeting welcomed a clarification and narrowing of the tolerance for permethrin isomer ratio [4].

The old FAO (1991) and WHO (1999) specifications for permethrin TC included clauses for control of water, acetone-insolubles and acidity. None of these clauses were included by the proposer in the specification and it was accepted by the Meeting. Moreover permethrin is stable under acidic conditions.

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[2] The acute RfD for permethrin was set on the basis of acute neurotoxicity of 40:60 *cis:trans* permethrin, not on the acute oral LD_{50} (JMPR 2002).

[3] The ADI for permethrin was originally set on the basis of data derived from 40:60 *cis:trans* permethrin but later confirmed as appropriate for 25:75 *cis:trans* permethrin (JMPR 1987).

[4] The 1991 FAO specification provided a tolerance of ±10% for the 40:60 ratio and the 1999 WHO specification provided a tolerance of ±10% for all ratios. Both were ambiguous because, with respect to a nominal 40:60 ratio, the tolerance might be interpreted as encompassing a range of 36-44:64-56, or 34-46:66-54, or 30-50:70-50.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 331/2009

Uses

Permethrin is a non-systemic pyrethroid insecticide, with contact and stomach action and some repellent effects. Its main uses are in public and animal health.

Identity of the active ingredient

ISO common name

permethrin (E-ISO), permethrine (F-ISO)

Chemical names

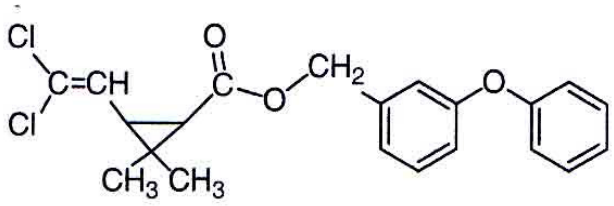
IUPAC: 3-phenoxybenzyl (1*RS*,*3RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclo-propanecarboxylate

CA: (3-Phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate

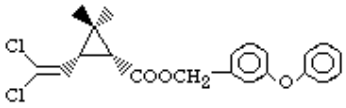
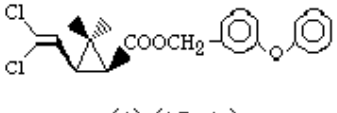
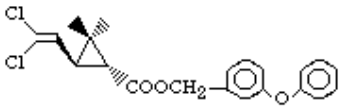
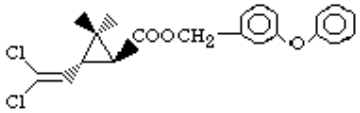
Synonyms

None

Structural formula



Two pairs of diastereomers (each consisting of a racemic pair of enantiomers; see below) are present in a ratio of approximately 25:75

Sl No	Name of isomer	Structure	Proportions
1	1R, *cis*	 (2) (1R,cis)	sum ≈ 25%
2	1S, *cis*	 (4) (1S,cis)	
3	1R, *trans*	 (1) (1R,trans)	sum ≈ 75%
4	1S, *trans*	 (3) (1S,trans)	

Molecular formula

$C_{21}H_{20}Cl_2O_3$

Relative molecular mass

391.3

CAS Registry number

52645-53-1

CIPAC number

331

Identity tests

GC retention times, IR spectrum.

Physico-chemical properties of permethrin

Table 1. Physico-chemical properties of technical grade permethrin having a *cis:trans* ratio of 25:75

Parameter	Value(s) and conditions	Purity % (*cis:trans)*	Method	Reference and date
Vapour pressure	0.749 mPa at 20℃	92.4 *(25:75)*	EEC A4	Report No. 3348/02 (14.12.2002)
Boiling point, Melting point, and/or temperature of decomposition	Boiling point: 277.3 ± 0.6℃ at 667mm Hg Melting point: 32-35 ℃	92.4 *(25:75)* 94.20 *(25:75)*	EEC A2 OECD 102	Report No. 3348/02 (14.12.2002) Report No. 15306 (17.01.2005)
Solubility in water	180 µg/l at 20 ± 1℃ at pH 7	92.4 *(25:75)*	OECD 105	Report No. 3348/02 (14.12.2002)
Octanol/water partition coefficient	log P_{OW} = 5.9 at 23 ± 1℃ at pH 7	92.4 *(25:75)*	EEC A8	Report No. 3348/02 (14.12.2002)
Hydrolysis characteristics	Abiotic aqueous hydrolysis should not contribute significantly to degradation at pH 4, 7, and 9, with <10% hydrolysis at the end of the 5-day study.	94.0 *(25:75)*	OECD 11	Report No. 14375 (12.05.2004)
Photolysis characteristics	The degree of photolytic degradation of permethrin was determined by polychromatic irradiation at wavelength above 290 nm with filtered xenon arc lamp. Here shortest half-lives between 6.42 x 105 and 3.35 x 1014 d were calculated.	93.61 *(25:75)*	Draft OECD Guideline	Report No. GAB-012/7-05, (10.07.2006)
Dissociation Characteristics	Does not dissociate	-	-	-

Table 2. Chemical composition and properties of technical permethrin having a *cis:trans* ratio of 25:75 (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 99.63-99.82%, and percentage of unknowns was virtually zero %.
Declared minimum permethrin content	920 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities < 1 g/kg and maximum limits for them	None
Stabilisers or other additives and maximum limits for them	None
Melting temperature range of the TC	32-35 ℃

Pure permethrin consists of a colourless light-yellow semi-solid, and the TC occurs as a yellow-brown to brown viscous liquid.

Hazard summary

Tagros 25:75 permethrin data were submitted by Agropharm Limited, UK to HSE, UK in 2003. Tagros data were evaluated and HSE accepted Tagros permethrin for use as a biocide under non-agricultural products approved under the Pesticides Regulations,1986 (permethrin is not included in the EU Regulation 91/414 Annex I for use as agricultural pesticide and hence permethrin containing formulations must not be used in agriculture).

Permethrin has been evaluated for toxicology by the FAO/WHO JMPR on a number of occasions, over many years. The ADI of 0-0.05 mg/kg bw, previously set by the JMPR, was extended from 40:60 permethrin to include 25:75 permethrin (JMPR 1987) and an acute ARfD of 1.5 mg/kg bw was subsequently allocated (JMPR 2002). The WHO hazard classification of permethrin is Class II, moderately hazardous (WHO 2002).

Formulations and co-formulated active ingredients

The main formulation types available are EC, DP and WP for agricultural use and EC and UL for public health use.

Methods of analysis and testing

The analytical method used for the identification and determination of the active ingredient (including identity tests) is the CIPAC method (CIPAC Handbook M, p. 155 for TC, EW and LN, and Handbook C, p. 2173, 1985 for WP, EC, WG, DP. Permethrin impurities were determined by capillary GC with FID detection.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD and US-EPA.

The permethrin content and isomer ratio are determined as per CIPAC 333/TC/M2/3 using GC-FID and the external standard method.

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as permethrin in g/kg or g/L, as the sum of *cis* and *trans* isomers, present in a nominal ratio of 25:75 (with 10% tolerance range of 22.5-27.5:77.5-72.5).

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes: Tagros Chemicals India Limited has provided written confirmation that the toxicological and ecotoxicological data included in the following summary were derived from permethrin having impurity profiles similar to those referred to in Table 2, above.

Table 3. Toxicology profile of permethrin technical material, based on acute toxicity, irritation and sensitization

Species	Test	Guideline, duration, doses and conditions	Result	% Purity (*cis:trans* ratio)	Reference or company report/date
Wistar Rats (*Rattus norvegicus*) (f)	Oral	Observation: 14 days Dosage: 2000 mg/kg bw Guideline: OECD 423	LD_{50} > 2000 mg/kg bw	93.35 (25:75)	Report No. 08236 / 26.09.2008
Wistar Rats (*Rattus norvegicus*) (m,f)	Dermal	Observation: 14 days Dosage: 2000 mg/kg bw Guideline: OECD 402	LD_{50} = > 2000 mg/kg bw	93.01 (25:75)	Report No. 06019 / 22.05.2006
Wistar Rats (*Rattus norvegicus*) (m,f)	Inhalation	Observation: 14 days Dosage: 0.45 mg/l air Guideline: OECD 403	LC_{50} > 0.45 mg/l of air at breathing zone (m & f – combined)	93.35 (25:75)	Report No. 08239 / 26.09.2008
New Zealand White rabbit (*Oryctolagus cuniculus*) (f)	Skin irritation	Observation: 1, 24, 48 & 72 h after patches were removed Dosage: 0.5 ml Guideline: OECD 404	Slight Irritant	93.35 (25:75)	Report No. 08237 / 26.09.2008
New Zealand White rabbit (*Oryctolagus cuniculus*) (f)	Eye irritation	Observation: 1, 24, 48 & 72 h after instillation Dosage: 0.1ml Guideline: OECD 405	Non-irritant	93.35 (25:75)	Report No. 08238 / 26.09.2008
Guinea Pigs (Dunkan Hartley) (m)	Skin sensiti-sation	Observation: 30 days Doses: Induction: 2000 mg Challenge: 500 mg Guideline: OECD 406	Non-sensitiser	93.7 (25:75)	Report No. 07234 / 27.10.2007

Permethrin has moderate acute toxicity when administered orally to the male and female rats. Clinical signs observed in groups treated with technical permethrin were moribund state, lethargy, tremors, nostril discharge, exophthalmos, diarrhoea and pilo-erection. In rats, permethrin is less toxic when the dermal test is applied. Permethrin is a mild-irritant to skin and non-irritant to eye of rabbits, although in the latter case, it was found in a study to be “minimally irritating” to the rabbit eye. Permethrin is non-sensitizer in the guinea pigs.

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

Species	Test	Guideline, duration, doses and conditions	Result	% Purity (*cis:trans* ratio)	Reference or company report/ date
Wistar Rats (*Rattus norvegicus*) (m,f)	28-day dietary range finding	Duration: 28 days Dosage: 0, 200, 800, 3000 & 10000 ppm Guideline: OECD 407	NOAEL = 800 ppm (68.6 mg/kg/ bw/day)	92.4 (25:75)	Report No. 3350/02 / 16-11-2002
Wistar Rats (*Rattus norvegicus*) (m,f)	90-day oral toxicity	Duration: 90 days Dosage: 0, 100, 600 & 2000 ppm Guideline: OECD 408	NOAEL = 100 ppm (8.6 mg/kg/ bw/day)	92.4 (25:75)	Report No. 3351/02 / 29-04-2003
Swiss albino mice (*Mus musculus*) (m,f)	Sub-acute oral toxicity	Duration: 90 days Dosage: 0, 20, 40 and 80 mg/kg bw Guideline: OECD 408	NOAEL = 40 mg/kg bw/day	94.04, 93.61 (25:75)	Report No. 05045 / 15-09-2006
Wistar rats (*Rattus norvegicus*) (m,f)	Sub-acute dermal toxicity	Duration: 90 days Dosage: 0, 500,1000 and 2000 mg/kg bw Guideline: OECD 411	NOAEL = 1000 mg/kg bw/day	94.04 & 92.86 (25:75)	Report No. 14996 / 05-04-2006
Wistar rats (*Rattus norvegicus*) (m,f)	Sub-acute inhalation toxicity	Duration: 90 days Concentration: 0, 0.15, 0.32 and 0.64 mg a.i./l air Guideline: OECD 413	NOAEL = 0.22 mg a.i./l air	94.04 93.1 92.2 & 93.61 (25:75)	Report No. 14995 / 03-04-2006
Wistar rats (*Rattus norvegicus*) (m,f)	Combined chronic toxicity/ carcino-genicity	Study duration: 2 years Doses: 1500 ppm, 3000 ppm and 6000 ppm Guideline: OECD 453	Non-carcino-genic NOAEL = 1500 ppm (Equivalent to 75 mg/kg bw)	94.2 92.86 92.29 93.61 & 93.01 (25:75)	Report No. 14994 / 17-11-2007
New Zealand White rabbit (*Oryctolagus cuniculus*) (f)	Terato-genicity toxicity	Duration: 10 months Dosage: 0, 125, 250 and 500 mg/kg bw per day Guideline: OECD 414	Not teratogenic-NOAEL for terato-genicity = 500 mg/kg bw/d NOAEL for maternal toxicity = 250 mg/kg bw/d	94.04 & 92.29 (25:75)	Report No. 14997 / 29-11-2006
Wistar rats (*Rattus norvegicus*) (m,f)	Oral two generation reprod-uction toxicity	Duration: 10 months Dosage: 0, 125, 250 and 500 mg/kg bw Guideline: ECD 416	Not a reprotoxic NOAEL = 500 mg/kg bw/day	94.20 94.04 & 92.29 (25:75)	Report No. 14998 / 18-12-2006

Permethrin is not carcinogenic when tested on rats. It is not a reprotoxic for rats and not teratogenic for rabbits.

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

Species	Test	Guideline, duration, doses and conditions	Result	% Purity (*cis:trans* ratio)	Reference or company report/date
Salmonella typhimurium TA100, TA102, TA1535, TA98 and TA1537	Bacterial reverse mutation assay (*In vitro*)	Dosage: 0.039, 0.078, 0.156, 0.313 and 0.625 µl/plate Guideline: OECD 471	Negative	93.35 (25:75)	Report 08241 / 03-10-2008
Cell line: CHO-K1 (Ovary, Chinese hamster (*Cricetulus griseus*)	Mammalian cell gene mutation (*In vitro*)	Dosage: 20, 60, 180 and 540 µg/ml with S-9 (Trial 1 & 2) 25, 63, 156 and 391 µg/ml without S-9 (Trial 1) 20, 55, 151 and 416 µg/ml without S-9 (Trial 2) Guideline: OECD 476	Negative	92.4 (25:75)	Report 3353/02 / 16-11-2002
CHO-K1 cell line (Ovary, Chinese hamster (*Cricetulus griseus)*	Mammalian chromoso-mal aber-ration test (*In vitro*)	Dosage: 70, 210 and 630 µg/ml with S-9 (Trial 1 & 2) 40, 120 and 360 µg/ml without S-9 (Trial 1) 15, 45 and 135 µg/ml without S-9 (Trial 2) Guideline: OECD 473	Negative	92.4 (25:75)	Report 3352/02 / 11-03-2003
Swiss Albino mouse *(Mus musculus)*	Mammalian bone marrow chromoso-mal aber-ration (*In vivo*)	Dosage: 100, 1000 and 2000 mg/kg bw Guideline: OECD 475	Negative	93.35 (25:75)	Report 08242 / 03.10.2008

Permethrin was tested for genotoxicity in a range of assays, both *in vitro* and *in vivo*. There was no evidence of genotoxicity in any of these assays.

Table 6. Ecotoxicology profile of permethrin technical material

Species	Test	Guideline, duration, doses and conditions	Result	% Purity (*cis:trans* ratio)	Reference or company report/date
Water flea (*Daphnia magna*)	48-hr Acute immobilization	Duration: 48 hr Dosage: 0.1, 0.2, 0.5, 1.1 and 2.3 µg /l water Guideline: OECD 202	EC_{50} = 0.32 µg /l water	93.35 (25:75)	Report 08240 / 27-09-2008
Water flea (*Daphnia magna*)	Reproduction test - semi-static exposure	Duration: 21 days Dosage: 3.0, 8.1, 22, 59 and 159 ng/l water Guideline: OECD 211	NOEC: 8.1 ng/l (Nominal) NOEC: 4.7 ng/l (Mean) LC10: 7.2 ng/l	93.61 (25:75)	Report GAB-012/4-21 / 19-06-2006
Freshwater fish (*Poecilia reticulate*)	Acute toxicity	Duration: 96 hr Dosage: 0, 2.2, 4.0, 7.1, 12.8 and 23.1 µg/l water Guideline: OECD 203	LC_{50} = 8.9 µg/l water	94.10 (25:75)	Report 13870 / 18-08-2004
Zebra fish (*Danio rerio*)	Early life stage toxicity test	Duration: 35 days Dosage: 0.06, 0.13, 0.25, 0.50 and 1.00 µg/l water Guideline: OECD 210	NOEC: 0.41 µg/l water LC10: 0.59 µg/l water	93.61 (25:75)	Report GAB-012/4-18 / 14-06-2006
Earthworm (*Lampito mauritii*)	Acute toxicity	Duration: 14 days Dosage: 75 – 1200 mg/kg dry weight soil Guideline: OECD 207	LC_{50} = > 1200 mg/kg dry weight soil	93.01 (25:75)	Report 06039 21-07-2006
(*Allium cepa, Avena sativa, Beta vulgaris, Cucumia sativus, Glycine max* & *Helianthus annus*)	Terrestrial plant tests - seedling emer-gence & seedling growth tests	Duration: 21 days Dosage: 0, 0.0128, 0.064, 0.32, 1.6, 8, 40, 200 & 1000 mg/kg oven dried soil Guideline: OECD 208 (A)	*Allium cepa* = LOER 1000, NOER 200 *Avena sativa* = LOER 8, NOER 1.6 *Beta vulgaris* = LOER 200, NOER 40 *Cucumia sativus* = LOER >1000, NOER 1000 *Glycine max* = LOER >1000, NOER 1000 *Helianthus annus* = LOER 40, NOER 8	93.07 (25:75)	Report 20064034/S1-FGSE / 10-08-2006
Soil microflora	Nitrogen transformation test	Duration: 42 days Dosage: 1.83 and 9.17 mg/kg dry soil Guideline: OECD 216	Permethrin technical had no effect on the soil nitrogen turnover and the short-term respiration in a field soil tested up to 6.875 kg of Permethrin technical/ha (corresponding to 5-fold application rate) 42 days after application.	93.61 (25:75)	Report 20051446/01-ABMF / 16-05-2006
Allium cepa, Avena sativa, Beta vulgaris, Cucumia sativus, Glycine max & *Helianthus annus*	Terrestrial plant test-vegetative vigour test	Duration: 21 days Dosage: 6875 g test item/ha Guideline: OECD 208 (B)	The most sensitive species with significant effect by permethrin technical on biomass reduction was *Allium cepa*. Since for none of the species tested the effects on biomasses were > 20%, permethrin technical is classified as at low risk.	93.07 (25:75)	Report 20064034/S1-FGVV / 10-08-2006

Permethrin is highly toxic to fish, but is considered low risk towards terrestrial plants. However, under field conditions, lasting adverse effects are not likely to occur under recommended conditions of use.

ANNEX 2

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