WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

PERMETHRIN

(40:60 *cis:trans* isomer ratio)

3-phenoxybenzyl (1*RS*,*3RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

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.

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 under the WHO Prequalification Team - Vector control products (PQT-VC) website.

PART ONE

SPECIFICATIONS

PERMETHRIN 40:60 *cis:trans*

INFORMATION

ISO common names

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

Chemical names

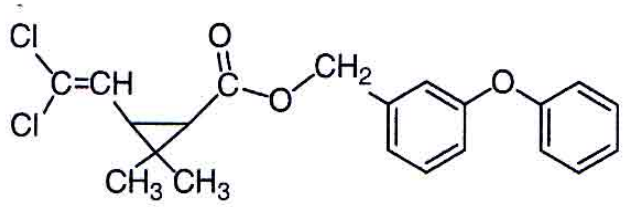
IUPAC: 3-phenoxybenzyl (1*RS*,*3RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

CA: (3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

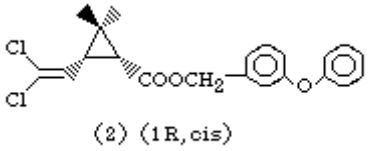
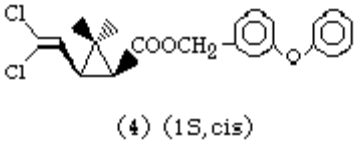
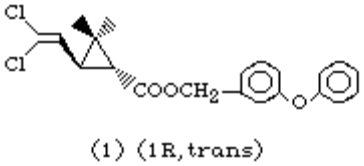
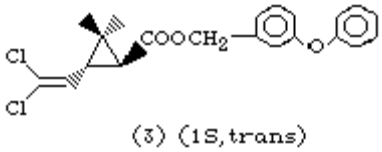
Synonyms

None

Structural formula



Two pairs of diastereomers (each consisting of a racemic pair of enantiomers; see below) are present in a ratio of approximately 40:60

Sl No	Name of isomer	Structure	Proportions
1	1R, *cis*	 (2) (1R,cis)	sum ≈ 40%
2	1S, *cis*	 (4) (1S,cis)	
3	1R, *trans*	 (1) (1R,trans)	sum ≈ 60%
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

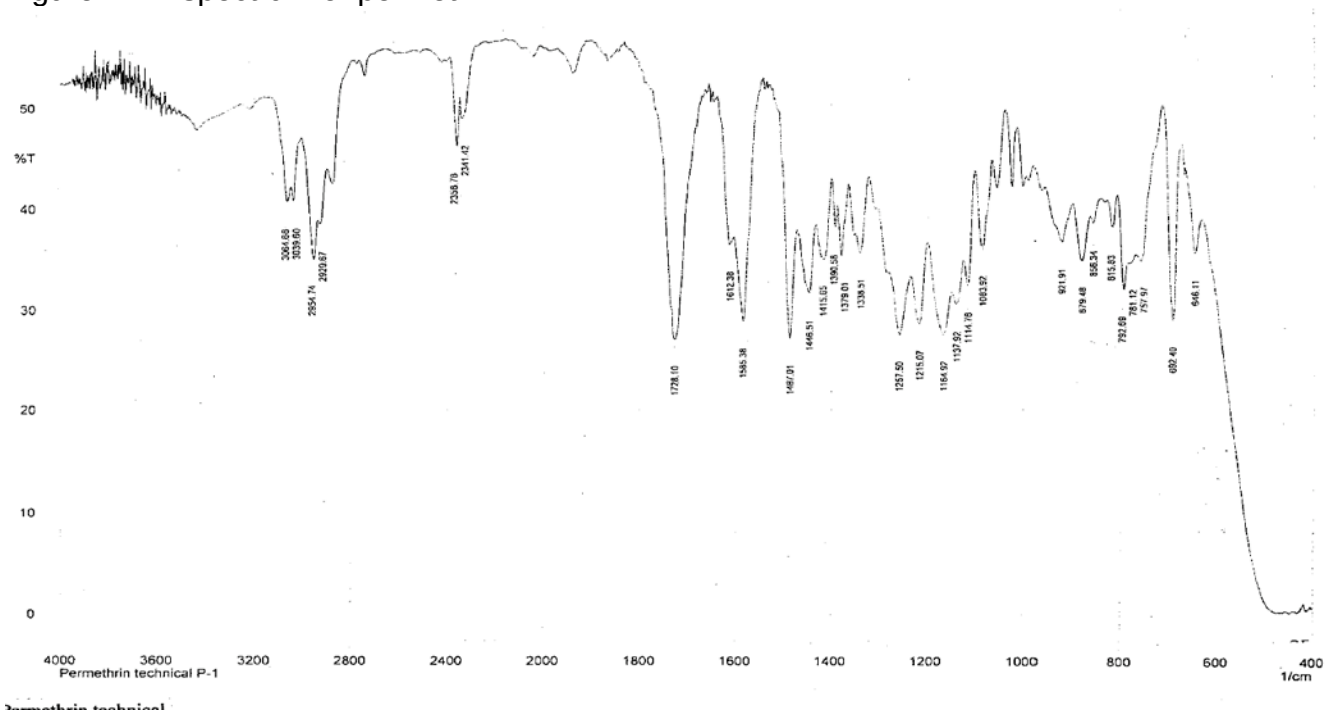
CIPAC number

331

Identity tests

GC retention times, IR spectrum.

Figure 1. IR spectrum of permethrin



WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

PERMETHRIN (40:60 *cis:trans*) TECHNICAL MATERIAL

WHO Specification 331/TC (September 2015*)

This specification, which is PART ONE of this publication, is based on evaluations of data submitted by the manufacturers whose names are listed in the evaluation reports (331/2008, 331/2012, 331/2015). It should be applicable to TC produced by these manufacturers 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 TC produced by other manufacturers. The evaluation reports (331/2008, 331/2012, 331/2015), as PART TWO, forms 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 950 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 30:70 to 50:50.

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* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Team - Vector control products (PQT-VC) website.

PART TWO

EVALUATION REPORTS

PERMETHRIN (40:60 *cis:trans*)

PERMETHRIN

FAO/WHO EVALUATION REPORT 331/2019

Recommendations

The Meeting recommended the following:

(i) The permethrin 40:60 TC, as proposed by Gharda Chemicals Ltd., should not be accepted as equivalent to the permethrin 40:60 reference profile.

(ii) The FAO specification for permethrin 40:60 TC should not be extended to encompass the material produced by Gharda Chemicals Ltd.

(iii) The WHO specification for permethrin 40:60 TC should not be extended to encompass the material produced by Gharda Chemicals Ltd.

Appraisal

The Meeting considered data and supporting information submitted in November 2017 by Gharda Chemicals Ltd. (Gharda) for the determination of the equivalence for permethrin TC with a nominal *cis/trans* ratio of 40:60. The data submitted were broadly in accordance with the requirements of the Manual on development and use of FAO and WHO specifications for Pesticides (2016, 3rd revision of the 1st Edition).

The Meeting was provided with commercially confidential data on the manufacturing process, the manufacturing specification and 5-batch analysis data for permethrin and all detectable impurities at or above 1 g/kg. The manufacturing process used by Gharda is fairly similar to those of the reference processes used by Sumitomo and Bilag, respectively.

Mass balances ranged from 989.7 to 992.5 g/kg in the 5-batch data. The maximum limits for the impurities were supported by the 5-batch data and statistically justified. The proposer declared the minimum purity of the permethrin 40:60 TC as 950 g/kg which is statistically justified and complies with the existing FAO and WHO specifications (950 g/kg).

The manufacturing process, impurity profile and five batch analyses data were compared to those submitted in support of the reference profile (Bilag/Sumitomo). The permethrin 40:60 TC manufactured by Gharda was found to differ from the impurity profile of the reference. It contains an additional impurity (structurally related to permethrin yet having a trichloromethyl moiety) that was not present above 1 g/kg in the reference profile. That new impurity was screened for toxicological alerts by two independent (Q)SAR models, the OECD toolbox and DEREK NEXUS - both models indicated a carcinogenic alert for the new impurity.

The Meeting concluded that the presence of this new impurity could not be *a priori* discounted. A decision on equivalence based on Tier-1 data was therefore not possible and the evaluation had to be taken to Tier-2.

A mutagenicity study (Ames test) for permethrin 40:60 TC has been conducted as Tier-1 data. Permethrin 40:60 TC does not show mutagenicity in *in vitro* bacterial assays (OECD 471).

Gharda had submitted a data package on the acute hazard profile of its permethrin TC. The comparison of the results of the toxicity studies showed that the TC produced by Gharda did not indicate that it was more hazardous than the reference TC in any of the tests.

The Meeting concluded that the permethrin 40:60 TC produced by Gharda was not equivalent to the permethrin reference TC based on Tier-1 evaluation due to the presence of a new impurity where two independent (Q)SAR models indicated a significant extension of the hazard. For this reason, the Meeting did not recommend the extension of the existing FAO and WHO TC specifications to the technical material produced by Gharda. The Meeting also recommended that the evaluation report should be published.

This being communicated to Gharda, the company requested the non-equivalence by Tier-2 to be reconsidered by the Meeting. The Meeting agreed to that request, subject to providing additional toxicity studies that might allow to confirm or rebut the (Q)SAR alert for carcinogenicity by testing that impurity by the COMET assay (OECD TG 489) and for neurotoxicity (research paper of Wolansky M. J. *& et al.* 2006). The outcome of these studies would then be discussed at the 2019 JMPS Closed Meeting.

In addition, the Meeting also noted that the limit of quantitation for a potentially relevant impurity called permethric acid anhydride (PMAA) in the the 5-batch data was 0.5 g/kg. This impurity had recently been identified as class 1A respiratory sensitizer present in transfluthrin. That pyrethroid shares the structure of the acid moiety - permethric acid - with permethrin, and thus it would be relevant if its concentration would be ≥ 0.1 g/kg. It could therefore not be excluded PMAA being a relevant impurity in the TC produced by Gharda. Therefore, Gharda did a preliminary study based on the published peer validated method for PMAA developed for transfluthrin although with some significant deviations for e.g. column, mobile phase and temperature and found, that under these conditions PMAA coelutes with the *trans*-permethrin stereoisomer and the method could not be used for permethrin. This was not further considered by the Meeting.

Later in early 2019 however, the company withdrew its commitment to have the studies commissioned for later submission to the JMPS Panel. With that renouncement (mail of S. Kumar, Gharda, to FAO, dated February 28, 2019), the 2018 conclusions of the JMPS Closed Meeting were considered as accepted by the company. The submission was rediscussed at the 2019 JMPS Closed Meeting with the reiterated recommendation, to proceed with the publication of the amended evaluation report on non-equivalence.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 331/2019

Physico-chemical properties of permethrin

Table 1. Chemical composition and properties of 40:60 *cis:trans* permethrin technical material (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were in the range of 989.7 g/kg to 992.5 g/kg
Declared minimum 40:60 *cis:trans* permethrin content	950 g/kg
cis:trans isomer ratio	40:60
Relevant impurities ≥ 1 g/kg and maximum limits for them	One impurity may be relevant
Relevant impurities < 1 g/kg and maximum limits for them	Permethric acid anhydride (PMAA), ≥ 0.1 g/kg
Stabilisers or other additives and maximum limits for them:	None
Melting temperature range of the TC	3 - 4°C

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

(i) The proposer confirmed that the toxicological data included in the summary below were derived from 40:60 *cis:trans* permethrin technical material having impurity profiles similar to those referred to in the table above.

(ii) The conclusions expressed in the summary below are those of Gharda Chemicals Limited unless otherwise specified.

Table 2. Toxicology profile of 40:60 *cis:trans* permethrin technical material, based on acute toxicity, irritation and sensitization

Species	Test	Purity % (*cis:trans* ratio)	Guideline, duration, doses and conditions	Result	Study number
Rat, Wistar	Acute oral	95.0% (40:60)	OECD 423	LD_{50} : >300-2000 mg /kg bw	T.PMO.073
Rat, Wistar	Acute dermal	95.0% (40:60)	OECD 402	LD_{50} : >2000 mg/kg bw	T.PMO.074
Rat, Wistar	Acute Inhalation	95.0% (40:60)	OECD 403	LC_{50} (4 hrs) : > 2.65 mg/L air (maximum attainable concentration)	T.PMO.078
Rabbit, New Zealand white	Dermal irritation	95.0% (40:60)	OECD 404	Non-irritant to rabbit skin	T.PMO.075
Rabbit, New Zealand white	Eyes irritation	95.0% (40:60)	OECD 405	Non-irritant to rabbit eyes	T.PMO.076
Guinea pig, Albino Dunkin Hartley	Skin sensitisation	95.0% (40:60)	OECD 406	Weak sensitizer (Grade 1)	T.PMO.077

Table 3. Mutagenicity profile of 40:60 *cis:trans* permethrin technical material based on *in vitro* tests

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number[4]
S*alomonella typhimurium* Strains TA 1535 TA 1537 TA 98 TA 100 TA 102	Bacterial Reverse Mutation Test	n.a.	OECD 471 Test concentrations: 0.038, 0.119, 0.376, 1.187 and 3.75 mg/plate, both in presence (+S9) and in absence (-S9) of metabolic activation	Non-mutagenic	-

ANNEX 2. REFERENCES

Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
M. J. Wolansky *et. al.*	2006	Relative Potencies for Acute Effects of Pyrethroids on Motor Function in Rats. Toxicological Sciences 89(1), 271-277.
FAO/WHO	2016	Manual on development and use of FAO and WHO specifications for pesticides. March 2016-third revision of the First Edition. FAO Plant Production and Protection Paper 228. www.fao.org/ag/AGP/AGPP/Pesticid/Default.htm
	2012	Permethrin 40:60: Laboratory Study of Hydrolysis in Buffer Solutions of pH 4, 7 and 9. Study No: 12232. Gharda Report No.: C.PMO.077. GLP. IIBAT. Unpublished report.
	2012	Acute oral toxicity study in rats with Permethrin 40:60. Study No: 3377. Gharda Report No.: T.PMO.073. GLP. Unpublished report.
	2012	Acute dermal toxicity study in rats with Permethrin 40:60. Study No: 3378. Gharda Report No.: T.PMO.074. GLP. Unpublished report.
	2012	Acute inhalation toxicity study in rats with Permethrin 40:60. Study No: 3382. Gharda Report No.: T.PMO.078. GLP. Unpublished report.
	2012	Acute dermal irritation/corrosion study in rabbits with Permethrin 40:60. Study No: 3379. Gharda Report No.: T.PMO.075. GLP. Unpublished report.
	2012	Acute eyes irritation/Corrosion study in rabbits with Permethrin 40:60. Study No: 3380. Gharda Report No.: T.PMO.076. GLP. Unpublished report.
	2012	Contact hypersensitivity in albino Guinea pigs, Maximization test (Magnusson and Kligman Method) with Permethrin 40:60. Study No: 3381. Gharda Report No.: T.IXO.077. GLP. Unpublished.
	2017	Bacterial Reverse Mutation assay with Permethrin 40:60 Technical. Study No: 7202. Gharda Report No.: T.PMO.082. GLP. Unpublished.
	2018	Analysis & Certification of Limits for Permethrin 40:60 Technical, Gharda Report No 17025, GLP. Unpublished.

PERMETHRIN

FAO/WHO EVALUATION REPORT 331/2015

Recommendations

The Meeting recommended the following.

(i) The permethrin 40:60 TC as proposed by Jiangsu Yangnong Chemical Co. Ltd. should be accepted as equivalent to the permethrin 40:60 reference profile.

(ii) The FAO permethrin 40:60 TC specification should be extended to encompass the material produced by Jiangsu Yangnong Chemical Co. Ltd.

(iii) The WHO permethrin 40:60 TC specification should be extended to encompass the material produced by Jiangsu Yangnong Chemical Co. Ltd.

Appraisal

The Meeting considered data and information submitted by Jiangsu Yangnong Chemical Co. Ltd. (Yangnong) in 2014 in support of extension of the existing FAO and WHO specifications for permethrin TC with a nominal *cis/trans* ratio of 40 to 60. The data submitted by Yangnong were in accordance with the requirements of the Manual on development and use of FAO and WHO specifications for pesticides (November 2010 - second revision of the First Edition) (Section 3.2).

The Meeting was provided by Yangnong with commercially confidential data on the manufacturing process, the manufacturing specification and 5-batch analysis data for permethrin and all detectable impurities at or above 1 g/kg. The manufacturing process used by Yangnong differs to those of the reference processes by Sumitomo and Bilag, respectively.

Yangnong stated that their permethrin TC has been submitted for registration in China. The confirmation of registration and a comparison of the confidential data submitted to the authority in China has been received (e-mail Chen T., May 2015).

The 5-batch analysis study was performed according to GLP guidelines. The CIPAC method 331/TC/M2/3 (capillary GC with flame ionization detection and internal standard) was used for determination of total permethrin and *cis/trans* ratio. The permethrin manufacturing impurities were determined by GC-FID and GC-MS, except for water that was determined using the CIPAC Karl Fischer method. All the analytical methods used in the 5-batch analysis study were fully validated on their specificity, linearity of response, accuracy, repeatability and limits of detection and quantification (for impurities).

The minimum purity of permethrin 40/60 in the TC is 950 g/kg and complies with the existing FAO/WHO specification of 950 g/kg. Mass balances were 98.6 – 99.4 %, with no unknowns detected.

Despite the manufacturing process is different from that of the references, the impurity profile was similar, with some minor exceptions. In all processes, alkylated aromatic solvents are used. The solvent used in the Yangnong process is a related

but different solvent, but 5-batch data show that residues of that solvent are efficiently removed (below 1 g/kg) what brings it below the generic threshold of 1 g/kg.

The Meeting was provided with a study on mutagenicity as determined by Ames test on *Salmonella typhimurium* (reverse mutation using various strains). The results of the Ames tests allowed the conclusion that no mutagenic effect could be observed.

On basis of all chemical evidence provided by Yangnong (manufacturing process, impurity profile, 5-batch analysis data) and the mutagenicity data, the Meeting concluded that the Yangnong permethrin 40:60 TC can be considered as equivalent by Tier-1 to the reference profile supporting the existing FAO and WHO specifications (FAO/WHO evaluation report 331/2008) and can be accommodated in the existing specification for permethrin 40:60.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 331/2015

Physico-chemical properties of permethrin

Table 1. Chemical composition and properties of 40:60 *cis:trans* permethrin technical material (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were 98.6-99.4 %.			
Declared minimum 40:60 *cis:trans* permethrin content	950 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			
Parameter	Value and conditions	Purity %	Method reference	Study number
Freezing temperature of the TC	-12 °C with normal atmospheric pressure	96.5	CIPAC MT 1	NC-2014-184
Solubility in organic solvents	250 g/L n-heptane 250 g/L p-xylene 250 g/L 1,2-dichloroethane 133-160 g/L propan-2-ol 250 g/L acetone 250 g/L ethyl acetate All at 25 °C.	96.5	CIPAC MT 181	3514090003

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

Test methods for determination of permethrin content and *cis:trans* isomer ratio of the technical active ingredient were CIPAC.

Physical properties

The 40:60 *cis:trans* permethrin technical materials 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.

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, specifically defined as a mixture of *cis*- and *trans*-isomers present in a nominal [1*RS*,3*RS*]:[1*RS*,3*SR*] (*cis*:*trans*) ratio of 40:60, with a permitted range for the average measured ratio of 30:70 to 50:50.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note:

The proposer confirmed that the toxicological data included in the summary below were derived from 40:60 *cis:trans* permethrin having impurity profiles similar to those referred to in the table above.

Table A. Mutagenicity profile of the 40:60 permethrin technical material based on *in vitro* tests

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number[4]
Salmonella typhimurium test strains TA97, TA98, TA100, TA102 and TA1535	Ames test	96.5	OECD 471: 0.5, 5, 50, 500, 5000 µg/plate in mutation test (in both the presence and absence of S-9 mix) 37 °C for 48 hours	Not mutagenic	2014-310-01-01

ANNEX 2. REFERENCES

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
	FAO	2013	FAO specification 331/TC and evaluation report 331/2008 and 331/2012, accessible at http://www.fao.org/agriculture/crops/core-themes/theme/pests/pm/jmps/en/.
NC-2014-182		2014	Preliminary Analysis and Enforcement Analytical Method of Permethrin TGAI. NC-2014-182. GLP.
3514090003		2014	Determination of the Solubility in Organic Solvents of Permethrin TC (40/60). 3514090003. GLP.
2014-310-01-01		2014	Bacterium Reverse Mutation Test for Permethrin 95% TC. 2014-310-01-01. GLP.
NC-2014-184		2014	The Determination of Freezing Point for Permethrin TGAI. NC-2014-184. GLP.

PERMETHRIN

FAO/WHO EVALUATION REPORT 331/2012

Recommendations

The Meeting recommended the following.

(i) The permethrin (40:60) TC as proposed by Tagros Chemicals India Limited should be accepted as equivalent to the permethrin (40:60) reference profile.

(ii) The existing FAO specification for permethrin (40:60) TC should be extended to encompass the corresponding product of Tagros Chemicals India Limited.

(iii) The existing WHO specification for permethrin (40:60) TC should be extended to encompass the corresponding product of Tagros Chemicals India Limited.

Appraisal

The Meeting considered data and information submitted by Tagros (India) in support of extension of the existing FAO and WHO specifications for permethrin TC with a cis/trans ratio of 40:60. The data submitted by Tagros were in accordance with the requirements of the Manual on development and use of FAO and WHO specifications for pesticides (November 2010 - second revision of the First Edition) (Section 3.2).

The Meeting was provided by Tagros with commercially confidential data on the manufacturing process, the manufacturing specification and 5-batch analysis data for permethrin and all detectable impurities at or above 1 g/kg. The manufacturing process provided by Tagros is similar but not exactly the same than those of the reference processes by Sumitomo and Bilag, respectively.

The 5-batch analysis study was performed according to GLP guidelines. The CIPAC method 331/TC/M2/3 (capillary GC with flame ionization detection and internal standard) was used for determination of total permethrin and cis/trans ratio. The permethrin manufacturing impurities were mostly determined by reverse phase HPLC-UV (with confirmation by HPLC-MS), except for water that was determined using the CIPAC Karl Fischer method and some residual solvents that were determined by GC-FID. All the analytical methods used in the 5-batch analysis study were fully validated for their specificity, linearity of response, accuracy, repeatability and limits of detection and quantification (for impurities).

The minimum purity of permethrin 40/60 in the TC is 970 g/kg and complies with the existing FAO/WHO specification of 950 g/kg. Mass balances are high (99.2 to 99.9%), with no unknowns detected.

A more in-depth comparison of the manufacturing specifications of the TC produced by Tagros with that of the reference (Sumitomo) however revealed, that the spectrum of impurities differed for some components significantly from that of the reference. Some impurities also present in the reference and considered non relevant were exceeded by more than the tolerated range of additional 3 g/kg or 50 % (Section 3.2, FAO/WHO

Manual), and some new impurities were specified in the Tagros material but not present in the reference spectrum at concentrations at or above 1 g/kg.

One of the new impurities is the solvent used in the last reaction step and some residues remain in the permethrin TC. Model calculation showed that, at the low levels present the residual solvent does not significantly contribute to the increase in hazard and can be declared non-relevant. The other impurities were screened for structural alerts and they would possibly qualify for being identified as relevant. In conclusion, the Tier-1 of the equivalence determination could not demonstrate equivalence according to the procedures as set out in the Manual, Section 3.2.

Tagros provided the Meeting with a data package on acute toxicity (supported by GLP studies) and on mutagenicity as determined by Ames test on *Salmonella typhimurium* (reverse mutation using various strains) and *in vivo* mouse bone marrow micronucleus test. Both tests did not indicate a mutagenic potential of the permethrin technical material.

The toxicological data indicated some significant differences in toxicological reference values in rat acute oral test (> 300 and > 2000 mg/kg bw for Tagros and Sumitomo respectively) and in eye irritation, where the reference product was not irritant and the Tagros product was found to be mild-irritant. The results of the Ames tests and mouse bone marrow micronucleus test revealed that no mutagenic effect could be observed.

A more in-depth evaluation of the studies where the endpoints were considered significantly different and based on the full studies led to the following conclusions. The acute oral toxicity study with the Tagros material was done according to OECD Guideline 423 in Wistar rats. The test item, permethrin with a cis/trans ratio of 50/50 and a purity of 94 %, was administered in corn oil. This vegetable oil is well known to accelerate the uptake of permethrin in the rat and hence to increase the toxicity. The test with the Sumitomo material was done according to the same Guideline, but with the undiluted material. The different range in the acute toxicity reference value – 300 to > 2000 g/kg bw – can therefore be attributed to the different vehicles in the acute toxicity study. In the 1999 JMPR toxicological evaluation, one of the main conclusions regarding acute oral toxicology was: “Studies of the acute toxicity of orally administered permethrin in mice and rats demonstrate that two factors that affect its toxicity are the concentration of the cis isomer and the vehicle. Permethrin with a cis:trans ratio of 80-100:20-0 is approximately 7-24 times more toxic than permethrin in which the cis:trans ratio is 10-25:90-75 when delivered in maize oil, and permethrin administered in maize oil is four to seven times more toxic than undiluted permethrin.

Regarding the eye irritation in the rabbit, the endpoint was “mildly irritating” with the Tagros material and non-irritating with the Sumitomo material. The full study done with the Tagros material however revealed that the GHS criteria for this classification “mildly irritating” are not met and the Tagros material should be considered as non-irritating as well.

On basis of all Tier-1 and Tier-2 data provided by Tagros (manufacturing process, impurity profile, 5-batch analysis data, acute toxicity and mutagenicity profile), the Meeting concluded that the Tagros permethrin TC can be considered as equivalent to the reference profile supporting the existing FAO and WHO specifications (FAO/WHO evaluation report 331/2008) in Tier-2 of the equivalence procedure.

Tagros stated that their permethrin TC has been submitted for registration in Indonesia. The company provided a letter of access to the national authority for pesticide registration in Indonesia. The confidential data package was provided to the national authority for the purpose of comparison with that held on file in Indonesia. A written confirmation by the National authority was received confirming that the confidential data package for permethrin 40/60 of Tagros is the same as submitted to JMPS and that products with this active ingredient are registered in this country.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 331/2012

Physico-chemical properties of permethrin

Table 1. Physico-chemical properties of pure 40:60 *cis:trans* permethrin

Parameter	Value(s) and conditions	Purity % (cis:trans)	Method	Reference
Vapour pressure	1.95 x 10^{-6} Pa at 20°C 6.18 x 10^{-6} Pa at 40°C	98.6 (40:60)	OECD 104, OPPTS 830.7950 & EEC A.4	Report 10484 29-10-2010
Freezing point	<-12°C with normal atmospheric pressure	98.6 (40:60)	OECD 102	Report 10485 18-10-2010
Temperature of decomposition	Decomposed at 270°C	98.6 (40:60)	OECD 103, OPPTS 830.7220 & EEC.A2.	Report 10486 02-09-2010
Solubility in water	0.0000052 g/L at 20 ± 0.5 °C	98.6 (40:60)	OECD 105, OPPTS 830.7840 & EEC A.6	Report 10489 29-10-2010
Octanol/water partition coefficient	log P_{OW} = 5.03 ± 0.01. K_{OW} =106304.3	98.6 (40:60)	OECD 107, OPPTS 830.7550 & EEC A.8	Report 10487 29-10-2010
Hydrolysis characteristics (Half-life)	Aqueous abiotic hydrolysis is expected to contribute significantly to the degradation of permethrin pure active (40:60) in water at pH 7 and 9	98.6 (40:60)	OECD 111	Report 10488 11-11-2010
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	"Phototransformation of Chemicals in Water-Direct and Indirect Photolysis" [1,2,3]	GAB-012/7-05 10-07-2006
Dissociation characteristics	Does not dissociate	-	-	-
Solubility in organic solvents	Acetone, methanol and p-xylene was >1000 g/L at 20 ± 0.5 °C	98.6 (40:60)	OECD 105, OPPTS 830.7840 & EEC A.6	Report 10490 12-10-2010

Table 2. Chemical composition and properties of 40:60 *cis:trans* permethrin technical material (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were 99.2-99.9 % with virtually no unknowns.
Declared minimum permethrin 40:60 content	950 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

Hazard summary

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, prepublished method for EC and Handbook C, p. 2173, 1985 for WP, WG and DP). Permethrin impurities were determined by reverse phase HPLC with UV detection, with the exception of water that was determined by Karl Fischer titration and some residual solvents determined by GC with flame ionization detection.

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

The permethrin content and isomer ratio are determined as per CIPAC 331/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 40:60.

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 40:60 having impurity profiles similar to those referred to in Table 2, above.

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

Species	Test	Duration and conditions or guideline adopted	Result	Purity % (cis:trans)	Reference
Wistar Rats (Rattus norvegicus) (m,f)	Oral	Observation: 14 days Dosage: 300 mg/kg bw in corn oil Guideline: OECD 423	LD_{50} = >300-2000 mg/kg bw	94.09 (50:50)	Report 08009/ 23-06-2008
Wistar Rats (Rattus norvegicus) (m,f)	Dermal	Observation: 14 days Dosage: 2000 mg/kg bw Guideline: OECD 402	LD_{50} = > 2000 mg/kg bw	94.09 (50:50)	Report 08038/ 23-06-2008
Wistar Rats (Rattus norvegicus) (m,f)	Inhalation	Observation: 14 days Dosage: 0.24 mg/l air Guideline: OECD 403	LC_{50} = > 0.24 mg/l of air at breathing zone	94.09 (50:50)	Report 08041/ 23-06-2008
New Zealand White rabbit (Oryctolagus cuniculus) (f)	Skin irritation	Observation: 1, 24, 48 and 72 hr after patches were removed Dosage: 0.5 ml Guideline: OECD 404	Non-irritant	94.09 (50:50)	Report 08039/ 23-06-2008
New Zealand White rabbit (Oryctolagus cuniculus) (m)	Eye irritation	Observation: 1,24,48 & 72 h after treatment Dosage: 0.1ml Guideline: OECD 405	Minimally irritant	94.09 (50:50)	Report 08040/ 23-06-2008
Guinea Pigs (Dunkan Hartley) (m)	Skin sensitisation	Observation: 30 days Doses: Induction: 2000 mg Challenge: 500 mg Guideline: OECD 406	Non-sensitiser	94.09 (50:50)	Report 08042/ 23-06-2008

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 non-irritant to skin and mild-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 B. Mutagenicity profile of permethrin technical material based on *in vitro* and *in vivo* tests

Species	Test	Conditions and guideline	Result	Purity % (cis:trans)	Reference
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	94.0 (50:50)	Report 08241 / 03-10-2008
Swiss Albino mouse *(Mus musculus)*	Mammalian bone marrow chromosomal aberration (*In vivo*)	Dosage: 100, 1000 and 2000 mg/kg bw Guideline: OECD 475	Negative	94.0 (50:50)	Report 08242 / 03.10.2008

Permethrin was tested for genotoxicity in *in vitro* (S. Typhimurium) and *in vivo*. (bone marrow chromosomal aberration). There was no evidence of genotoxicity in these assays.

ANNEX 2. REFERENCES

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
-	Y. Purvanti	2013	Confirmation of the identity of the confidential data package and registration of permethrin 40:60 by Tagros in Indonesia. Ministry of Agriculture, Republic of Indonesia.
11639	Uma Ganesh	2012	Chemical Composition of Five Batches of Permethrin technical. Preliminary Analysis and Enforcement Analytical Methods for Permethrin TGAI: fulfilling the Requirements of OPPTS Guideline 830.1700 and 830.1800 and EC Council Directive 94/37/EC Article 1.9 to 1.11. Tagros Chemicals India Limited, GLP unpublished report.
10484	Uma Venkata Satish Pakki	2010	Permethrin pure active (40:60): Laboratory Study of Vapour Pressure. Tagros Chemicals India Limited, GLP unpublished report.
10485	Ch. Rajaskharam	2010	Permethrin pure active (40:60): Laboratory Study of Freezing point. Tagros Chemicals India Limited, GLP unpublished report.
10486	Ch. Rajaskharam	2010	Permethrin pure active (40:60): Laboratory Study of Thermal decomposition point. Tagros Chemicals India Limited, GLP unpublished report.
10489	K. Sowjanya	2010	Permethrin pure active (40:60): Laboratory Study of Water Solubility. Tagros Chemicals India Limited, GLP unpublished report.
10487	M. Thiripura Sundari	2010	Permethrin pure active (40:60): Laboratory Study of Partition Coefficient. Tagros Chemicals India Limited, GLP unpublished report.
10488	M. Thiripura Sundari	2010	Permethrin pure active (40:60): Laboratory Study of Hydrolysis in Buffer Solutions of pH 4,7 and 9. Tagros Chemicals India Limited, GLP unpublished report.
10490	K. Sowjanya	2010	Permethrin pure active (40:60): Laboratory Study of Solubility in Organic Solvents. Tagros Chemicals India Limited, GLP unpublished report.
1591	Neha B.D. Bakili R.A. Nagarajan	1998	Acute Oral toxicity study with Permethrin technical in Rats. Tagros Chemicals India Limited, GLP unpublished report.
1593	Neha B.D. Bakili R.A. Nagarajan	1998	Acute Dermal toxicity study with Permethrin technical in Rats. Tagros Chemicals India Limited, GLP unpublished report.
1595	Girish J. Sakhivelan S.M.	1998	Acute Inhalation toxicity study with Permethrin technical in Rats. Tagros Chemicals India Limited, GLP unpublished report.
1590	Neha B.D., Bakili R.A.	1998	Acute Dermal irritation study of Permethrin technical in Rabbits. Tagros Chemicals India Limited, GLP unpublished report.
1589	Neha B.D., Bakili, R.A.	1998	Acute Eye irritation study of Permethrin technical in Rabbits. Tagros Chemicals India Limited, GLP unpublished report.

PERMETHRIN

FAO/WHO EVALUATION REPORT 331/2008

Recommendations

The Meeting recommended that:

(i) the specification for 40:60 *cis:trans* permethrin TC, proposed by Sumitomo Chemical Co. Ltd and relating to permethrin TC produced by Bilag Industries Pvt Ltd (India), should be adopted by FAO and WHO;

(ii) the existing (1991) FAO specifications for permethrin TC, WP, DP and EC, and the existing (1999) WHO specifications for permethrin TC and EC, should be withdrawn.

Appraisal

The Meeting considered data and a draft specification (TC only), submitted by Sumitomo Chemical Co. Ltd but including information from Bilag Industries Ltd, for the review of existing (1991) FAO specifications for permethrin TC, WP, DP and EC, and existing (1999) WHO specifications for permethrin TC and EC.

Permethrin is no longer under patent and has been widely manufactured for many years. Technical grade permethrin is composed of 4 stereoisomers, due to the chirality at two carbon atoms in the cyclopropane ring, leading to 2 *cis* and 2 *trans* isomers. The pairs of *cis* and *trans* isomers can be separated using non-chiral techniques but separation of the 2 *cis*, or the 2 *trans*, isomers would require a chiral separation technique and is rarely done routinely.

Differing manufacturing processes lead to different *cis:trans* ratios in technical grade permethrin but, generally in the market, the nominal *cis:trans* ratio is either 25:75 or 40:60. Manufacturing tolerances around these two nominal ratios lead to specification ranges that overlap slightly. The existing FAO (1991) and WHO (1999) specifications for permethrin encompass both nominal ratios. The data submitted for the present review were in support of a proposed FAO/WHO specification for TC, which encompassed only permethrin with a nominal 40:60 *cis:trans* ratio.

Sumitomo provided details of the manufacturing processes and 5-batch analysis data, relating to two sources of 40:60 permethrin, together with manufacturing limits for purity and all impurities ≥1 g/kg. The two sources were Sumitomo (Japan) (SM permethrin) and Bilag (India) (BL permethrin), both in current production but the proposed FAO/WHO specification applies to BL permethrin. Mass balances in the 5-batch analytical data were good in the case of SM permethrin (99.0–99.9%). The Meeting questioned the rather low mass balances (97.8-98.2%, unaccountable fraction ~20 g/kg) in the case of BL permethrin. The manufacturer stated that the unaccountable fraction was believed to represent components, such as water and inorganics, which were undetectable by the GC techniques used. Data used to support registration in the USA showed a similar picture and the Meeting accepted the explanation.

The minimum permethrin content of the TCs were 950 g/kg for both SM and BL permethrin. The data on SM and BL permethrin were stated by Sumitomo to be identical to those submitted by the company for registration of BL permethrin by Sumitomo in the USA but, for reasons beyond the control of the company, FAO and WHO, this could not be confirmed independently.

The original manufacturers of permethrin no longer produce it and therefore no information was available to the Meeting about the manufacturing limits for impurities applying to the materials used to generate most of the original, very extensive and publicly available database on permethrin hazard characteristics. In the absence of this key information, the original manufacturers' data on hazards could not form the basis of JMPS reference profiles for permethrin.

To address the requirement for reference profiles to support FAO/WHO specifications, Sumitomo provided hazard data generated 20-30 years earlier, using SM permethrin. The proposed FAO/WHO specification was intended to apply to BL permethrin, only, but TC from this source was supported by a limited data package. Therefore, to enable the Meeting to decide whether or not there was sufficient information to support the development of FAO/WHO specifications for 40:60 permethrin, it was necessary: (i) to determine whether or not BL permethrin is equivalent to SM permethrin; and (ii) to define the reference profiles in this case.

Determination of equivalence was not straightforward. The impurity profile originally used as the manufacturing specification for SM permethrin had subsequently been shown by Sumitomo to be incorrect, following the introduction of improved analytical technology. Consequently, the company had recently revised the manufacturing limits for impurities in SM permethrin. However, Sumitomo stated that the manufacturing process had remained unchanged throughout the entire period during which SM permethrin had been produced (a statement was supported by 5-batch analytical data relating to 1998-2005 production) and, on this basis, the Meeting agreed that it was reasonable to assume that the revised manufacturing limits also applied to the TC batches used to generate the hazard data on SM permethrin. Thus the chemical and hazard profiles of SM permethrin were considered by the Meeting to be directly linked.

Although the manufacturing process for BL permethrin differs from that used for SM permethrin, it had been carefully refined to ensure that the manufacturing limits for purity and all impurities were within the (recently revised) manufacturing limits for SM permethrin. Thus, on the basis of their chemical profiles, BL permethrin in current production was considered to be equivalent to SM permethrin. WHO/PCS advised the Meeting that the acute toxicology data on BL permethrin indicate that it is toxicologically equivalent to SM permethrin (Table A). Overall, therefore, the Meeting concluded that BL permethrin is equivalent to SM permethrin.

Given the overall equivalence of BL permethrin and SM permethrin, the Meeting agreed that the purity/impurity profile of BL permethrin and the toxicology profile of SM permethrin (Tables A-D of this evaluation) should be designated as the reference profiles for 40:60 *cis:trans* permethrin.

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[1] and ADI[2] 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 BL permethrin should be designated as relevant.

The analytical methods for determination of the active ingredient (including tests for identity and isomer ratio) involve capillary GC-FID and internal standardization with triphenylphosphate. The methods were adopted by CIPAC in 2006, for analysis of permethrin TC and LN. Permethrin impurities were determined by the manufacturers, using capillary GC-FID.

Permethrin is a viscous liquid at room temperature; it does not dissociate in water and has extremely low water solubility and volatility. It is stable to hydrolysis at pH 4–7 but is slowly hydrolysed at pH 9. Permethrin only decomposes at extremely high temperature and, although photochemical degradation was observed in laboratory studies, this was stated by Sumitomo to be of negligible significance in the field.

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

The Meeting welcomed the increase in minimum active ingredient content from 900 g/kg to 950 g/kg. The Meeting also welcomed a clarification and narrowing of the tolerance for permethrin isomer ratio[3].

The existing FAO (1991) and WHO (1999) specifications for permethrin TC included clauses for control of water, acetone-insolubles and acidity but the permethrin TC is not used by the proposer to prepare EC formulations and permethrin is stable under acidic conditions. None of these characteristics was therefore considered to be an appropriate quality criterion for the purposes of the FAO/WHO specification.

The proposer declared that the 40:60 *cis:trans* permethrin manufactured by Bilag and sold by Sumitomo complies with the proposed FAO/WHO specification for TC.

The Meeting noted that the existing (1991) FAO specifications for permethrin DP, WP and EC, and the existing (1999) WHO specification for permethrin EC, were not supported by the manufacturer.

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[1] 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).

[2] 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).

[3] 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 331/2008

Uses

Permethrin is a non-systemic pyrethroid insecticide, with contact and stomach action and some repellent effects. It has many applications in agriculture, animal health and public health.

Identity

ISO common names[1]

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

Chemical names[1]

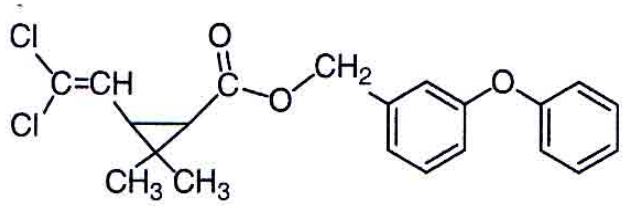
IUPAC: 3-phenoxybenzyl (1*RS*,*3RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

CA: (3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate

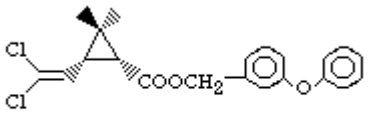
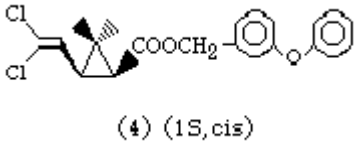
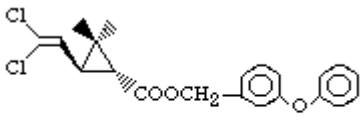
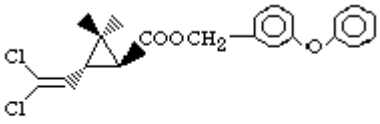
Synonyms

none

Structural formula



Two pairs of diastereoisomers are present in a ratio of approximately 40:60:

 (2) (1R,cis)	sum ≈ 40%
 (4) (1S,cis)	
 (1) (1R,trans)	sum ≈ 60%
 (3) (1S,trans)	

[1] Note: the ISO common names and the IUPAC and CA names do not define the isomer ratio.

Molecular formula

$C_{21}H_{20}Cl_2O_3$

Relative molecular mass

391.3

CAS Registry number[1]

52645-53-1

CIPAC number[1]

331

Identity tests

GC retention time, IR spectrum.

Physico-chemical properties of permethrin

Table 1. Physico-chemical properties of pure 40:60 cis:trans permethrin or the resolved diastereoisomers

Parameter	Value(s) and conditions	Purity %	Method	Reference
Vapour pressure	6.9×10^{-6} Pa at 25°C	99.6	OECD 104	0483/0059
Melting point	Melting point: <20°C	99.6	OECD 102	0483/0059
Temperature of decomposition	252°C	99.6	OECD 102	0483/0059
Solubility in water at 20°C	11.1 µg/l at 20 ± 0.5°C at pH 7.0-9.3	100% (*trans* isomer)	OECD 105	JP-0023
Octanol/water partition coefficient	log P_{OW} >6.5 at 40°C	99.6	OECD 117	0483/0059
Hydrolysis characteristics, half-life at 25ºC	Sterile aqueous buffer solutions at pH 4, 7, and 9 in the dark, testing *cis* and *trans* isomers separately (both cyclopropyl 1-^{14}C labelled). pH 4 and 7, both isomers stable. half-life at pH 9: *cis* = 42.3 d *trans* = 37.7 d.	Radiochemical purity, both isomers >98%	Japan-MAFF guideline No.12-Nosan No.8147, Part 2-6-1 (similar to OECD)	JM-0014
Photolysis characteristics	Xenon lamp with filter (blocking IR & radiation <290 nm), in sterile buffer solution (pH 4) or synthetic humic water (SHW), with dark control, testing *cis* and *trans* isomers separately (both cyclopropyl 1-^{14}C labelled). Irradiation equivalent to natural sunlight (Tokyo, 35°N, April-June) for 30 days. Half-life: c*is* = 23.1 d (buffer), 14.6 d (SHW) *trans* = 36.8 d (buffer), 25.5 d (SHW)	Radiochemical purity, both isomers >98%98%	Japan-MAFF guideline No.12-Nosan No.8147, Part 2-6-2 (similar to OECD)	JM-0016

[1] Note: the CAS Registry No. and CIPAC number do not define the isomer ratio.

Table 2. Chemical composition and properties of technical (BL) 40:60 *cis:trans* permethrin (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were 97.8-98.2%, no unidentified impurities were reported.
Declared minimum 40:60 *cis:trans* permethrin content	950 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 of the TC	<20°C

Pure permethrin *cis*-isomer forms colourless crystals at room temperature but a mixture of *cis* and *trans* isomers normally occurs as a liquid, with its appearance depending on the ratio of isomers. Pure permethrin (40:60) is a colourless, viscous liquid, whereas the TC is a yellow to yellow-brown viscous liquid.

Hazard summary

SM permethrin was evaluated by the Japanese Ministry of Health and Welfare in 1977[1]. Data on SM and BL permethrin, submitted by Valent BioSciences Corporation (a subsidiary company of Sumitomo Chemical Co., Ltd. in the USA), were evaluated by US-EPA and led to registration of BL permethrin in the USA in 2005[2].

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 RfD 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

The formulation type available for public health applications is LN, in which the permethrin is not co-formulated with other pesticides. The LN formulations are registered and sold in Colombia, Dominican republic, Honduras, Indonesia, Kenya, Malaysia, Myanmar, Peru, Philippines, Singapore, Sri Lanka, Thailand, Tanzania and Trinidad.

Methods of analysis and testing

The analytical method for the active ingredient (including identity tests and isomer ratio) is carried out by capillary GC with FID and internal standardization with

[1] Permethrin/Eksmin, registration number 52AP-409, 5 March 1977.

[2] PramexB technical insecticide, registration number 73049-418, 14 September 2005.

triphenylphosphate. The method was adopted as a full CIPAC method in 2007[1], for the analysis of TC and LN.

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.

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, specifically defined as a mixture of *cis*- and *trans*-isomers present in a nominal [1*RS*,3*RS*]:[1*RS*,3*SR*] (*cis*:*trans*) ratio of 40:60, with a permitted range for the average measured ratio of 30:70 to 50:50.

[1] Methods for the identification and determination of permethrin content and permethrin isomer ratio in TC and LN were adopted by CIPAC in 2006 but are not yet published in a Handbook. Prior to publication of the Handbook, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: Sumitomo Chemical Co. Ltd. (Japan) 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 A. Toxicology profile of SM permethrin and BL permethrin technical material, based on acute toxicity, irritation and sensitization

Species	Test and permethin used	Purity % & *cis:trans* ratio	Duration and conditions or guideline adopted	Result	Reference
Rat, Sprague-Dawley (f)	Acute oral SM & BL permethrin in the same study	SM: 96.3, 40:60 BL: 96.9, 40:60	Observation: 14 d, dose: 2000 mg/kg bw, OECD guideline 423	No mortality, no clinical signs observed. LD_{50} >2000 mg/kg bw for both SM and BL permethrin	QJT-0001
Mouse, dd strain (m)	Acute oral SM permethrin only	92.4, 46:54	Observation: 14 d, no guideline[1]	LD_{50} >650 mg/kg bw (m)	JT-0009
Rat, Sprague-Dawley, (m)	Acute oral SM permethrin only	92.4, 46:54	Observation: 14 d, guideline not stated	LD_{50} >430 mg/kg bw (m)	JT-0009
Rat, Sprague-Dawley (m,f)	Acute dermal SM & BL permethrin in the same study	SM 96.3, 40:60 BL 96.9, 40:60	Observation: 14 d dose: 2,000 mg/kg bw OECD guideline 402	No mortality, no clinical signs observed. LD_{50} >2000 mg/kg bw for both SM and BL permethrin	QJT-0002
Mouse, dd strain (m,f)	Acute dermal SM permethrin only	92.4, 46:54	Observation: 14 d, no guideline[1]	LD_{50} >2500 mg/kg bw	JT-0009
Rat, Sprague-Dawley, (m,f)	Acute dermal SM permethrin only	92.4, 46:54	Observation: 14 d, no guideline[1]	LD_{50} >2500 mg/kg bw	JT-0009
Rat, Sprague-Dawley (m,f)	Acute inhalation SM & BL permethrin in the same study	SM 96.3, 40:60 BL 96.9, 40:60	Exposure 4 h, observation 14 d, dose 5000 mg/m^3	BL permethrin: initial tremor, no mortality observed, LC_{50} >5000 mg/m^3 SM permethrin: initial tremor, 2 f died, LC_{50} >5000 mg/m^3	QJT-0003
Mouse, dd strain (m,f)	Acute inhalation SM permethrin only	92.4, 45:55	Exposure period 3 h, observation 28 d, no guideline[1]	LC_{50} >685 mg/m^3	JT-0015
Rat, Sprague-Dawley (m,f)	Acute inhalation SM permethrin only	92.4, 45:55	Exposure period 3 h, observation 28 d, no guideline[1]	LC_{50} >685 mg/m^3	JT-0015
Rabbit, Japanese White (f)	Skin irritation BL permethrin only	96.9, 40:60	OECD guideline 404	Non-irritant	QJT-0005

[1] Study conducted prior to the introduction of guidelines but techniques and conditions equivalent to current international guidelines.

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

Species	Test and permethin used	Purity % & *cis:trans* ratio	Duration and conditions or guideline adopted	Result	Reference
Rabbit, Japanese White (m)	Skin irritation SM permethrin only	91.8, 40:60	No guideline[1]	Non-irritant	JT-0046
Rabbit, Japanese White (f)	Eye irritation BL permethrin only	96.9, 40:60	OECD guideline 405	Non-irritant	QJT-0004
Rabbit, Japanese White (m)	Eye irritation SM permethrin only	91.8, 40:60	No guideline[1]	Non-irritant	JT-0046
Guinea pig, Hartley (f)	Skin sensitization BL permethrin only	96.9, 40:60	OECD guideline 406	Non-sensitizer	QJT-0006
Guinea pig, Hartley (m)	Skin sensitization SM permethrin only	94.6, 40:60	No guideline[1]	Non-sensitizer	JT-0011

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

Species	Test	Purity % & *cis:trans* ratio	Duration and conditions or guideline adopted	Result	Reference
Rat, Sprague-Dawley (m,f)	Feeding toxicity	93.3, 40:60	No guideline[1], duration 180 d, doses: 375, 750, 1500, 3000 ppm	NOEL = 1500 ppm, equivalent to 92.9 mg/kg bw/d (m) 110 mg/kg bw/d (f)	JT-0013
Rat, Sprague-Dawley (m,f)	Inhalation toxicity	92.4, 40:60	No guideline[1], duration 28 d consecutive, 3 h/d, doses: 20, 50, 100 mg/m^3	NOAEL = 50 mg/m^3 (m,f)	JT-0015
Rat, Sprague-Dawley (m,f)	Feeding, teratogenicity, embryotoxicity	92.4, 40:60	No guideline[1], oral exposure during days 9-14 of gestation. Doses: 10, 20, 50 mg/kg bw/d.	The dams treated with 50 mg/kg bw/d showed slight toxic symptoms, (ataxia, tremor, hyper-sensitivity)	JT-0102
Rabbit, Japanese White (m,f)	Feeding, teratogenicity, embryotoxicity	92.5, 40:60	No guideline[1], oral gavage, 4 doses during days 6-18 inclusive of pregnancy, doses: 600, 1200, 1800 mg/kg bw/d	Embryotoxic at the two higher levels of treatment, toxic to dams at 1800 mg/kg bw/day but not teratogenic at any level	JT-0082

[1] Study conducted prior to the introduction of guidelines but techniques and conditions equivalent to current international guidelines.

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

Species	Test	Purity % & *cis:trans* ratio	Conditions and doses	Result	Reference
Salmonella typhimurium (TA100, TA98, TA1535, TA1537, TA1538), Escherichia coli (WP-2 hcr^-)	Gene mutation, Ames test (*in vitro*)	93.3, 40:60	10, 50, 100, 500, 1000, 5000 µg/plate, ±S9, in-house method equivalent to OECD guideline 471	Negative	JT-0024
Mouse, ICR (m) *Salmonella typhimurium* (G46)	Host-mediated assay, gene mutation (*in vivo & in vitro*)	93.3, 40:60	50, 200 mg/kg bw, administered orally twice, in-house method	Negative	JT-0024
Bacillus subtilis M45 rec^- and H17 strains	Recombinant DNA, damage and repair (*in vitro*)	93.3, 40:60	20, 100, 200, 500, 1000, 2000 µg/disc, in-house method	Negative	JT-0024

Table D. Ecotoxicology profile of SM permethrin technical material

Species	Test	Purity % & *cis:trans* ratio	Duration and conditions	Results	Reference
Pseudokirchneriella subcapitata (freshwater green alga)	Effect on growth	94.4, 40:60	OECD 201	EC_{50} (72hr) = 540 µg/l NOEC (72hr) = 0.21 µg/l	JW-0041
Colinus virginianus (northern bobwhite)	Acute oral toxicity	94.4, 40:60	EPA OPPTS 850.2100	LD_{50} >2000 mg/kg	JW-0040

ANNEX 2. REFERENCES

Sumitomo document number or other reference	Year and title of report or publication details
0483/0059	2008. Permethrin pure active ingredient (cis/trans=4/6): Determination of Physico-Chemical properties.
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JP-0023	2001. Solubility of trans-Permethrin in water.
JT-0009	1979. Acute oral, dermal, and subcutaneous toxicities of permethrin (Eksmin) in rats and mice.
JT-0011	1976. Dermal sensitization test of Eksmin in guinea pigs.
JT-0013	1979. Six-month subacute oral toxicity of nrdc 143 in sprague dawley rats.
JT-0015	1976. Acute and subacute inhalation toxicity studies of permethrin (Eksmin) in mice and rats.
JT-0024	1978. Mutagenicity of s-3151 in bacterial test systems.
JT-0046	1981. Primary eye and skin irritation tests of Eksmin in rabbits.
JT-0082	1980. Permethrin: Teratogenicity study in the rabbit.
JT-0102	1976. Teratogenic evaluation with permethrin in rat.
JW-0040	2004. Permethrin - acute oral toxicity test (LD50) with northern bobwhite quail (*Colinus virginianus*).
JW-0041	2004. Permethrin - toxicity to the freshwater green alga, *Pseudokirchneriella subcapitata.*
QJT-0001	2006. Acute oral toxicity study of Permethrin in rats.
QJT-0002	2006. Acute dermal toxicity study of Permethrin in rats.
QJT-0003	2006. Acute inhalation toxicity study of Permethrin in rats.
QJT-0004	2006. An eye irritation study of Permethrin in rabbits.
QJT-0005	2006. A skin irritation study of Permethrin in rabbits.
QJT-0006	2006. A skin sensitization study of Permethrin in guinea pigs.
WHO 2002	The WHO recommended classification of pesticides by hazard and guidelines to classification, 2000-2002. World Health Organization, Geneva, 2002.