FAO SPECIFICATIONS AND EVALUATIONS
FOR AGRICULTURAL PESTICIDES

PERMETHRIN
(40:60 cis:trans isomer ratio)

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

2019
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FAO specifications are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements.

Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

Furthermore, pesticides which are manufactured to comply with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable to their manufacture, sale, transportation, storage, handling, preparation and/or use.

FAO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may arise as a result of, or in connection with, the manufacture, sale, transportation, storage, handling, preparation and/or use of pesticides which are found, or are claimed, to have been manufactured to comply with these specifications.

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

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\[1\] This disclaimer applies to all specifications published by FAO.
INTRODUCTION

FAO establishes and publishes specifications\(^*\) for technical material and related formulations of agricultural pesticides, with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 2002, the development of WHO specifications follows the New Procedure, described in the 1\(^{st}\) edition of “Manual for Development and Use of FAO and WHO Specifications for Pesticides” (2002) - currently available as 3\(^{rd}\) revision of the 1\(^{st}\) edition (2016) - , which is available only on the internet through the FAO and WHO web sites.

This New Procedure follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPM, rather than the JMPS.]

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently from the year 2000 onwards the publication of FAO specifications under the New Procedure 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 “Manual on development and use of FAO and WHO specifications for pesticides”.

**Part Two: The Evaluation Report(s)** of the pesticide, reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the “FAO/WHO Manual on Pesticide Specifications” and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

FAO specifications developed under the New Procedure do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. FAO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

**Specifications bear the date (month and year) of publication of the current version.**

\(^*\) NOTE: PUBLICATIONS ARE AVAILABLE ON THE INTERNET AT (http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/ps-new/en/) OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.
<table>
<thead>
<tr>
<th>PART ONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PART ONE</td>
</tr>
<tr>
<td>SPECIFICATIONS</td>
</tr>
</tbody>
</table>

**PERMETHRIN**

<table>
<thead>
<tr>
<th>PERMETHRIN (40:60) INFORMATION</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>40:60 <em>cis:trans</em> PERMETHRIN TECHNICAL MATERIAL (AUGUST 2015)</td>
<td>6</td>
</tr>
</tbody>
</table>
PERMETHRIN 40:60 cis:trans

**ISO common names**
permethrin (E-ISO), permethrine (F-ISO)

**Chemical names**

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

**CA:** (3-phenoxyphenyl)methyl 3-(2,2-dichloroethyl)-2,2-dimethylcyclopropanecarboxylate

**Synonyms**
None

**Structural formula**

![Structural formula of permethrin 40:60](image)
Two pairs of diastereomers (each consisting of a racemic pair of enantiomers; see below) are present in a ratio of approximately 40:60

<table>
<thead>
<tr>
<th>Sl No</th>
<th>Name of isomer</th>
<th>Structure</th>
<th>Proportions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1R, cis</td>
<td><img src="image" alt="Structure 1R, cis" /></td>
<td>sum ≈ 40%</td>
</tr>
<tr>
<td>2</td>
<td>1S, cis</td>
<td><img src="image" alt="Structure 1S, cis" /></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1R, trans</td>
<td><img src="image" alt="Structure 1R, trans" /></td>
<td>sum ≈ 60%</td>
</tr>
<tr>
<td>4</td>
<td>1S, trans</td>
<td><img src="image" alt="Structure 1S, trans" /></td>
<td></td>
</tr>
</tbody>
</table>

*Molecular formula*

C\textsubscript{21}H\textsubscript{20}Cl\textsubscript{2}O\textsubscript{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
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 technical materials 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 technical materials produced by other manufacturers. The evaluation reports (331/2008, 331/2012 & 331/2015), 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 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 \([1RS,3RS]:[1RS,3SR] (cis:trans)\) permethrin isomer ratio shall be declared and, when determined, the average measured ratio shall be in the range 30:70 to 50:50.

*Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: [http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/ps-new/en/](http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/ps-new/en/)
## PART TWO

### EVALUATION REPORTS

**PERMETHRIN 40:60 cis:trans**

<table>
<thead>
<tr>
<th>Year</th>
<th>FAO/WHO evaluation report</th>
<th>Supporting information</th>
<th>Annex 1: Hazard summary provided by the proposer</th>
<th>Annex 2: References</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019</td>
<td>based on data submitted by Gharda Chemicals Ltd. (non-equivalence of TC)</td>
<td>8</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>2015</td>
<td>based on data submitted by Jiangsu Yangnong Chemical Ltd. (TC)</td>
<td>16</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>2012</td>
<td>based on data submitted by Tagros Chemicals India Limited (TC)</td>
<td>23</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>2008</td>
<td>based on data submitted by Sumitomo Chemical Company (incorporating data from Bilag, India) (TC)</td>
<td>33</td>
<td>41</td>
<td>45</td>
</tr>
</tbody>
</table>
PERMETHRIN 40:60 cis:trans

FAO/WHO EVALUATION REPORT 331/2019

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

<table>
<thead>
<tr>
<th></th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declared minimum permethrin 40:60 content</td>
<td>950 g/kg</td>
</tr>
<tr>
<td>cis:trans isomer ratio</td>
<td>40:60</td>
</tr>
<tr>
<td>Relevant impurities ≥ 1 g/kg and maximum limits for them</td>
<td>One impurity may be relevant</td>
</tr>
<tr>
<td>Relevant impurities &lt;1 g/kg and maximum limits for them</td>
<td>Permethric acid anhydride (PMAA), ≥ 0.1 g/kg</td>
</tr>
<tr>
<td>Stabilizers or other additives and maximum limits for them</td>
<td>None</td>
</tr>
<tr>
<td>Melting temperature range of the TC</td>
<td>3 - 4°C</td>
</tr>
</tbody>
</table>
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 the 40:60 cis:trans permethrin technical material, based on acute toxicity, irritation and sensitization.

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Purity% (cis:trans ratio)</th>
<th>Guideline, duration, doses and conditions</th>
<th>Result</th>
<th>Study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, Wistar</td>
<td>Acute oral</td>
<td>95.0% (40:60)</td>
<td>OECD 423</td>
<td>LD$_{50}$ : &gt;300-2000 mg /kg bw</td>
<td>T.PMO.073</td>
</tr>
<tr>
<td>Rat, Wistar</td>
<td>Acute dermal</td>
<td>95.0% (40:60)</td>
<td>OECD 402</td>
<td>LD$_{50}$ : &gt;2000 mg/kg bw</td>
<td>T.PMO.074</td>
</tr>
<tr>
<td>Rat, Wistar</td>
<td>Acute Inhalation</td>
<td>95.0% (40:60)</td>
<td>OECD 403</td>
<td>LC$_{50}$ (4 hrs) : &gt; 2.65 mg/L air (maximum attainable concentration)</td>
<td>T.PMO.078</td>
</tr>
<tr>
<td>Rabbit, New Zealand white</td>
<td>Dermal irritation</td>
<td>95.0% (40:60)</td>
<td>OECD 404</td>
<td>Non-irritant to rabbit skin</td>
<td>T.PMO.075</td>
</tr>
<tr>
<td>Rabbit, New Zealand white</td>
<td>Eyes irritation</td>
<td>95.0% (40:60)</td>
<td>OECD 405</td>
<td>Non-irritant to rabbit eyes</td>
<td>T.PMO.076</td>
</tr>
<tr>
<td>Guinea pig, Albino Dunkin Hartley</td>
<td>Skin sensitisation</td>
<td>95.0% (40:60)</td>
<td>OECD 406</td>
<td>Weak sensitizer (Grade 1)</td>
<td>T.PMO.077</td>
</tr>
</tbody>
</table>
Table 3. Mutagenicity profile of the 40:60 *cis:trans* permethrin technical material based on *in vitro* tests

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Purity %</th>
<th>Guideline, duration, doses and conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella typhimurium</em></td>
<td>Bacterial Reverse Mutation Test</td>
<td>n.a.</td>
<td>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</td>
<td>Non-mutagenic</td>
</tr>
<tr>
<td>TA 1535</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA 1537</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA 98, TA 100, TA 102</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OECD 471* test concentration: 0.038, 0.119, 0.376, 1.187, and 3.75 mg/plate, both in presence (+S9) and in absence (-S9) of metabolic activation.
## ANNEX 2

### REFERENCES

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. J. Wolansky et. al.</td>
<td>2006</td>
<td>Relative Potencies for Acute Effects of Pyrethroids on Motor Function in Rats. Toxicological Sciences 89(1), 271-277.</td>
</tr>
</tbody>
</table>
Recommendations

The Meeting recommended the following.

(i) The permethrin 40:60 TC as proposed by Jiangsu Yangnong Chemical 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 Ltd.

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

Appraisal

The Meeting considered data and information submitted by Jiangsu Yangnong Chemical 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 led to 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, mutagenicity profile), 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
Table 1. Chemical composition and properties of 40:60 cis:trans permethrin technical material (TC)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value and conditions</th>
<th>Purity %</th>
<th>Method reference</th>
<th>Study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freezing temperature of the TC</td>
<td>-12 °C with normal atmospheric pressure</td>
<td>96.5</td>
<td>CIPAC MT 1</td>
<td>NC-2014-184</td>
</tr>
<tr>
<td>Solubility in organic solvents</td>
<td>250 g/L n-heptane</td>
<td>96.5</td>
<td>CIPAC MT 181</td>
<td>3514090003</td>
</tr>
<tr>
<td></td>
<td>250 g/L p-xylene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>250 g/L 1,2-dichloroethane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>133-160 g/L propan-2-ol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>250 g/L acetone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>250 g/L ethyl acetate</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>All at 25 °C</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 [1RS,3RS]:[1RS,3SR] (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

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

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Purity %</th>
<th>Guideline, duration, doses and conditions</th>
<th>Result</th>
<th>Study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella typhimurium test strains TA97, TA98, TA100, TA102 and TA1535</td>
<td>Ames test</td>
<td>96.5</td>
<td>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</td>
<td>Not mutagenic</td>
<td>2014-310-01-01</td>
</tr>
</tbody>
</table>
## ANNEX 2

### References

<table>
<thead>
<tr>
<th>Study number</th>
<th>Author(s)</th>
<th>year</th>
<th>Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3514090003</td>
<td>2014</td>
<td></td>
<td>Determination of the Solubility in Organic Solvents of Permethrin TC (40/60). 3514090003. GLP.</td>
</tr>
<tr>
<td>2014-310-01-01</td>
<td>2014</td>
<td></td>
<td>Bacterium Reverse Mutation Test for Permethrin 95% TC. 2014-310-01-01. GLP.</td>
</tr>
<tr>
<td>NC-2014-184</td>
<td>2014</td>
<td></td>
<td>The Determination of Freezing Point for Permethrin TGAI. NC-2014-184. GLP.</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value(s) and conditions</th>
<th>Purity % (cis:trans)</th>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vapour pressure</td>
<td>1.95 x 10⁻⁶ Pa at 20°C 6.18 x 10⁻⁶ Pa at 40°C</td>
<td>98.6 (40:60)</td>
<td>OECD 104, OPPTS 830.7950 &amp; EEC A.4</td>
<td>Report 10484 29-10-2010</td>
</tr>
<tr>
<td>Freezing point</td>
<td>&lt;-12°C with normal atmospheric pressure</td>
<td>98.6 (40:60)</td>
<td>OECD 102</td>
<td>Report 10485 18-10-2010</td>
</tr>
<tr>
<td>Temperature of decomposition</td>
<td>Decomposed at 270°C</td>
<td>98.6 (40:60)</td>
<td>OECD 103, OPPTS 830.7220 &amp; EEC.A2.</td>
<td>Report 10486 02-09-2010</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>0.0000052 g/L at 20 ± 0.5 °C</td>
<td>98.6 (40:60)</td>
<td>OECD 105, OPPTS 830.7840 &amp; EEC A.6</td>
<td>Report 10489 29-10-2010</td>
</tr>
<tr>
<td>Octanol/water partition coefficient</td>
<td>log P&lt;sub&gt;OW&lt;/sub&gt; = 5.03 ± 0.01. K&lt;sub&gt;OW&lt;/sub&gt; =106304.3</td>
<td>98.6 (40:60)</td>
<td>OECD 107, OPPTS 830.7550 &amp; EEC A.8</td>
<td>Report 10487 29-10-2010</td>
</tr>
<tr>
<td>Hydrolysis characteristics (Half-life)</td>
<td>Aqueous abiotic hydrolysis is expected to contribute significantly to the degradation of permethrin pure active (40:60) in water at pH 7 and 9</td>
<td>98.6 (40:60)</td>
<td>OECD 111</td>
<td>Report 10488 11-11-2010</td>
</tr>
<tr>
<td>Photolysis characteristics</td>
<td>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.</td>
<td>93.61</td>
<td>“Phototransformation of Chemicals in Water-Direct and Indirect Photolysis” [1,2,3]</td>
<td>GAB-012/7-05 10-07-2006</td>
</tr>
<tr>
<td>Dissociation characteristics</td>
<td>Does not dissociate</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Solubility in organic solvents</td>
<td>Acetone, methanol and p-xylene was &gt;1000 g/L at 20 ± 0.5 °C</td>
<td>98.6 (40:60)</td>
<td>OECD 105, OPPTS 830.7840 &amp; EEC A.6</td>
<td>Report 10490 12-10-2010</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data</th>
<th>Confidential information supplied and held on file by FAO and WHO. Mass balances were 99.2-99.9 % with virtually no unknowns.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declared minimum permethrin 40:60 content</td>
<td>950 g/kg</td>
</tr>
<tr>
<td>Relevant impurities ≥ 1 g/kg and maximum limits for them</td>
<td>None</td>
</tr>
<tr>
<td>Relevant impurities &lt; 1 g/kg and maximum limits for them</td>
<td>None</td>
</tr>
<tr>
<td>Stabilisers or other additives and maximum limits for them</td>
<td>None</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Duration and conditions or guideline adopted</th>
<th>Result</th>
<th>Purity % (cis:trans)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wistar Rats (Rattus norvegicus) (m,f)</td>
<td>Oral</td>
<td>Observation: 14 days Dosage: 300 mg/kg bw in corn oil Guideline: OECD 423</td>
<td>LD$_{50}$ = &gt;300-2000 mg/kg bw</td>
<td>94.09 (50:50)</td>
<td>Report 08009/23-06-2008</td>
</tr>
<tr>
<td>Wistar Rats (Rattus norvegicus) (m,f)</td>
<td>Dermal</td>
<td>Observation: 14 days Dosage: 2000 mg/kg bw Guideline: OECD 402</td>
<td>LD$_{50}$ = &gt; 2000 mg/kg bw</td>
<td>94.09 (50:50)</td>
<td>Report 08038/23-06-2008</td>
</tr>
<tr>
<td>Wistar Rats (Rattus norvegicus) (m,f)</td>
<td>Inhalation</td>
<td>Observation: 14 days Dosage: 0.24 mg/l air Guideline: OECD 403</td>
<td>LC$_{50}$ = &gt; 0.24 mg/l of air at breathing zone</td>
<td>94.09 (50:50)</td>
<td>Report 08041/23-06-2008</td>
</tr>
<tr>
<td>New Zealand White rabbit (Oryctolagus cuniculus) (f)</td>
<td>Skin irritation</td>
<td>Observation: 1, 24, 48 and 72 hr after patches were removed Dosage: 0.5 ml Guideline: OECD 404</td>
<td>Non- Irritant</td>
<td>94.09 (50:50)</td>
<td>Report 08039/23-06-2008</td>
</tr>
<tr>
<td>New Zealand White rabbit (Oryctolagus cuniculus) (m)</td>
<td>Eye irritation</td>
<td>Observation: 1,24,48 &amp; 72 h after treatment Dosage: 0.1 ml Guideline: OECD 405</td>
<td>Minimally irritant</td>
<td>94.09 (50:50)</td>
<td>Report 08040/23-06-2008</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Conditions and guideline</th>
<th>Result</th>
<th>Purity % (cis:trans)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella typhimurium</em> TA100, TA102, TA1535, TA98 and TA1537</td>
<td>Bacterial reverse mutation assay (<em>in vitro</em>)</td>
<td>Dosage: 0.039, 0.078, 0.156, 0.313 and 0.625 µl/plate Guideline: OECD 471</td>
<td>Negative</td>
<td>94.0 (50:50)</td>
<td>Report 08241 / 03-10-2008</td>
</tr>
<tr>
<td>Swiss Albino mouse (<em>Mus musculus</em>)</td>
<td>Mammalian bone marrow chromosomal aberration (<em>in vivo</em>)</td>
<td>Dosage: 100, 1000 and 2000 mg/kg bw Guideline: OECD 475</td>
<td>Negative</td>
<td>94.0 (50:50)</td>
<td>Report 08242 / 03.10.2008</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study number</th>
<th>Author(s)</th>
<th>year</th>
<th>Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.</th>
</tr>
</thead>
</table>
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$^2$ 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 BL permethrin should be designated as relevant.

---

$^2$ 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).
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 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$^4$.

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 \textit{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.

---

$^4$ 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 331/2008
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
permethrin (E-ISO), permethrine (F-ISO)

Chemical names
IUPAC: 3-phenoxybenzyl (1RS,3RS;1RS,3SR)-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:

<table>
<thead>
<tr>
<th>Isomer</th>
<th>Structure</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2) (1R, cis)</td>
<td><img src="image" alt="Structure 2" /></td>
<td>sum ≈ 40%</td>
</tr>
<tr>
<td>(4) (1S, cis)</td>
<td><img src="image" alt="Structure 4" /></td>
<td></td>
</tr>
<tr>
<td>(1) (1R, trans)</td>
<td><img src="image" alt="Structure 1" /></td>
<td>sum ≈ 60%</td>
</tr>
</tbody>
</table>

Note: the ISO common names and the IUPAC and CA names do not define the isomer ratio.
**Molecular formula**

\[ \text{C}_{21}\text{H}_{20}\text{Cl}_{2}\text{O}_{3} \]

**Relative molecular mass**

391.3

**CAS Registry number**

52645-53-1

**CIPAC number**

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**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value(s) and conditions</th>
<th>Purity %</th>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vapour pressure</td>
<td>(6.9 \times 10^{-6}) Pa at 25°C</td>
<td>99.6</td>
<td>OECD 104</td>
<td>0483/0059</td>
</tr>
<tr>
<td>Melting point</td>
<td>Melting point: &lt;20°C</td>
<td>99.6</td>
<td>OECD 102</td>
<td>0483/0059</td>
</tr>
<tr>
<td>Temperature of decomposition</td>
<td>252°C</td>
<td>99.6</td>
<td>OECD 102</td>
<td>0483/0059</td>
</tr>
<tr>
<td>Solubility in water at 20°C</td>
<td>11.1 µg/l at 20 ± 0.5°C at pH 7.0-9.3</td>
<td>100% (trans isomer)</td>
<td>OECD 105</td>
<td>JP-0023</td>
</tr>
<tr>
<td>Octanol/water partition coefficient</td>
<td>(\log P_{OW} &gt; 6.5) at 40°C</td>
<td>99.6</td>
<td>OECD 117</td>
<td>0483/0059</td>
</tr>
<tr>
<td>Hydrolysis characteristics, half-life at 25°C</td>
<td>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.</td>
<td>Radiochemical purity, both isomers &gt;98%</td>
<td>Japan-MAFF guideline No.12-Nosan No.8147, Part 2-6-1 (similar to OECD)</td>
<td>JM-0014</td>
</tr>
</tbody>
</table>

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Note: the CAS Registry No. and CIPAC number do not define the isomer ratio.
Table 1. Physico-chemical properties of pure 40:60 cis:trans permethrin or the resolved diastereoisomers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value(s) and conditions</th>
<th>Purity %</th>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photolysis characteristics</td>
<td>Xenon lamp with filter (blocking IR &amp; radiation &lt;290 nm), in sterile buffer solution (pH 4) or synthetic humic water (SHW), with dark control, testing cis and trans isomers separately (both cyclopropyl 1-14C labelled). Irradiation equivalent to natural sunlight (Tokyo, 35°N, April-June) for 30 days. Half-life: cis = 23.1 d (buffer), 14.6 d (SHW) trans = 36.8 d (buffer), 25.5 d (SHW)</td>
<td>Radiochemical purity, both isomers &gt;98% 98%</td>
<td>Japan-MAFF guideline No.12-Nosan No.8147, Part 2-6-2 (similar to OECD)</td>
<td>JM-0016</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data</th>
<th>Confidential information supplied and held on file by FAO and WHO. Mass balances were 97.8-98.2%, no unidentified impurities were reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declared minimum 40:60 cis:trans permethrin content</td>
<td>950 g/kg</td>
</tr>
<tr>
<td>Relevant impurities &lt; 1 g/kg and maximum limits for them</td>
<td>None</td>
</tr>
<tr>
<td>Stabilisers or other additives and maximum limits for them</td>
<td>None</td>
</tr>
<tr>
<td>Melting temperature of the TC</td>
<td>&lt;20°C</td>
</tr>
</tbody>
</table>

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. 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.

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

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7 Permethrin/Eksmin, registration number 52AP-409, 5 March 1977.
8 PramexB technical insecticide, registration number 73049-418, 14 September 2005.
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 triphenylphosphate. The method was adopted as a full CIPAC method in 2007, 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 [1RS,3RS]:[1RS,3SR] (cis:trans) ratio of 40:60, with a permitted range for the average measured ratio of 30:70 to 50:50.

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9 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](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

<table>
<thead>
<tr>
<th>Species</th>
<th>Test and permethrin used</th>
<th>Purity % &amp; cis:trans ratio</th>
<th>Duration and conditions or guideline adopted</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, Sprague-Dawley (f)</td>
<td>Acute oral SM &amp; BL permethrin in the same study</td>
<td>SM: 96.3, 40:60 BL: 96.9, 40:60</td>
<td>Observation: 14 d, dose: 2000 mg/kg bw, OECD guideline 423</td>
<td>No mortality, no clinical signs observed. LD$_{50}$ &gt;2000 mg/kg bw for both SM and BL permethrin</td>
<td>QJT-0001</td>
</tr>
<tr>
<td>Mouse, dd strain (m)</td>
<td>Acute oral SM permethrin only</td>
<td>92.4, 46:54</td>
<td>Observation: 14 d, no guideline$^{10}$</td>
<td>LD$_{50}$ &gt;650 mg/kg bw (m)</td>
<td>JT-0009</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley, (m)</td>
<td>Acute oral SM permethrin only</td>
<td>92.4, 46:54</td>
<td>Observation: 14 d, guideline not stated</td>
<td>LD$_{50}$ &gt;430 mg/kg bw (m)</td>
<td>JT-0009</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley (m,f)</td>
<td>Acute dermal SM &amp; BL permethrin in the same study</td>
<td>SM 96.3, 40:60 BL 96.9, 40:60</td>
<td>Observation: 14 d, dose: 2000 mg/kg bw OECD guideline 402</td>
<td>No mortality, no clinical signs observed. LD$_{50}$ &gt;2000 mg/kg bw for both SM and BL permethrin</td>
<td>QJT-0002</td>
</tr>
<tr>
<td>Mouse, dd strain (m,f)</td>
<td>Acute dermal SM permethrin only</td>
<td>92.4, 46:54</td>
<td>Observation: 14 d, no guideline$^{1}$</td>
<td>LD$_{50}$ &gt;2500 mg/kg bw</td>
<td>JT-0009</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley (m,f)</td>
<td>Acute dermal SM permethrin only</td>
<td>92.4, 46:54</td>
<td>Observation: 14 d, no guideline$^{1}$</td>
<td>LD$_{50}$ &gt;2500 mg/kg bw</td>
<td>JT-0009</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley (m,f)</td>
<td>Acute inhalation SM &amp; BL permethrin in the same study</td>
<td>SM 96.3, 40:60 BL 96.9, 40:60</td>
<td>Exposure 4 h, observation 14 d, dose 5000 mg/m$^3$</td>
<td>BL permethrin: initial tremor, no mortality observed, LC$<em>{50}$ &gt;5000 mg/m$^3$ SM permethrin: initial tremor, 2 f died, LC$</em>{50}$ &gt;5000 mg/m$^3$</td>
<td>QJT-0003</td>
</tr>
<tr>
<td>Mouse, dd strain (m,f)</td>
<td>Acute inhalation SM permethrin only</td>
<td>92.4, 45:55</td>
<td>Exposure period 3 h, observation 28 d, no guideline$^{1}$</td>
<td>LC$_{50}$ &gt;685 mg/m$^3$</td>
<td>JT-0015</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley (m,f)</td>
<td>Acute inhalation SM permethrin only</td>
<td>92.4, 45:55</td>
<td>Exposure period 3 h, observation 28 d, no guideline$^{1}$</td>
<td>LC$_{50}$ &gt;685 mg/m$^3$</td>
<td>JT-0015</td>
</tr>
<tr>
<td>Rabbit, Japanese White (f)</td>
<td>Skin irritation BL permethrin only</td>
<td>96.9, 40:60</td>
<td>OECD guideline 404</td>
<td>Non-irritant</td>
<td>QJT-0005</td>
</tr>
</tbody>
</table>

$^{10}$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

<table>
<thead>
<tr>
<th>Species</th>
<th>Test and permethin used</th>
<th>Purity % &amp; cis:trans ratio</th>
<th>Duration and conditions or guideline adopted</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit, Japanese White (m)</td>
<td>Skin irritation SM permethrin only</td>
<td>91.8, 40:60</td>
<td>No guideline&lt;br&gt;OECD guideline 405</td>
<td>Non-irritant</td>
<td>JT-0046</td>
</tr>
<tr>
<td>Rabbit, Japanese White (f)</td>
<td>Eye irritation BL permethrin only</td>
<td>96.9, 40:60</td>
<td>OECD guideline 405</td>
<td>Non-irritant</td>
<td>QJT-0004</td>
</tr>
<tr>
<td>Rabbit, Japanese White (m)</td>
<td>Eye irritation SM permethrin only</td>
<td>91.8, 40:60</td>
<td>No guideline&lt;br&gt;OECD guideline 406</td>
<td>Non-irritant</td>
<td>JT-0046</td>
</tr>
<tr>
<td>Guinea pig, Hartley (f)</td>
<td>Skin sensitization BL permethrin only</td>
<td>96.9, 40:60</td>
<td>OECD guideline 406</td>
<td>Non-sensitizer</td>
<td>QJT-0006</td>
</tr>
<tr>
<td>Guinea pig, Hartley (m)</td>
<td>Skin sensitization SM permethrin only</td>
<td>94.6, 40:60</td>
<td>No guideline&lt;br&gt;OECD guideline 406</td>
<td>Non-sensitizer</td>
<td>JT-0011</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Purity % &amp; cis:trans ratio</th>
<th>Duration and conditions or guideline adopted</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, Sprague-Dawley (m,f)</td>
<td>Feeding toxicity</td>
<td>93.3, 40:60</td>
<td>No guideline&lt;br&gt;NOEL = 1500 ppm,</td>
<td>NOEL = 1500 ppm,</td>
<td>JT-0013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>equivalent to 92.9 mg/kg bw/d (m)</td>
<td>equivalent to 92.9 mg/kg bw/d (f)</td>
<td>JT-0013</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley (m,f)</td>
<td>Inhalation toxicity</td>
<td>92.4, 40:60</td>
<td>No guideline&lt;br&gt;NOAEL = 50 mg/m³ (m,f)</td>
<td>NOAEL = 50 mg/m³ (m,f)</td>
<td>JT-0015</td>
</tr>
<tr>
<td>Rat, Sprague-Dawley (m,f)</td>
<td>Feeding, teratogenicity, embryotoxicity</td>
<td>92.4, 40:60</td>
<td>No guideline&lt;br&gt;oral exposure during days 9-14 of gestation.</td>
<td>The dams treated with 50 mg/kg bw/d showed slight toxic symptoms, (ataxia, tremor, hypersensitivity)</td>
<td>JT-0102</td>
</tr>
</tbody>
</table>

11 Study conducted prior to the introduction of guidelines but techniques and conditions equivalent to current international guidelines.
### Table B. Toxicology profile of SM permethrin technical material, based on repeated administration (sub-acute to chronic)

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Purity % &amp; cis:trans ratio</th>
<th>Duration and conditions or guideline adopted</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit, Japanese White (m,f)</td>
<td>Feeding, teratogenicity, embryotoxicity</td>
<td>92.5, 40:60</td>
<td>No guideline¹, oral gavage, 4 doses during days 6-18 inclusive of pregnancy, doses: 600, 1200, 1800 mg/kg bw/d</td>
<td>Embryotoxic at the two higher levels of treatment, toxic to dams at 1800 mg/kg bw/day but not teratogenic at any level</td>
<td>JT-0082</td>
</tr>
</tbody>
</table>

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

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

### Table D. Ecotoxicology profile of SM permethrin technical material

<table>
<thead>
<tr>
<th>Species</th>
<th>Test</th>
<th>Purity % &amp; cis:trans ratio</th>
<th>Duration and conditions</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudokirchneriella subcapitata</em> (freshwater green alga)</td>
<td>Effect on growth</td>
<td>94.4, 40:60</td>
<td>OECD 201</td>
<td>EC₅₀ (72hr) = 540 µg/l NOEC (72hr) = 0.21 µg/l</td>
<td>JW-0041</td>
</tr>
<tr>
<td><em>Colinus virginianus</em> (northern bobwhite)</td>
<td>Acute oral toxicity</td>
<td>94.4, 40:60</td>
<td>EPA OPPTS 850.2100</td>
<td>LD₅₀ &gt;2000 mg/kg</td>
<td>JW-0040</td>
</tr>
</tbody>
</table>
## ANNEX 2. REFERENCES

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumitomo document number or other reference</td>
<td>Year and title of report or publication details</td>
</tr>
<tr>
<td>JT-0046</td>
<td>1981. Primary eye and skin irritation tests of Eksmin in rabbits.</td>
</tr>
<tr>
<td>QJT-0002</td>
<td>2006. Acute dermal toxicity study of Permethrin in rats.</td>
</tr>
<tr>
<td>QJT-0004</td>
<td>2006. An eye irritation study of Permethrin in rabbits.</td>
</tr>
<tr>
<td>QJT-0005</td>
<td>2006. A skin irritation study of Permethrin in rabbits.</td>
</tr>
<tr>
<td>QJT-0006</td>
<td>2006. A skin sensitization study of Permethrin in guinea pigs.</td>
</tr>
</tbody>
</table>