Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

2017

PYRIPROXYFEN

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

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DISCLAIMER[1]

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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.

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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 FAO specifications follows the **New Procedure**, described in the 1st edition of "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (2002) - currently available as 3rd revision of the 1st 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 2002 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 Specifications** 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. Evaluations bear the date (year) of the Meeting at which the recommendations were made by the JMPS.

* NOTE: PUBLICATIONS ARE AVAILABLE ON THE INTERNET AT (http://www.fao.org/pest-and-pesticide-management/expert-bodies-coventions/faowho-joint-meeting-on-pesticide-specifications-jmps/en/) OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.

PART ONE

SPECIFICATIONS

PYRIPROXYFEN

PYRIPROXYFEN

INFORMATION

ISO common name

pyriproxyfen (BSI, E-ISO)

Synonyms

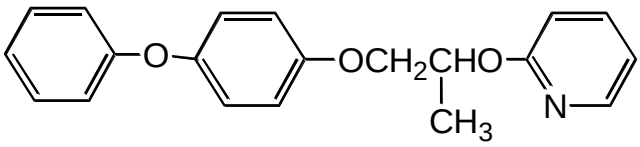
none

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

FAO 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). It should be applicable to TC produced by these manufacturers but it is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for TC produced by other manufacturers. The evaluation reports (715/2005, 715/2015, 715/2017), 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.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/pest-and-pesticide-management/expert-bodies-conventions/faowho-joint-meeting-on-pesticide-specifications-jmps/en/

PYRIPROXYFEN EMULSIFIABLE CONCENTRATE

FAO Specification 715 / EC (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, 715/2017). It 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, 715/2017), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of technical pyriproxyfen, complying with the requirements of FAO specification 715/TC (October 2017), dissolved in suitable solvents, together with any other necessary formulants. It shall be in the form of a stable homogeneous liquid, free from visible suspended matter and sediment, to be applied as an emulsion after dilution in water.

2 Active ingredient

2.1 **Identity tests** (715/EC/M/2, CIPAC Handbook M, p.183, 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/EC/M/3, CIPAC Handbook M, p.183, 2009)

The pyriproxyfen content shall be declared (g/kg or g/l at 20 ± 2ºC, Note 1) and, when determined, the average measured content shall not differ from that declared by more than the following tolerances:

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

3 Relevant impurities

3.1 **Water** (MT 30.5, CIPAC Handbook J, p.120, 2000)

Maximum: 3 g/kg.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/pest-and-pesticide-management/expert-bodies-coventions/faowho-joint-meeting-on-pesticide-specifications-jmps/en/

4 **Physical properties** (Note 2)

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

The pH range: 4 to 7.

4.2 **Emulsion stability and re-emulsification** (MT 36.3, CIPAC Handbook K, p.137, 2003) (Note 3)

The formulation, when diluted at 25 ± 5°C with CIPAC CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of stability
0 h	Initial emulsification complete
0.5 h	"Cream", maximum: 0.5 ml
2.0 h	"Cream", maximum: 0.5 ml
	"Free oil", maximum: 0.5 ml
24 h	Re-emulsification complete
24.5 h	"Cream", maximum: 0.5 ml
	"Free oil": maximum :trace
Note: in applying MT 36.3, tests at 24 h are required only where the results at 2 h are in doubt.	

4.3 **Persistent foam** (MT 47.3, CIPAC Handbook O, p.177, 2017)

Maximum: 20 ml after 1 min.

5 **Storage stability**

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

After storage at 0 ± 2°C for 7 days, the volume of solid and/or liquid which separates shall not be more than 0.3 ml.

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

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 97% relative to the determined average content found before storage (Note 4) and the formulation shall continue to comply with the clauses for:

- pH range (4.1);
- emulsion stability and re-emulsification (4.2).

Note 1 If the buyer requires both g/kg and g/l at 20°C, then in case of dispute the analytical results shall be calculated as g/kg.

Note 2 Flash point may be an important safety characteristic in some cases but the risks are dependent upon both climate and the specific use, so FAO/WHO specifications cannot provide global specifications for this characteristic. In all cases, strict adherence to national requirements is essential.

Note 3 The formulation should be tested at the highest and lowest rates of use recommended by the supplier. This test will normally only be carried out after the heat stability test: 5.2.

Note 4 Samples of the formulation taken before and after the storage stability test may be analyzed concurrently after the test in order to reduce the analytical error.

PYRIPROXYFEN EMULSION, OIL IN WATER

FAO Specification 715 / EW (October 2017*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (715/2010). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated source. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of manufacturers who use TC from other sources. The evaluation report (715/2010), as PART TWO, forms an integral part of this publication.

1 Description

The formulation shall consist of an emulsion of technical pyriproxyfen, complying with the requirements of FAO specification 715/TC (October 2017) in the form of white or off-white viscous liquid with faint characteristic odor, in an aqueous phase together with suitable formulants. After gentle agitation, the formulation shall be homogeneous (Note 1) and suitable for dilution in water.

2 Active ingredient

2.1 Identity tests (715/EW/M/2, CIPAC Handbook M, p.184, 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/EW/M/3, CIPAC Handbook M, p.184, 2009)

The pyriproxyfen content shall be declared (g/kg or g/l at 20 ± 2ºC, Note 2) and, when determined, the average measured content shall not differ from that declared by more than the following tolerance:

Declared content, g/kg or g/l at 20 ± 2ºC	Tolerance
above 100 up to 250	± 6% of the declared content

3 Physical properties

3.1 Pourability (MT 148.1, CIPAC Handbook F, p.348, 1995)

Maximum "residue": 6 %.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/pest-and-pesticide-management/expert-bodies-coventions/faowho-joint-meeting-on-pesticide-specifications-jmps/en/

3.2 **Emulsion stability and re-emulsification** (MT 36.3, CIPAC Handbook K, p.137, 2003)

The formulation, when diluted at 25 ± 2°C (Note 3) with CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of stability
0 h	Initial emulsification complete
0.5 h	"Cream", maximum: 0.5 ml
2.0 h	"Cream", maximum: 0.5 ml
	"Free oil", maximum: 0.5 ml
24 h	Re-emulsification complete
24.5 h	"Cream", maximum: 0.5 ml
	"Free oil": maximum trace
Note: in applying MT 36.3, tests at 24 h are required only where the results at 2 h are in doubt.	

3.3 **Persistent foam** (MT 47.3, CIPAC Handbook O, p.177, 2017)

Maximum: 20 ml after 1 min.

4 Storage stability

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

After storage at 0 ± 2°C for 7 days, no separation of particulate or oily matter shall be visible after gentle agitation.

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

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 97% relative to the determined average content found before storage (Note 4) and the formulation shall continue to comply with the clauses for:

– emulsion stability and re-emulsification (3.2).

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

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

Note 2 If the buyer requires both g/kg and g/l at 20°C, then in case of dispute the analytical results shall be calculated as g/kg.

Note 3 The formulation should be tested at the highest and lowest rates of use recommended by the supplier.

Note 4 Samples of the formulation taken before and after the storage stability test may be analyzed concurrently after the test in order to reduce the analytical error.

PART TWO

EVALUATION REPORTS

PYRIPROXYFEN

PYRIPROXYFEN

FAO/WHO EVALUATION REPORT 715/2017

Recommendation

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 ^{1}H-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 specification 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 method.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 715/2017

Table 1. Chemical composition and properties of pyriproxyfen technical material

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

(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 2. Mutagenicity profile of the pyriproxyfen technical material based on *in vitro* tests

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium TA 97a, TA 98, TA100, 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

(sorted by study number)

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 715/2015

Recommendation

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 715/2010

Recommendation

The meeting recommended that the specification for pyriproxyfen EW formulation, 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 specification for EW. FAO Specifications were established by the 2002 JMPS for pyriproxyfen TC and EC.

At that time the Meeting concluded that none of the impurities should be designated as relevant. The analytical method for determination of pyriproxyfen in TC, EC and EW is based on reversed-phase HPLC with UV detection at 254 nm and internal standardization with dicyclohexyl phthalate. The method was validated by collaborative study and adopted by CIPAC in 2006. The method is published in Handbook M.

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

The proposed specification for the emulsion, oil in water, is essentially in accordance with the requirements of the Specification manual (FAO/WHO 2006).

PYRIPROXYFEN

FAO/WHO EVALUATION REPORT 715/2005

Recommendation

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 dicyclohexyl phthalate. 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 area comparison, 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. 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, EC and EW. 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 dicyclohexyl phthalate. 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 area comparison, 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
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.