WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

PYRIPROXYFEN

4-Phenoxyphenyl (Rs)-2-(2-Pyridyloxy)Propyl Ether

World Health Organization

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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 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.

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

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[1] This disclaimer applies to all specifications published by WHO.

INTRODUCTION

WHO establishes and publishes specifications[2] 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. Evaluation reports include 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 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.

[2] Publications available on the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website, https://extranet.who.int/pqweb/vector-control-products

PART ONE: SPECIFICATIONS

PYRIPROXYFEN **Page**

Pyriproxyfen Information

ISO common name

Pyriproxyfen (BSI, E-ISO)

Synonyms

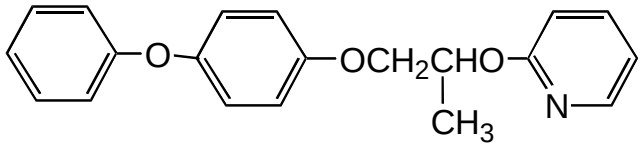
None

Chemical names

IUPAC 4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether

CA 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine

Structural formula



Empirical formula

$C_{20}H_{19}NO_3$

Relative molecular mass

321.37 g/mol

CAS Registry number

95737-68-1

CIPAC number

715

Identity tests

HPLC retention time, IR spectrum.

Pyriproxyfen Technical Material

WHO specification 715/TC (October 2017*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports (715/2005, 715/2015, 715/2017.1, 715/2017.2, 715/2021.2). This specification 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 (715/2005, 715/2015, 715/2017.1, 715/2017.2), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of pyriproxyfen together with related manufacturing impurities and shall be a white to pale yellow solid or a colourless to yellow clear liquid, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (715/TC/M/2, CIPAC Handbook M, p.181, 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 **Pyriproxyfen content** (715/TC/M/3, CIPAC Handbook M, p.181, 2009)

The pyriproxyfen content shall be declared (not less than 970 g/kg), and when determined, the average measured content shall not be lower than the declared minimum content.

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* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website, http://www.who.int/whopes/quality/en/https://extranet.who.int/pqweb/vector-control-products

Pyriproxyfen Granules

WHO specification 715/GR (December 2021*)

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 (715/2005, 715/2015, 715/2021.1). This specification should be applicable to relevant products of these manufacturers and those of any other formulators who use only TC from the evaluated source. The specification is not an endorsement of those products nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of manufacturers who use TC from other sources. The evaluation reports (715/2005, 715/2015, 715/2021.1), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of granules containing technical pyriproxyfen, complying with the requirements of WHO specification 715/TC together with pumice and any necessary formulants. It shall be dry, free flowing, essentially non-dusty and free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 **Identity tests** (715/GR/M/2, CIPAC Handbook M, p.185, 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 **Pyriproxyfen content** (715/GR/M/3, CIPAC Handbook M, p.185, 2009)

The pyriproxyfen content shall be declared (5 g/kg), and when determined, the average measured content shall not differ from that declared by more than ± 15%.

3 Physical properties

3.1 **Nominal size range** (MT 170, CIPAC Handbook F, p.420, 1995)

The nominal size range of the formulation shall be declared (300 to 1000 µm). Not less than 850 g/kg of the formulation shall be within the nominal declared size range.

3.2 **Dustiness** (MT 171.1, CIPAC Handbook P, p.235, 2021) (Note 1)

The formulation shall have a maximum collected dust of 30 mg by the gravimetric method or a maximum dust factor of 25 by the optical method.

3.3 Attrition resistance (MT 178, CIPAC Handbook H, p.304, 1998)

Minimum: 98% attrition resistance.

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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 Unit – Vector Control Product Assessment Team (PQT/VCP) website, http://www.who.int/whopes/quality/en/https://extranet.who.int/pqweb/vector-control-products

4 Storage stability

4.1 **Stability at elevated temperature** (MT 46.4, CIPAC Handbook P, p.232, 2021)

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

- nominal size range (3.1)
- dustiness (3.2)
- attrition resistance (3.3).

Note 1 Measurement of dustiness must be carried out on the sample "as received" and, where practicable, the sample should be taken from a newly opened container because changes in the water content of samples may influence dustiness significantly. The optical method of MT 171.1 usually shows good correlation with the gravimetric method and can therefore be used as an alternative where the equipment is available. Where the correlation is in doubt, it must be checked with the formulation to be tested. In case of dispute, the gravimetric method shall be used.

Note 2 Samples of the formulation taken before and after the accelerated storage stability test may be analysed concurrently after the test in order to reduce the analytical error.

Pyriproxyfen Matrix Release

WHO specification 715/MR (June 2025*)

This specification, which is PART ONE of this publication, is based on evaluations of data submitted by the manufacturer whose name is listed in the evaluation reports (715/2016, 715/2021.1, 715/2025. This specification should be applicable to relevant products of this manufacturer, but it is not an endorsement of those products nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers, irrespective of the source of TC. The evaluation reports (715/2016, 715/2021.1, 715/2025), given in PART TWO, form an integral part of this publication.

The material, sampled from any part of the consignment in accordance with the procedure described in Note 1 or any other acceptable procedure, shall comply with the specification.

1 Description

The product shall be formed mainly from polymer treated with technical pyriproxyfen complying with the requirements of WHO specification 715/TC together with any necessary other formulants. The product shall appear clean and shall be free from visible extraneous matter, visible damage (such as splitting or tearing) and visible manufacturing defects and shall be suitable for use as a pesticide formulation with controlled release activity (Note 2).

2 Active ingredient

2.1 **Identity tests** (715/MR/M/2, CIPAC Handbook P, p.177, 2021) (Note 3)

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 **Pyriproxyfen content** (715/MR/M/3, CIPAC Handbook P, p.177, 2021) (Note 3)

The pyriproxyfen content shall be declared (20 g/kg), and, when determined, the average content shall not differ from that declared by more than 25%.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Unit – Vector Control Product Assessment Team (PQT/VCP) website, http://www.who.int/whopes/quality/en/https://extranet.who.int/pqweb/vector-control-products.

2.3 **Retention rate of pyriproxyfen** (MT 200, CIPAC Handbook P, p.255, 2021 Note 3)

The retention rate of pyriproxyfen from the polymer, when measured, shall comply with the following criteria.

Elution time25 ± 2°C	Retention rate
1h	102% - 80%
2h	100% - 75%
4h	96% - 69%

3 Physical properties

3.1 Floating or sinking ability (Note 4)

The product, when used, should sink in water.

4 Storage stability

4.1 Stability at elevated temperature (MT 46.4, CIPAC Handbook P, p.232, 2021) (Note 5)

After storage at 54 ± 2°C for 2 weeks, the determined total active ingredient content must not be lower than 95%, relative to the determined average content found before storage (Notes 6 and 7), and the formulation shall continue to comply with the clauses for:

– retention rate of pyriproxyfen (2.3)

Note 1 Sampling

General requirements:

a) Samples shall be stored in such a manner that there is no deterioration of the material.
b) The sampling instrument shall be clean and dry.
c) Samples shall be protected against contamination.

Sampling, testing and acceptance:

a) In any consignment, all the master cartons containing matrix release formulation products of the same type shall constitute a lot. Each master carton contains several containers.
b) Samples shall be drawn from each lot and individually tested to ascertain whether the material complies with the specified requirements.
c) Any sample failing to comply with the specified requirements shall be termed as defective. The acceptance number shall be the maximum number of defective samples permissible for a lot to be accepted.
d) The number of containers/samples to be drawn from the lot and the acceptance number shall be as shown in the following table.

Total number of containers/samples in lot	Number of containers/samples to be tested	Acceptance number
300 or less	3	0
301 to 1200	6	1
1201 to 2000	13	2
2001 to 7000	21	3
7001 to 15000	29	4
15001 to 24000	48	6
24001 to 41000	84	9
Over 41000	126	13

e) Each of the containers/samples to be tested shall be drawn from a different master carton, which shall be selected at random. In order to ensure randomness of selection, random number tables shall be used. If such tables are not available, the following procedure may be adopted.

Starting from any master carton, count the master cartons as 1, 2, 3 ..... r in a systematic manner. Every r^{th} carton shall be drawn, r being the integral part of N/n, where N is the total number of master cartons in the lot and n is the number of master cartons to be selected.

Note 2 The MR device shall be formed of a polymer resin (incorporated type) mesh formed into a circular (MR) convex disc.

Note 3 Samples must be of a sufficient quantity to conduct all tests required and representative of the product. A sufficient quantity of samples must be selected by taking at random, and in some cases, the total amount of product must be used.

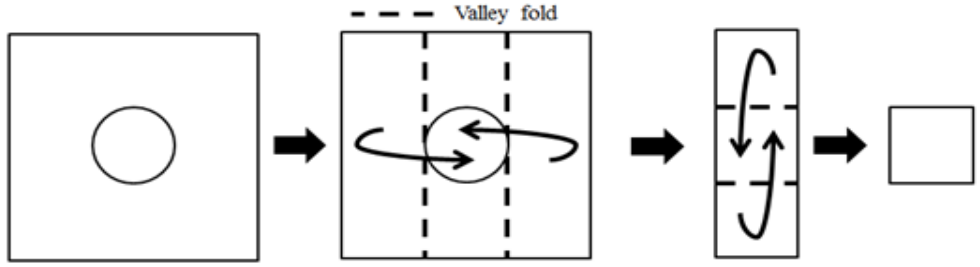
Use sharp scissors or equivalent to minimize damage to the product and thus avoid any consequential bias in the results of certain tests. Put the small portion in labelled, new, clean aluminum foil prior to analysis. Samples should be kept cool, avoiding heat sources (including sun heat) or freezing, and should be analysed/tested with minimum delay.

Note 4 Drop one piece of the product in a sufficiently large beaker containing CIPAC standard water D. Stir thoroughly using a glass rod to ensure complete wetting. Check to confirm that air bubbles are completely removed. After 1 minute, state the test result.

Note 5 MT 46.4 allows for storage of MR in sales packs or individual MR wrapped in aluminium foil (see Note 5 therein).

If the original carton box packaging is used as a storage container, seal it tightly in a plastic bag before starting accelerated storage stability testing to avoid the possibility of pyriproxyfen contaminating other items in temperature-controlled oven.

When individual MR devices are stored, do not use a plastic bag. Use only aluminium foil as a storage container to avoid the possibility of migration of active ingredient to the plastic bag. Once wrapped in foil, seal this tightly in a plastic bag before starting accelerated storage stability tests. Wrapping in aluminium foil is recommended as follows:



1. Put sample in the center of a sheet of the aluminum foil.
2. Fold the right third of the foil across followed by the left third.
3. Fold down the top third of the foil followed by the bottom third.

Note 6 Samples of the formulation taken before and after the accelerated storage stability test may be analysed concurrently after the test in order to reduce the analytical error.

Note 7 When a whole MR device is used to analyse the active ingredient in accordance with CIPAC method (715/MR/M/3), it is important to consider the variation among each MR device.

MR is a heterogeneous formulation, so the initial active ingredient content can differ slightly between devices. This variation is least between MR devices in the same carton box, as these are manufactured at almost the same time. To minimize variation, take samples of MR devices for accelerated storage stability tests from the same commercial package for testing before storage.

PART TWO: EVALUATION REPORTS

PYRIPROXYFEN

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FAO/WHO Evaluation Report 715/2025

Recommendations

The Meeting recommended that the revised specification for pyriproxyfen MR, as proposed by Sumitomo, and as amended, should be adopted by WHO.

Appraisal

The Meeting considered information submitted by Sumitomo Chemical Co., Ltd. in May 2025 for the revision of the WHO specification for pyriproxyfen MR. The exisiting specification for pyriproxyfen MR was published in December 2021 based on revisions to the original data package provided by Sumitomo Chemical Co., Ltd..

The company proposed an amendment to remove Note 2, referring to the resin composition.

The Meeting noted that the amemdment proposed was in accordance with the relevant template of the 2021 second edition of the FAO/WHO Manual on development and use of FAO and WHO specificatons for chemical pesticides, which does not have a Note specifying the resin composition.

The meeting agreed with the change, as WHO specifications for public health pesticides are meant to be global norms and standards, and not product specific. It was noted that various polymers could be used to produce an MR product and that the specification should not limit innovation.

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FAO/WHO Evaluation Report 715/2021.2

Summary of Action

In October 2021, the company Nantong Gongcheng Fine Chemical Co., Ltd. confirmed to WHO that their company name had changed to Jiangsu Gongcheng Bio-tech Co. It was concluded that the manufacturing site and processes for manufacturing of pyriproxyfen TC are not affected by this change, and that Jiangsu Gongcheng Bio-tech Co. ensures the continued support of the WHO specification for pyriproxyfen TC.

PYRIPROXYFEN

FAO/WHO Evaluation Report 715/2021.1

Recommendations

The Meeting recommended that the revised specification for pyriproxyfen MR, as proposed by Sumitomo, and as amended, should be adopted by WHO.

Appraisal

The Meeting considered information and draft specification submitted by Sumitomo in early 2020 for the revision of the WHO specification for pyriproxyfen MR. The specification for pyriproxyfen MR was published in October 2017 based on a data package provided by Sumitomo. The draft revised specification for pyriproxyfen MR was in accordance with the relevant template of the 2016 third edition of the first edition of the FAO/WHO Manual on development and use of pesticide specifications.

The reason for the update is the recent adoption of the revised and extended CIPAC method for the accelerated storage of pesticide formulations, MT 46.4. This new version of the method now incorporates all different types of formulations, including devices used in vector control such as LN or MR. Whereas the previous version, MT 46.3, had been amended with several sub-methods (one of them applying for MR), these sub-methods are now all consolidated in MT 46.4.

MT 46.4 no longer offers the detailed instructions that were provided in sub-method 5 of MT 46.3. This includes, for example, wrapping of the MR device individually in aluminium foil during exposure in a thermostatically controlled oven for the appropriate time-temperature combination. The instructions for MR are understandably general in nature (Quotation: "Unless storage of entire MR device(s) in original sales pack is intended, individually wrap each MR device tightly in aluminium foil and seal it in a plastic bag or alternatively seal the MR, e.g., in a bag without an inner plastic layer to avoid migration of active ingredient during storage.")

Therefore, the manufacturer and the Meeting agreed that the specification for pyriproxyfen MR should refer to MT 46.4 but provide more detailed instructions in footnote 6 in order to allow the correct execution of the tests carried out to check the compliance of a consignment of MR with the specification.

The manufacturer also proposed to clarify in a footnote that, as pyriproxyfen MR is a heterogeneous formulation, the pyriproxyfen content before and after the accelerated storage stability test should be performed on devices taken from the same commercial package in order to reduce the sampling error. The Meeting agreed.

Besides these updates, no limits or clauses were modified.

Additional action proposed by the Meeting

The Meeting also recommended updating the GR and MR specifications to align with the latest versions of CIPAC methods and specification templates in the Manual. They include:

- The reference to CIPAC methods for pyriproxyfen identity, content and retention rate, as published in CIPAC Handbook P for the MR

- The replacement of method for accelerated storage stability MT 46.3 by MT 46.4 as published in CIPAC Handbook P for the GR and MR
- The reference to CIPAC method MT 171.1 for dustiness as published in CIPAC Handbook P for the GR
- The update of some footnotes.

The revised CIPAC MT methods are considered to provide equivalent results as the previous versions, so all limits in the concerned clauses should remain the same as the previous versions.

PYRIPROXYFEN

FAO/WHO Evaluation Report 715/2017.2

Recommendations

The Meeting recommended the following:

(i) The pyriproxyfen TC proposed by Rudong Zhongyi Chemical Co., Ltd. should be accepted as equivalent to the pyriproxyfen reference profile.

(ii) The existing FAO and WHO pyriproxyfen TC specifications, respectively, should be extended to the technical material produced by Rudong Zhongyi Chemical Co., Ltd.

(iii) The existing FAO specification for pyriproxyfen EC should be extended to the formulation produced by Rudong Zhongyi Chemical Co., Ltd.

Appraisal

The Meeting considered data and supporting information submitted in September 2016 by Rudong Zhongyi Chemical Co., Ltd. (Rudong Zhongyi, the company) for the determination of the equivalence for pyriproxyfen TC (FAO/WHO specification 715/TC) and pyriproxyfen EC (FAO specification 715/EC). The data submitted were 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) and supported the draft specifications. The reference specification and supporting data for pyriproxyfen were provided by Sumitomo Chemical Co., Ltd and the FAO/WHO specifications have been published in 2005.

The confidential data submitted are the same as those submitted for registration in the EU (evaluated by HSE, CRD - UK).

Pyriproxyfen was evaluated by JMPR in 1999 and 2001. It is not under patent and the main formulation type available is EC. Pyriproxyfen is not co-formulated with other pesticides.

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on all impurities present at or above 1 g/kg, as well as any relevant impurities below 1 g/kg, and their manufacturing limits in the TC. Mass balances ranged from 99.23% to 99.64% in the 5-batch data. The maximum limits for the impurities were supported by the 5-batch data and are statistically justified. The proposer declared the minimum purity of the pyriproxyfen TC as 980 g/kg which is statistically justified and it is somewhat higher than the existing FAO/WHO specifications (970 g/kg).

The manufacturing process, impurity profile and five batch analyses were compared with the data submitted for the reference profile. The Rudong Zhongyi manufacturing process utilizes the same synthetic route as that of the reference material.

The pyriproxfen TC of Rudong Zhongyi does not contain additional impurities, or any impurities at a higher level than present in the reference source.

In addition, the possible presence of polychlorinated dioxins in the Rudong Zhongyi TC at or above the level of 0.1 ppb TEQ (Toxic Equivalents) was evaluated. The company submitted a study showing that levels of polychlorinated dioxins are below 0.1 ppb TEQ. The analysis was performed by GC-high resolution MS.

A mutagenicity study (Ames test) for pyriproxyfen has been conducted as Tier-1 data. Pyriproxyfen TC does not show mutagenicity in in vitro bacterial assays (OECD 471).

The company used an in-house HPLC-UV-DAD method with external standardization for the determination of the active ingredient content in pyriproxyfen TC instead of the CIPAC official method published in CIPAC Handbook M. The Meeting therefore requested the proposer to provide supporting evidence or a bridging study to demonstrate that the in-house method used for the determination of the active ingredient in pyriproxyfen TC provides comparable results with the CIPAC method for pyriproxyfen. The in-house method used for the determination of the active ingredient was validated in one laboratory with respect to specificity, linearity of response, linearity range, precision and accuracy. The proposer responded with submission of a bridging study that confirmed that the in-house analytical method and the CIPAC method gave equivalent results with respect to determination of pyriproxyfen content in the TC.

The determination of residual solvent was achieved using a validated GC-MS method; whereas the determination of an impurity was achieved using an external standardization HPLC-UV-DAD method. Both methods are validated with respect to specificity, linearity of response, precision, accuracy, limit of detection and quantification.

The content of inorganic impurities was determined by the content of material insoluble in acetone using CIPAC method MT 27, whereas loss on (vacuum) drying was determined by the gravimetric method CIPAC MT 17.3. The water content of the technical material was determined using CIPAC method MT 30.5 (Karl Fischer titration).

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

The confirmation of structural identity of pyriproxyfen and the impurity was achieved using 1H-Nuclear magnetic resonance.

The Meeting concluded that the Rudong Zhongyi Chemical Co., Ltd. pyriproxyfen TC was equivalent to the pyriproxyfen reference TC based on Tier-1 evaluation. Therefore, the Meeting recommended extending the existing FAO and WHO specifications for pyriproxyfen to the technical material produced by Rudong Zhongyi. The Meeting concluded also that the pyriproxyfen EC proposed by Rudong Zhongyi was equivalent to the reference EC specification. Furthermore, the Meeting recommended to update the FAO specifications for pyriproxyfen EC and EW with respect to the CIPAC methods for persistent foam (MT 47.3 instead of MT 47.2) and emulsion stability (MT 36.3), to be in line with the current CIPAC methods.

The Meeting recommended also to remove "substantially odourless" in the description clause of the specification for pyriproxyfen TC, as olfactory tests are no recommended. Sumitomo Chemical Co, Ltd. (reference holder) and Tagros Chemicals India Limited (equivalence holder) were consulted and agreed with this amendment.

Supporting Information
for
Evaluation Report 715/2017.2

Physico-chemical properties of pyriproxyfen

Table 1. Chemical composition and properties of pyriproxyfen 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 99.23 - 99.64 % and percentages of unknowns were 0.36 - 0.77 %.		
Declared minimum pyriproxyfen content		980.0 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
Melting temperature range of the TC	47.8 – 48.8°C	98.08	OECD 102, 1995 OPPTS 830.7200, 1998	15055.005.077.14
Solubility in organic solvents	1167 g/l in acetone at 20.1°C 56 g/l in methanol at 20.1°C	98.08	OECD 105, 1995 OPPTS 830.7840, 1996	15055.008.139.14

Formulations and co-formulated active ingredients

The main formulation type available is EC. The formulations are registered and sold in many countries like Turkey, Belgium, Cyprus, Denmark, France, Greece and Hungary. Pyriproxyfen is not co-formulated with other pesticides.

Methods of analysis and testing

The analytical method used for the determination of the active ingredient in the TC is a validated in-house HPLC-UV-DAD method with external standardization and UV detection at 235 nm. The in-house method is different than the official CIPAC method (715/TC/M) regarding sample preparation and chromatographic analysis. The company was therefore requested to prove the applicability of the existing CIPAC method (715/TC/M) for the determination of the active substance content in the technical product [CIPAC Handbook M]. In response to this point the company provided a bridging study that confirmed that the in-house method and the CIPAC method gave equivalent results with respect to pyriproxyfen content in the TC.

Further methods were submitted for the determination of the detected impurities. The method for the determination of an impurity is a validated HPLC-UV-DAD method, whereas the method used for the determination of the remaining solvent is a validated GC-MS method. The content of inorganic impurities was determined by the content of material insoluble in acetone using CIPAC method MT 27. The content of loss on vacuum drying was determined to constant weight by gravimetric method CIPAC MT 17.3. Finally a Karl Fischer titration method was submitted for the determination of water. The company also checked and demonstrated that dioxins are not present at

or above the level of 0.1 ppb. The analysis was performed by gas chromatography with high resolution mass spectrometry (GC-HRMS).

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

Containers and packaging

No special requirements for containers and packaging have been defined.

Expression of the active ingredient

The active ingredient is expressed as pyriproxyfen.

Annex 1: Hazard Summary Provided by the Proposer

Notes:

i. The proposer confirmed that the mutagenicity data included in the summary below were derived from pyriproxyfen having impurity profiles similar to those referred to in the table above.
ii. The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table A. Mutagenicity profile of pyriproxyfen technical material based on *in vitro* tests

Species	Test	Purity %	Guideline, duration, doses and conditions	Results	References
Salmonella typhimurium TA 97a, TA 98, TA 100, TA 102 and TA 1535	*In vitro*, Ames Test, reverse mutation assay	98.50	OECD 471 0.03, 0.1, 0.3, 1.0, 3.0 and 5.0 mg/plate with and without metabolic activation.	Negative	15055.401.098.14

Annex 2: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
15055.030.073.14		2015	Qualitative and Quantitative Profile of the test substance Pyriproxyfen (Five Batch Analysis), 15055.030.073.14, GLP.
		2017	Environmental Analysis Report, Dioxins/Furans. Eurofins, Lancaster Laboratories.
15055.005.077.14		2015	Melting point and range of PYRIPROXYFEN. Study #:15055.005.077.14, GLP.
15055.008.139.14		2015	Solubility in water and organic solvents of PYRIPROXYFEN. Study #:15055.008.139.14, GLP.
15055.401.098.14		2015	Evaluation of the mutagenic potential of the test substance Pyriproxyfen by reverse mutation assay in *Salmonella enterica* serovar *Typhimurium* (Ames Test). Study #:15055.401.098.14, GLP.

PYRIPROXYFEN

FAO/WHO Evaluation Report 715/2017.1

Recommendations

The Meeting recommended the following:

(i) The pyriproxyfen TC proposed by Nantong Gongcheng Fine Chemical Co., Ltd. should be accepted as equivalent to the pyriproxyfen reference profile

(ii) The existing WHO pyriproxyfen TC specification should be extended to the technical material produced by Nantong Gongcheng Fine Chemical Co., Ltd.

Appraisal

The Meeting considered data and supporting information submitted in September 2015 by Nantong Gongcheng Fine Chemical Co., Ltd (Nantong Gongcheng) for the determination of the equivalence with the WHO specification for pyriproxyfen TC (WHO specification 715/TC). The data submitted were in accordance with the requirements of the Manual on Development and Use of FAO and WHO specifications for Pesticides (November 2010 - 2nd revision of the 1st edition) and supported the draft specifications. The reference specification and supporting data for pyriproxyfen were provided by Sumitomo Chemical Co., Ltd and the FAO/WHO specifications have been published in 2005.

This source of pyriproxyfen is registered for use in China, and a certificate of registration has been received from ICAMA. Pyriproxyfen was evaluated by JMPR in 1999 and 2001. It is not under patent, and the main formulation types for public health use are GR and EW. These formulations are registered and sold in China. Pyriproxyfen is not co-formulated with other pesticides.

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on all impurities present at or above 1 g/kg, as well as any relevant impurities below 1 g/kg, and their manufacturing limits in the TC. Mass balances ranged from 99.63% to 99.80% in the 5-batch data. The maximum limits for the impurities were supported by the 5-batch data and they are statistically justified. The proposer declared the minimum purity of the pyriproxyfen TC as 970 g/kg which is statistically justified and it is in line with the existing specifications (not less than 970 g/kg).

The manufacturing process, impurity profile and five batch analyses were compared with the data submitted in the reference profile. The Nantong Gongcheng manufacturing process utilizes the same synthetic route as that of the reference product. The pyriproxyfen TC of Nantong Gongcheng does not contain additional impurities, or any non-relevant impurities at a level 50% higher than present in the reference source.

Additionally it was checked and demonstrated by Nantong Gongcheng that polychlorinated dioxins are not present at or above the level of 0.1 ppb TEQ (Toxic Equivalents). The analysis was performed by GC-high resolution MS.

A mutagenicity study (Ames test) for pyriproxyfen has been conducted as tier-1 data. Pyriproxyfen TC does not show mutagenicity in *in vitro* bacterial assays (OECD 471).

The proposer used an in-house HPLC-UV method with external standardization for the determination of the active ingredient content in pyriproxyfen TC instead of the CIPAC method published in Handbook M. However, a bridging study was submitted to demonstrate that the in-house method provides comparable results as the CIPAC method. The in-house method used for the determination of the active ingredient was validated in one laboratory with respect to specificity, linearity of response, linearity range, precision and accuracy.

The determination of impurities was achieved using the same HPLC-UV method as referred to above for the active ingredient. As mentioned above, the method was validated with respect to specificity, linearity of response, precision, accuracy, limit of detection and quantification for impurities.

The water content of the technical material was determined using CIPAC method MT 30.5 (Karl Fischer titration).

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

The confirmation of structural identity of pyriproxyfen and the impurities was achieved using HPLC and LC-MS based on elution pattern, retention time and mass and the functional groups were confirmed by FT-IR and ^{1}H-Nuclear Magnetic Resonance.

The Meeting concluded that the Nantong Gongcheng pyriproxyfen TC was equivalent to the pyriproxyfen reference TC based on Tier-1 evaluation and recommended the extension of the existing WHO TC specification to the technical material produced by Nantong Gongcheng Chemical Co. Ltd.

Supporting Information
for
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Physico-chemical properties of pyriproxyfen

Table 1. Chemical composition and properties of pyriproxyfen technical material (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by WHO. Mass balances were 99.63 - 99.80 % and percentages of unknowns were 0.20 - 0.37 %.			
Declared minimum pyriproxyfen content	970 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
Melting temperature range of the TC	47.8 - 49.1°C	99.17	OECD 102	JRF Study No 202-2-11-14060

Formulations and co-formulated active ingredients

The main formulation types available are GR and EW. These formulations are registered and sold in China. Pyriproxyfen is not co-formulated with other pesticides.

Methods of analysis and testing

The analytical method used for the determination of the active ingredient in the TC is a validated in-house HPLC-UV method with external standardization and UV detection at 220 nm. This in-house method is different than the official CIPAC method (715/TC/M) regarding sample preparation and chromatographic analysis. The company was therefore requested to prove the applicability of the existing CIPAC method (715/TC/M) for the determination of the active substance content in the technical product [CIPAC Handbook M]. In response to this point the company provided a bridging study that confirmed that the in-house method and the CIPAC method gave equivalent results with respect to pyriproxyfen content in the TC.

The same method as described above was submitted for the determination of the detected impurities. A Karl Fischer titration method was submitted for the determination of water.

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

Containers and packaging

No special requirements for containers and packaging have been defined but containers should comply with pertinent national and international transport and safety regulations.

Expression of the active ingredient

The active ingredient is expressed as pyriproxyfen.

Annex 1: Hazard Summary Provided by the Proposer

Notes:

i. The proposer confirmed that the mutagenicity data included in the summary below were derived from pyriproxyfen having impurity profiles similar to those referred to in the table above.
ii. The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table A. Mutagenicity profile of pyriproxyfen technical material based on *in vitro* tests

Species	Test	Purity %	Guideline, duration, doses and conditions	Results	References
Salmonella typhimurium, TA 98, TA 100, TA 102, TA 1535 and TA 1537	*In vitro*, Ames Test, reverse mutation assay	97.6%	OECD 471 1.5, 5.0, 15, 50, 150, 500, 1500, 5000 µg/plate with and without metabolic activator.	Negative	JRF Study Number: 481-1-06-14059

Annex 2: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
227-2-12-1532 (Vol I)	H. Desai	2011	Preliminary analyses of five representative production batches of Pyriproxyfen active ingredient and its associated impurities, JRF Study Number 227-2-12-1532 (Final Report), GLP.
227-2-12-1532 (Vol II)	H. Desai	2011	Validation of analytical method for the determination of Pyriproxyfen active ingredient and its associated impurities, JRF Study Number 227-2-12-1532 (Final Report), GLP.
		2016	The Analytical Results Using the In-house Method and the CIPAC Method for Analysis of One Batch Pyriproxyfen TC. Nantong Gongcheng Fine Chemical Co., Ltd.
202-2-11-14060	J. Patel	2016	Melting Point/Melting Range of Pure Pyriproxyfen, JRF Study Number 202-2-11-14060 (Final Report), GLP.
481-1-06-14059	P.D. Tekale	2016	Bacterial Reverse Mutation Test of Pyriproxyfen Technical Material using Salmonella Typhimurium, JRF Study Number 481-1-06-14059 (Final Report), GLP.
D17030031		2017	Inspection and Analysis Centre Shanghai Advanced Research Institute, CAS Testing Report. Dioxin Analysis. Report number D17030031.

PYRIPROXYFEN

FAO/WHO Evaluation Report 715/2016

Recommendations

The Meeting recommended that the specification for pyriproxyfen MR, proposed by Sumitomo, as amended, should be adopted by WHO.

Appraisal

A draft specification and a data package were submitted in 2015 by Sumitomo Chemical Co. Ltd in support of a new matrix release formulation (MR) in order to extend the range of pyriproxyfen WHO specifications.

The product contains pyriproxyfen incorporated in an ethylene copolymer resin disc and is intended to be used in water containers. The formulation, in contact with water, liberates small amounts of the insecticide to the water phase to produce concentrations sufficient to control mosquito larvae. Pyriproxyfen is gradually released from the polymer material until it reaches an equilibrium state of the dissolved active ingredient with that in the MR formulation (low µg/L range). The product was tested and evaluated by WHOPES, which recommended its use as a mosquito larvicide in water containers for control of *Aedes* spp., the vectors of dengue, Chikungunya and Zika (WHO 2017).

Active ingredient content and retention

The nominal content of pyriproxyfen in the resin is 20 g/kg. The extension of the CIPAC method for determination of pyriproxyfen in MR formulations was presented at the Annual Meeting in Athens in 2015 and was provisionally adopted. This method was accepted as full CIPAC method in 2016. The supporting data show a good homogeneity of the content in different lots of the MR formulation with RSD significantly below the tolerance of ± 25 %.

The method to determine the retention of pyriproxyfen in the MR formulation was also presented in Athens in 2015, and tentatively adopted with the request of additional validation data. Briefly, the formulation is equilibrated with an ethanol/water mixture for three defined periods of time (1, 2 and 4 hours) and the remaining pyriproxyfen is analyzed in the formulation. The limits and ranges therefore refer to the ability of the formulation to retain a certain proportion of the active ingredient after defined time periods. However, the Meeting questioned the expression of the retention in the draft specification as they did not refer to ranges for the time points 1 and 4 hours and the statistical basis was unclear. The company reconsidered the expression how the retention at the three time points is defined and proposed some ranges, that were found to be well in accordance with the results from the test. Additional validation data (small scale collaborative trial) were also presented in 2016 at the CIPAC Meeting in Tokyo demonstrating the applicability and acceptable reproducibility of the method for retention rate of pyriproxyfen, and the method was accepted as a full CIPAC MT method.

Physical-chemical parameters

As the formulation does not mix nor dissolve in water, the only parameter to control with regard to its behaviour with water is floating or sinking of the MR formulation. The formulation should sink in water because it is designed as such for the stable release

of the active ingredient. It would also minimize interaction when water from the container is removed and replenished.

Storage stability

Under accelerated storage conditions - after 2 weeks at 54°C - at least 95% of the initial concentration of the active ingredient should be present and the criteria for retention of pyriproxyfen should be met. As the format of the intact MR formulation is not compatible with the glass bottles used in CIPAC MT 46.3, the company proposes to wrap the MR in aluminium foil and expose it to accelerated storage conditions as per MT 46.3. The Meeting considered the deviation from the adopted MT 46.3 for a justification and asked the company for bridging data to show that exposure of the MR formulation leads to similar results as the storage in glass bottles. The company presented a small scale study at the CIPAC Meeting in Tokyo demonstrating that different pyriproxyfen MR samples stored in aluminium foil show minimal differences when analyzed. CIPAC accepted the extension of MT 46.3 as tentative method.

The Meeting agreed also to update, in the specification for pyriproxyfen GR, the CIPAC method for dustiness (MT 171.1 instead of MT 171) to be in line with the current CIPAC method.

Annex 1: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
CIPAC/4997/m	Makiko Mukumoto *et al.*	2015	Pyriproxyfen. Method extension of CIPAC 715/TC/M/- to pyriproxyfen MR. June 2015.
CIPAC/4999/m	Makiko Mukumoto *et al.*	2015	Pyriproxyfen. Retention properties method of pyriproxyfen MR. June 2015.
CIPAC/5046/R	Takashi Sasaki *et al.*	2016	Extension of CIPAC method MT 46.3 to MR (accelerated storage procedure). Small Scale Collaborative Trial. Report to CIPAC. June 2016.
HPTR-2015	Takano, M.	2015	Actual data on the proposed specification for pyriproxyfen MR. No GLP.
HPTR-2016	Takano, M.	2016	Generation of data to support the proposed specification of Pyriproxyfen 2% MR formulation (Sumilarv 2MR).
	WHO	2017	Report of the 20th WHOPES Working Group Meeting, WHO/HQ, Geneva, 20 - 24 March 2017. Available at : http://www.who.int/whopes/recommendations/wgm/en/

PYRIPROXYFEN

FAO/WHO Evaluation Report 715/2015

Recommendations

The Meeting recommended the following:

(i) The pyriproxyfen TC as proposed by Tagros Chemicals India Limited should be accepted as equivalent to the Sumitomo reference profile.

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

(iii) The existing WHO specifications for pyriproxyfen TC and GR should be extended to encompass the corresponding products of Tagros Chemicals India Limited.

Appraisal

The Meeting considered data, specifications and information submitted by Tagros Chemicals India Limited in support of extension of the existing WHO specifications for pyriproxyfen TC and GR. The company confirmed also later to apply for extension of FAO specification for pyriproxyfen TC.

The Meeting was provided by Tagros with commercially confidential information on the manufacturing process, the manufacturing quality controls limits and 5-batch analysis data for active ingredient and impurities. The manufacturer stated that all impurities ≥ 0.05 g/kg were quantified.

The manufacturing process was considered by the Meeting and was concluded to be similar to this previously provided for FAO/WHO specification for pyriproxyfen TC. In the 5-batch analysis data (commercial scale batches manufactured from May to September 2014), mass balances were very high (99.49 - 99.71%). Percentage of unknown compounds was below 0.5 % which is acceptable. The minimum purity of pyriproxyfen in the TC of Tagros is 970 g/kg. No relevant impurities were declared in the specification for pyriproxyfen TC from Tagros.

The manufacturer provided full validation data (specificity, linearity of response, accuracy, repeatability ...) for analytical methods for active ingredient and impurities content. Nevertheless, the analytical method for determination of active ingredient content was not the CIPAC method (determination using HPLC-DAD at 225 nm and not at 254 nm and no use of an internal standard). The Meeting requested the manufacturer to provide a new 5-batch analysis data or a bridging study. A justification from the laboratory was provided to explain the difference between the CIPAC method and the method used in the 5-batch analysis data. This justification was not considered as acceptable. The manufacturer provided later a report with the determination of the active ingredient using the CIPAC method and it was considered as acceptable by the Meeting.

A new impurity was determined in the pyriproxyfen from Tagros. Nevertheless, the Meeting declared this impurity as not relevant. The analytical method used for determination of impurities was HPLC-UV at 225 nm and full validation data were provided by the manufacturer. The identity of active ingredient and impurities was confirmed using LC-MS.

The Meeting agreed that the purity / impurity profile of pyriproxyfen TC from Tagros is similar to the reference profile previously published by FAO/WHO and concluded that the pyriproxyfen TC of Tagros comply with the existing FAO/WHO specification.

The confidential information (manufacturing process, purity and impurity profile) submitted to FAO/WHO was confirmed by the Australian Authorities (APVMA) as being identical to that submitted for registration in Australia, and was evaluated and considered acceptable by the APVMA.

Tagros did not provide data on the physical-chemical properties of pure pyriproxyfen.

An Ames test was performed with a pyriproxyfen TC of 98.6 % purity. No other toxicological studies neither ecotoxicological studies were provided. Nevertheless, this was agreed as acceptable as the purity / impurity profile and the mutagenicity profile of the pyriproxyfen TC of Tagros were considered to be similar to the reference profile.

Chemical and physical properties of the GR formulation were determined by CIPAC methods, as indicated in the specification. The proposed specification is in accordance with the existing WHO specification for pyriproxyfen GR.

The Meeting proposed to update in the specification for pyriproxyfen GR the CIPAC method for nominal size range (MT 170 instead of MT 58) to be in line with the current CIPAC method.

The Meeting proposed also to revise in the GR specification the limit for dustiness from "Essentially non-dusty" to "The formulation shall have a maximum collected dust of 30 mg by the gravimetric method or a maximum dust factor of 25 by the optical method", as recommended in the amendments to the FAO/WHO specification Manual published on the FAO and WHO websites.

The Meeting agreed also to update, in the FAO specifications for pyriproxyfen EC and EW, the CIPAC method for persistent foam (MT 47.3 instead of MT 47.2) to be in line with the current CIPAC method.

Supporting Information
for
Evaluation Report 715/2015

Physico-chemical properties of pyriproxyfen

Table 1. Chemical composition and properties of pyriproxyfen 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 99.5-99.7%. Percentage of unknown was ≤ 0.5%.
Declared minimum pyriproxyfen content	970 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities < 1 g/kg and maximum limits for them	None
Stabilizers or other additives and maximum limits for them	None

Formulations

Tagros proposed a specification only for a GR formulation used in public health.

Annex 1: Hazard Summary Provided by the Proposer

Note:

Tagros Chemicals India Limited provided written confirmation that the toxicological data included in the following summary were derived from pyriproxyfen having impurity profiles similar to those referred to in Table 1, above.

Table A. Mutagenicity profile of pyriproxyfen technical material based on *in vitro* tests

Species	Test	Purity %	Guideline, duration, doses and conditions	Results	References
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA102	Point mutation, Ames test, *in vitro*	98.6	OCDE 471 Dose range: Trial 1 : 312.5, 625, 1250, 2500, 5000 µg/plate with (5%) and without S9. Trial 2 : 128 to 5000 µg/plate with (10%) and without S9 to confirm negative results of trial 1	Not mutagenic	14_14_075

Annex 2: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
14_14_075		2014	Bacterial reverse mutation test of pyriproxyfen technical in *Salmonella Typhimurium* tester strains. Unpublished report, GLP.
DNA 2789		2015	Analysis of 5 batches of Pyriproxyfen Technical Material to Determine the Content of Active Ingredient and specified impurities, with associated validation, in Compliance with Good Laboratory Practice. Unpublished report, GLP.
RCC study number 4987		2014	Determination of Dustiness of pyriproxyfen 0.5 % granules. GLP report.
RCC study number 4988		2014	Determination of nominal size range of pyriproxyfen 0.5 % granules. GLP report.
RCC study number 4989		2014	Determination of Attrition Resistance of pyriproxyfen 0.5 % granules. GLP report.
RCC study number 4990		2014	Accelerated storage stability (relevant physical and chemical parameters and active ingredient content) of pyriproxyfen 0.5 % granules. GLP report.
RCC study number 4991		2014	Determination of the active ingredient content of pyriproxyfen 0.5 % granules. GLP report.

PYRIPROXYFEN

FAO/WHO Evaluation Report 715/2005

Recommendations

The Meeting recommended that:

i. The specifications for pyriproxyfen TC and GR proposed by Sumitomo, as amended, should be adopted by WHO;

ii. The specifications for pyriproxyfen TC and EC proposed by Sumitomo, as amended, should be adopted by FAO.

Appraisal

The Meeting considered data and information submitted by Sumitomo Chemical Co. Ltd, in support of proposed new FAO and WHO specifications for TC, GR and EC.

Pyriproxyfen is not under patent. It is under review in the EU.

Pyriproxyfen is a juvenile hormone mimicking insecticide, used for control of flies, beetles, midges and mosquitoes in public health applications. It is also used in agriculture in some countries, e.g. the USA.

Pyriproxyfen is a solid (melting range 48-50ºC) of low volatility and only slightly soluble in water. It has no discernible acidic or basic characteristics and is stable to hydrolysis at pH 4-9 at 25C, but is prone to slow photolysis.

The Meeting was provided with commercially confidential information on the manufacturing process and 5- batch analysis data on all impurities ≥1 g/kg. Mass balances were very high (99.5–99.8%), with no unknowns detected. The data were confirmed as essentially similar to those submitted for registration in Italy.

The Meeting agreed with the manufacturer that none of the impurities should be designated as relevant.

The analytical method for determination of pyriproxyfen in TC, GR and EC is based on reversed-phase HPLC with UV detection at 254 nm and internal standardization with p-benzyldiphenyl. The method was validated by collaborative study and adopted by CIPAC in 2006.

Analytical methods for the determination of impurities were GC-FID using ethyl benzene internal standard, for residual solvent, and reversed-phase HPLC with external standardization, for the other impurities.

Physical properties of the formulations are determined by CIPAC methods, as indicated in the specifications.

The proposed specifications were in accordance with the requirements of the manual (FAO/WHO 2002).

TC. The description clause indicates that pyriproxyfen TC may be in the form of a solid or liquid, despite having a melting point in the range 48-50°C. The manufacturer explained that crystallization occurs very slowly, even in a refrigerator, and therefore the TC may remain in liquid form for a relatively long period after shipment.

GR. The manufacturer proposed the use of hand sieving to determine compliance with the clause for size range but the Meeting agreed that the standard method, MT 58, should be referenced in the specification.

EC. The specification is for agricultural products only, presently containing approximately 100 g/l pyriproxyfen. The manufacturer proposed that flash point (minimum 60ºC) should be included in the specification, in order to prevent the introduction of more hazardous products onto the market. The Meeting observed that FAO/WHO specifications do not include a clause for flash point, because the minimum acceptable is location and application dependent. It was agreed that a footnote should be inserted into the specification, to draw attention to the need for products to adhere national requirements for flash point.

Supporting Information
for
Evaluation Report 715/2005

Physico-chemical properties of pyriproxyfen

Table 1. Physico-chemical properties of pure pyriproxyfen

Parameter	Value(s) and conditions	Purity %	Method	Reference
Vapour pressure	<1.33 x 10^{-5} Pa at 22.8°C	100	EPA 63-9/OECD 104	NNP-0030
Melting point	48.0-50.0°C	100	OECD 102	NNP-0054
Boiling point	318°C	99.7	OECD 103	NNP-0086
Temperature of decomposition	Not available	-	-	-
Solubility in water, at 25ºC and pH6	0.367 ± 0.004 mg/l	99.4	EPA CG-1500	NNP-0026
Octanol/water partition coefficient, at 25ºC and pH 5.6	log P K_{OW} = 5.37	99.4	OECD 107	NNP-0025
Hydrolysis characteristics, at 25ºC	Stable at pH 5, 7 and 9	Radiochemical purity: 99.3 & 99.4%	OECD 111	NNM-0015
Photolysis characteristics	Photo-degradation in water under artificial sunlight, approximately equivalent to double the light intensity of natural midday sunlight at 43º N in July: Half-life = 3.72-6.36 days at 25°C and pH 7	Radiochemical purity: 99.9 & 99.2%	EPA161-2	NNM-0037
Dissociation characteristics	Dissociation constant could not determined due to low water solubility	-	-	NNP-0022

Table 2. Chemical composition and properties of technical pyriproxyfen (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 99.5-99.8%, with no unknowns.
Declared minimum pyriproxyfen content	970 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	48-50°C

Hazard summary

Pyriproxyfen was evaluated by the FAO/WHO JMPR in 1999 and 2001. The 1999 JMPR established an ADI of 0-0.1 mg/kg bw, on the basis of a 1-year study in dogs and a safety factor of 100 and concluded that it was not necessary to establish an acute reference dose because of low acute toxicity of pyriproxyfen. The 2001 JMPR

assessed the safety of pyriproxyfen as a mosquito larvicide in potable water and concluded that intake at the target concentration for control would not present unacceptable risks.

The WHO hazard classification of pyriproxyfen is: U, unlikely to present acute hazard in normal use (WHO 2002).

Formulations

The main formulation types available are GR and EC. These formulations are registered and sold in Turkey, UAE, Saudi Arabia, Belgium, Cyprus, Denmark, France, Greece, Hungary, Netherlands, Poland and Spain. Pyriproxyfen is not co-formulated with other pesticides.

Methods of analysis and testing

The analytical method for the active ingredient (including identity tests) is based on reversed phase HPLC, using UV detection at 254 nm and internal standardization with *p*-benzyldiphenyl (NNA-0011). The method was validated by collaborative study and adopted by CIPAC in 2006.

Impurities in pyriproxyfen were determined by reversed-phase HPLC, using UV detection at 254 nm and external standardization, and GC-FID and internal standardization with ethylbenzene for the residual solvent.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD and EPA, while those for the formulations were CIPAC, as indicated in the specifications.

Physical properties

The physical properties, the methods for testing them and the limits proposed for the GR and EC formulations, comply with the requirements of the FAO/WHO manual (1st edition).

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as pyriproxyfen.

Annex 1: Hazard Summary Provided by the Proposer

Note: Sumitomo provided written confirmation that the toxicological and ecotoxicological data included in the following summary were derived from pyriproxyfen having impurity profiles similar to those referred to in Table 2, above.

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

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Rat (m,f)	oral	97.2	EPA Guideline 81-1	LD_{50} >5000 mg/kg bw (m,f)	NNT-0005
Rat (m,f)	dermal	97.2	EPA Guideline 81-2	LD_{50} >2000 mg/kg bw (m,f)	NNT-0006
Rat (m,f)	inhalation	97.0	EPA Guideline 81-3	LC_{50} >1300 mg/m^3 (m,f)	NNT-0022
Rabbit (m,f)	skin irritation	97.2	EPA Guideline 81-5	Non-irritating	NNT-0004
Rabbit (m,f)	eye irritation	97.2	EPA Guideline 81-4	Minimally irritating	NNT-0004
Guinea pig	skin sensitization	97.2	Maximization method, EPA Guideline 81-6	Not a sensitizer	NNT-0003

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

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Rat (m,f)	feeding, toxicity	95.3	90 d, EPA82-1	NOAEL = 23 mg/kg/d (m) NOAEL = 28 mg/kg/d (f)	NNT-0045
Rat (m,f)	inhalation, toxicity	97.0	28 d, in-house method close to OECD 412	NOAEL = 482 mg/m^3/d (m,f)	NNT-0031
Dog (m,f)	Feeding (capsule) toxicity	95.3	52 weeks, EPA 83-1	NOAEL = 10 mg/kg/d (m) NOAEL = 30 mg/kg/d (f)	NNT-0081 NNT-0102
Rat (m,f)	feeding, carcinogenicity	95.3	104 weeks, EPA 83-5	NOAEL = 27.31 mg/kg/d (m) NOAEL = 35.1 mg/kg/d (f) Carcinogenicity: negative	NNT-0085
Mouse (m,f)	feeding, carcinogenicity	95.	78 weeks, EPA 83-2	NOAEL = 16.37 mg/kg/d (m) NOAEL = 107.3 mg/kg/d (f) Carcinogenicity: negative	NNT-0084
Rat (m,f)	feeding, 2 generation reproduction	95.3	EPA83-4	NOAEL (parental systemic toxicity) = 1000 ppm NOAEL (parental reproductive effect) = 5000 ppm, NOEL (pup developmental toxicity) = 1000 ppm	NNT-0087
Rat (f)	feeding, teratogenicity and embryotoxicity	97.2	EPA 83-3	NOAEL (maternal) = 100 mg/kg bw/d, NOAEL (developmental) = 100 mg/kg bw/d NOAEL (reproduction) = 1000 mg/kg bw/d Not teratogenic	NNT-0029

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

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Rabbit (f)	feeding, teratogenicity and embryotoxicity	97.2	EPA 83-3	NOAEL (maternal) = 100 mg/kg bw/d, NOAEL (developmental) = 300 mg/kg bw/d Not teratogenic	NNT-0033

Table C. Mutagenicity profile of pyriproxyfen technical material based on in vitro and in vivo tests

Species	Test	Purity %	Conditions and doses	Result	Reference
Salmonella typhimurium, *Escherichia coli*	Ames test, *in vitro*, gene mutation	97.2	With and without S9 mix: 10, 50, 100, 500, 1000 or 5000 µg/plate	Negative	NNT-0034
Chinese hamster ovary cell (CHO-K1)	Chromosomal aberration *in vitro*	97.2	Without S9 mix: 10, 30 or 100 µg/ml With S9 mix: 30, 100 or 300 µg/ml	Negative	NNT-0054
Chinese hamster lung cell (V79)	Gene mutation in mammalian cell *in vitro*	95.3	Without S9 mix: 10, 30 or 100 µg/ml With S9 mix: 3, 10, 30, or 100 µg/ml	Negative	NNT-0067
Mouse (m,f) bone marrow cell	Micronucleus assay *in vivo*	95.3	5000 mg/kg bw (p.o.)	Negative	NNT-0082

Table D. Ecotoxicology profile of pyriproxyfen technical material

Species	Test	Purity %	Duration and conditions	Results	Reference
Daphnia magna	Acute	95.3	EPA 72-2 flow through, 48 h	LC_{50} = 0.4 mg/l	NNW-0036
Rainbow trout	Acute	95.3	EPA 72-1 flow through, 96 h	LC_{50} >0.325 mg/l	NNW-0035
Bluegill sunfish	Acute	95.3	EPA 72-1 flow through, 96 h	LC_{50} >0.270 mg/l	NNW-0034
Selenastrum capricornutum (alga)	Effect on growth	97.2	OECD 201, 72 h	EC_{50} = 0.064 mg/l NOEC = 0.02 mg/l	NNW-0068
Earthworm	Acute	99.0	OECD 207	LC_{50} >1000 mg/kg dry soil	NNW-0012
Apis mellifera (honey bee)	Acute oral and contact	99.7	OECD 213/214, 48 h	Contact and oral LD_{50} >0.1 mg ai/bee	NNW-0149
Bobwhite quail	Acute oral	95.3	EPA71-1	LD_{50} >2000 mg/kg	NNW-0028
Mallard duck	Acute oral	95.3	EPA71-1	LD_{50} >2000 mg/kg	NNW-0027

Annex 2: References

Sumitomo document number or other reference	Year and title of report or publication details
FAO/WHO 2002	Manual on the development and use of FAO and WHO specifications for pesticides, 1st edition. FAO plant production and protection paper, 173. FAO, Rome, 2002.
NNA-0011	1988. Analytical methods to verify certified limits of Sumilarv technical grade.
NNM-0015	1989. Hydrolysis of S-31183 in buffered aqueous solutions.
NNM-0037	1995. Artificial sunlight photodegradation of pyriproxyfen in aqueous media at pH 7.
NNP-0022	1989. Dissociation constant of Sumilarv.
NNP-0025	1989. Partition coefficient (n-octanol/water) of pyriproxyfen.
NNP-0026	1989. Water solubility of pyriproxyfen.
NNP-0030	1989. Vapour pressure determination of Sumilarv.
NNP-0054	1993. Melting point determination of pyriproxyfen.
NNP-0086	2001. Determination of boiling point of pyriproxyfen.
NNT-0003	1986. Skin sensitization test with S-31183 in guinea pigs.
NNT-0004	1987. Primary eye and skin irritation tests with S-31183 in rabbits.
NNT-0005	1987. Acute oral toxicity of S-31183 in rats.
NNT-0006	1987. Acute dermal toxicity of S-31183 in rats.
NNT-0022	1987. Acute inhalation toxicity of S-31183 in rats.
NNT-0029	1988. Study by administration of S-31183 during the period of fetal organogenesis in rats.
NNT-0031	1988. Subacute inhalation toxicity study of S-31183 in rats.
NNT-0033	1988. Study of S-31183 by oral administration during the period of fetal organogenesis in rabbits.
NNT-0034	1988. Reverse mutation test of S-31183 in bacterial systems.
NNT-0045	1989. Subchronic toxicity study with S-31183 in rats.
NNT-0067	1990. *In vitro* gene mutation test of S-31183 in V79 Chinese hamster cells.
NNT-0054	1989. *In vitro* chromosomal aberration test of pyriproxyfen in Chinese hamster ovary cells (CHO-K1).
NNT-0081	1991. Amended final report: S-31183: Toxicity study by oral (capsule) administration to beagle dogs for 52 weeks.
NNT-0082	1991. Mouse micronucleus test on S-31183.
NNT-0084	1991. Oncogenicity study in mice with S-31183.
NNT-0085	1991. Combined chronic toxicity and oncogenicity study in rats with S-31183.
NNT-0087	1991. A dietary 2-generation (1 litter) reproduction study of S-31183 in the rat.
NNT-0102	1993. S-31183: Toxicity study by oral (capsule) administration to beagle dogs for 52 weeks (additional investigation).
NNW-0012	1988. Acute toxicity (LC_{50}) study of S-31183 to earthworms.
NNW-0027	1989. The avian single-dose oral LD_{50} study of S-31183 to the mallard duck.
NNW-0028	1989. The avian single-dose oral LD_{50} study of S-31183 to the bobwhite quail.
NNW-0034	1989. Acute flow-through toxicity of Sumilarv to bluegill (Lepomis macrochirus).
NNW-0035	1989. Acute flow-through toxicity of Sumilarv to rainbow trout (Salmo gairdneri).
NNW-0036	1989. Acute flow-through toxicity of Sumilarv to Daphnia magna.
NNW-0068	1991. Acute toxicity of pyriproxyfen to Selenastrum capricornutum Prinz.
NNW-0149	2001. Pyriproxyfen – Acute contact and oral toxicity tests with honey bees (*Apis mellifera*).
WHO 2002	The WHO recommended classification of pesticides by hazard and guidelines to classification, 2000-2002. World Health Organization, Geneva, 2002.