FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

PROCHLORAZ

N-propyl-*N*-[2-(2,4,6-trichlorophenoxy)ethyl]imidazole-1-carboxamide

FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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

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

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

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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 1999, the development of FAO specifications has followed the **New Procedure**, described in the 1st edition of "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (2002) and amended with the supplement of this manual (2006), 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 JMPS, rather than the JMPS.]

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently from the year 2000 onwards the publication of FAO specifications under the **New Procedure** has changed. Every specification consists now of two parts namely the specifications and the evaluation report(s):

Part One: **The Specification** of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the "Manual on development and use of FAO and WHO specifications for pesticides".

Part Two: **The Evaluation Report(s)** of the plant protection product reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are to be provided by the manufacturer(s) according to the requirements of Appendix A, annex 1 or 2 of the "Manual on the development and use of FAO and WHO specifications for pesticides" 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. Dates of publication of the earlier versions, if any, are identified in a footnote. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

* NOTE: PUBLICATIONS ARE AVAILABLE ON THE INTERNET AT (http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/ps-new/en/) OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.

PART ONE

SPECIFICATIONS

PROCHLORAZ

PROCHLORAZ

INFORMATION

ISO common name

Prochloraz (ISO 1750, published)

Chemical name(s)

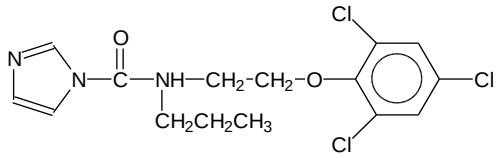
IUPAC: *N*-propyl-*N*-[2-(2,4,6-trichlorophenoxy)ethyl]imidazole-1-carboxamide

CA: *N*-propyl-*N*-[2-(2,4,6-trichlorophenoxy)ethyl]-1*H*-imidazole-1-carboxamide

Synonyms

None

Structural formula



Molecular formula

$C_{15}H_{16}Cl_3N_3O_2$

Relative molecular mass

376.7 g/mol

CAS Registry number

67747-09-5

CIPAC number

407

Identity tests

HPLC retention time; IR, UV, NMR and mass spectra.

PROCHLORAZ TECHNICAL MATERIAL

FAO specification 407 / TC (May 2016*)

*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 (*407/2007 & 407/2015*). It should be applicable to TC produced by these manufacturers but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for TC produced by other manufacturers. The evaluation reports (*407/2007 & 407/2015*), as PART TWO, form an integral part of this publication.*

1 Description

The material shall consist of prochloraz together with related manufacturing impurities and shall be a brownish waxy solid, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (CIPAC 407/TC/M, Handbook M, p. 165, 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 **Prochloraz content** (CIPAC 407/TC/M, Handbook M, p. 165, 2009)

The prochloraz 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.

3 Relevant impurities (Note 1)

Note 1 There are no relevant impurities to be controlled in products of the manufacturers identified in evaluation report 407/2007 and 407/2015. However, dioxins can occur as a result of certain manufacturing processes. If 2,3,7,8-tetrachlorodibenzodioxin (2,3,7,8-TCDD) occurs at ≥0.1 µg/kg (of prochloraz) in the products of other manufacturers, it may be designated as a relevant impurity and a clause may be required to limit its concentration.

*Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/ps-new/en/

PROCHLORAZ EMULSIFIABLE CONCENTRATE

FAO specification 407 / EC (May 2016*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose names is listed in the evaluation report (*407/2007*). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated source. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation report (*407/2007*), as PART TWO, forms an integral part of this publication.*

1 Description

The material shall consist of technical prochloraz, complying with the requirements of FAO specification 407/TC (May 2016), 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 (CIPAC 407/EC/M, Handbook M, p. 165, 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 Prochloraz content (CIPAC 407/EC/M, Handbook M, p. 165, 2009)

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

Declared content in g/kg or g/l at 20 ± 2ºC	Tolerance
Above 250 up to 500 Note: the upper limit is included in the range	±5% of the declared content

3 Relevant impurities (Note 2)

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/ps-new/en/

4 Physical Properties

4.1 **Acidity** (MT 191, CIPAC Handbook L, p.143, 2006)

Maximum: 1 g/kg calculated as H_2SO_4.

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

The formulation, when diluted at 30 ± 2ºC with CIPAC standard waters A and D, shall comply with the following:

Time after dilution	Limits of stability, MT 36.3
0 h	initial emulsification complete
0.5 h	"cream", maximum: 0 ml
2.0 h	"cream", maximum: 2 ml
	"free oil", maximum: 0.2 ml
24 h	re-emulsification complete
24.5 h	"cream", maximum: 2 ml
	"free oil", maximum: 0.2 ml

Note: tests after 24 h are required only where results at 2 h are in doubt.

4.3 **Persistent foam** (MT 47.3) (Notes 3 & 4)

Maximum: 25 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 95% relative to the determined average content found before storage (Note 5) and the formulation shall continue to comply with the clauses for:

- acidity (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 There are no relevant impurities to be controlled in products of the manufacturers identified in evaluation reports 407/2007 and 407/2015. However, dioxins could occur as a result of certain manufacturing processes. If 2,3,7,8-tetrachlorodibenzodioxin (2,3,7,8-TCDD) occurs at ≥0.1 µg/kg (of prochloraz) in the products of other manufacturers, it may be designated as a relevant impurity and a clause may be required to limit its concentration.

Note 3 The mass of the sample to be used in the test should be specified at the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 4 MT 47.3 is a revised version of MT 47.2 using a standard measuring cylinder. This new method was accepted as a full CIPAC method in 2013. Prior to publication of the method in a Handbook, copies of the method may be obtained through the CIPAC website, http://www.cipac.org/index.php/methods-publications/pre-published-methods.

Note 5 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.

PROCHLORAZ EMULSION, OIL IN WATER

FAO specification 407 / EW (May 2016*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose names is listed in the evaluation report (*407/2015*). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated source. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation report (*407/2015*), as PART TWO, forms an integral part of this publication.*

1 Description

The material shall consist of technical prochloraz, complying with the requirements of FAO specification 407/TC (May 2016), dissolved in suitable solvents, together with any other necessary formulants. It shall be in the form of a stable homogeneous liquid (Note 1), free from visible suspended matter and sediment, to be applied as an emulsion after dilution in water.

2 Active ingredient

2.1 Identity tests (CIPAC 407/EC/M, Handbook M, p. 165, 2009) (Note 2)

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 Prochloraz content (CIPAC 407/EC/M, Handbook M, p. 165, 2009) (Note 2)

The prochloraz content shall be declared (g/kg or g/l at 20 ± 2ºC, Note 3) and, when determined, the average content measured shall not differ from that declared by more than the following tolerance

Declared content in g/kg or g/l at 20 ± 2ºC	Tolerance
Above 250 up to 500 Note: the upper limit is included in the range	±5% of the declared content

3 Relevant impurities (Note 4)

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/ps-new/en/

4 Physical properties

4.1 **Acidity** (MT 191, CIPAC Handbook L, p.143, 2006)

Maximum: 1 g/kg calculated as H_2SO_4.

4.2 **Pourability** (MT 148.1)

Maximum "residue": 5%.

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

The formulation, when diluted at 30 ± 2ºC (Note 5) with CIPAC standard waters A and D, shall comply with the following:

Time after dilution	Limits of stability, MT 36.3
0 h	initial emulsification complete
0.5 h	"cream", maximum: 0.5 ml
2.0 h	"cream", maximum: 2. ml
	"free oil", maximum: 0.2 ml
24 h	re-emulsification complete
24.5 h	"cream", maximum: 2 ml
	"free oil", maximum: 0.2 ml
Note: tests after 24 h are required only where results at 2 h are in doubt.	

4.4 **Persistent foam** (MT 47.3) (Notes 6 & 7)

Maximum: 25 ml after 1 min.

5 Storage stability

5.1 **Stability at 0 °C** (MT 39.3)

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)

After storage 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 8) and the formulation shall continue to comply with the clauses for:

- acidity (4.1),
- emulsion stability and re-emulsification (4.3),

Note 1 All physical and chemical tests listed in this specification are to be performed with a 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 The CIPAC methods for identification of prochloraz and for determination of the prochloraz content in EC formulations were shown to be applicable to EW formulations as well based on the criteria in the CIPAC Guideline "Extension of the scope of methods", available under www.cipac.org.

Note 3 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 4 There are no relevant impurities to be controlled in products of the manufacturers identified in evaluation reports 407/2007 and 407/2015. However, dioxins could occur as a result of certain manufacturing processes. If 2,3,7,8-tetrachlorodibenzodioxin (2,3,7,8-TCDD) occurs at $\geqslant$0.1 µg/kg (of prochloraz) in the products of other manufacturers, it may be designated as a relevant impurity and a clause may be required to limit its concentration.

Note 5 As outlined in CIPAC MT 36.3, the test concentrations should be based on those in the recommended directions for use supplied with the product. Where several concentrations are recommended, the highest and lowest concentrations within the scope of the method should be used.

Note 6 MT 47.3 is a revised version of MT 47.2 using a standard measuring cylinder. This new method was accepted as a full CIPAC method in 2013. Prior to publication of the method in a Handbook, copies of the method may be obtained through the CIPAC website, http://www.cipac.org/index.php/methods-publications/pre-published-methods.

Note 7 The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 8 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

PROCHLORAZ

PROCHLORAZ

FAO EVALUATION REPORT 407 / 2015

Recommendations

The meeting recommended that:

(i) The prochloraz TC produced by Jiangsu Huifeng should be accepted as equivalent to the prochloraz reference profile
(ii) The existing FAO specification for prochloraz TC should be extended to encompass the corresponding product of Jiangsu Huifeng
(iii) The new EW specification proposed by Jiangsu Huifeng, and as amended, should be adopted by FAO

Appraisal

The Meeting considered data submitted in October 2014 by Jiangsu Huifeng Agrochemical Co., Ltd (Jiangsu Huifeng) for the determination of the equivalence for TC and a new specification for EW formulation. The data were broadly in accordance with the requirements of the 2010 revision of the FAO/WHO Manual.

The reference specification and supporting data were provided by Makhteshim (now ADAMA) in 2004 and published in 2007.

Prochloraz is not under patent. Prochloraz was evaluated several times by the FAO/WHO JMPR, the last time for toxicology in 2001 and for residues in 2009.
It was evaluated by the European Commission and included in the positive list of active ingredients in 2012 (until 2021).

The manufacturer submitted confidential data on the manufacturing process, together with the manufacturing specification and 5-batch analysis data on purity and impurities ≥1 g/kg including the toxicological studies supporting a possible Tier-2 equivalence determination.

According to the company, the confidential data presented to FAO are identical to those submitted for registration in China, Thailand, Philippine and South Korea. For China, this was confirmed by the Chinese pesticide registration authority, ICAMA (T. Chen, 2015).

In the existing specification 2,3,7,8-tetrachlorodibenzodioxin (2,3,7,8-TCDD) is listed as potential relevant impurity when occurring at levels ≥ 0.1 µg/kg. Jiangsu Huifeng submitted analytical results for seven “typical” batches, showing that the content of 2,3,4,7-TCDD and WHO(2005)-PCDD/ TEQ is clearly below this limit.

Initially two substances and water were stated as relevant impurity, but later the company confirmed that after a training on pesticide specifications by FAO and WHO in Hangzhou

China in Nov, 2014, the meaning of relevant impurity was better understood and the listed compounds are indeed the identified impurities, not the relevant ones.

A comparison of the 5 batch data of the reference with that of Jiangsu Huifeng revealed, that there were several new impurities in the technical material from Jiangsu Huifeng; for two impurities occurring in both manufacturing specifications the maximum level was increased by more than the threshold of 50% or 3 g/kg as set out in the Manual. For these reasons, equivalence could not be determined on Tier-1 of the two-tiered process in the Manual.

However, the toxicological data submitted allowed to assess equivalence based on the acute hazard data. The results and outcome of the studies led to the conclusion, that the material produced by Jiangsu is not more hazardous than the reference and hence the equivalence can be concluded on Tier-2.

The batch data for the EW formulation were generated using CIPAC-method 407/EC/M, with some differences (guard column, detection wavelength, quantitative composition of the mobile phase), but the Meeting considered these differences as minor.

The Meeting discussed the issue, that the company had used the CIPAC analytical method for the EC to analyze the EW. The Meeting however agreed that the published CIPAC-EC method, in that particular case is also applicable to the EW formulation due to the fact, that the EW formulation contains the active ingredient dissolved in an oil phase, even when the continous phase is water. In addition, the concentration range is the same (250 to 500 g/L) as for the EC formulation and the company submitted validation data to prove the assumption. The Meeting accepted the explanations.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 407/2015

Table 1. Chemical composition and properties of prochloraz technical materials (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 ranged from 99.78 – 100.15 %.
Declared minimum prochloraz 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	46 – 52 °C	96.9 - 97.1	CIPAC MT 2	HF/TC/140817-1
Solubility in organic solvents	968 g/L in ethylalcohol 1199 g/L in toluene 12120 g/L in n-hexane, all at 22°C	96.9 – 97.1	CIPAC MT 181	HF/TC/140817-2

FORMULATIONS AND CO-FORMULATED ACTIVE INGREDIENTS

The main formulation types available are emulsions, oil in water (EW), used as agricultural fungicides. Prochloraz may be co-formulated with other pesticides.

These formulations are registered and sold in many countries in Asia and Europe.

METHODS OF ANALYSIS AND TESTING

The content of prochloraz is determined by reversed-phase HPLC, using UV detection at 230 nm and external standardisation.
The methods for determination of impurities are based on reversed-phase HPLC with UV detection, GC/FID or Karl-Fischer-Titration.
Test methods for determination of physical-chemical properties of the technical active ingredient were OECD, EPA, EEC, 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 EW formulations, comply with the requirements of the FAO/WHO Manual (2010 2nd revision of the 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 prochloraz.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

(i) The proposer confirmed that the toxicological data included in the summary below were derived from prochloraz having impurity profiles similar to those referred to in the table above. But there are some exceptions. The acute toxicity studies and the short-term toxicity (rat) was conducted with higher purity prochloraz TC

(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table 2. Toxicology profile of the prochloraz technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Purity % Note[1]	Guideline, duration, doses and conditions	Result	Study number
Rat, Sprague – Dawley (female)	oral	98.11	Single dose administered as solution in maize oil, followed by 14-d observation. OECD 423 300 and 2000 mg/kg bw	LD_{50} >300 – 2000 mg/kg bw	S-10430
Rat (male, female)	dermal	98.11	Single dermal application in place 24h, 14-d observation. OECD 402 2000 mg/kg bw	LD_{50} >2000 mg/kg bw	S-10431
Rat(male, female)	inhalation	98.11	4-h exposure followed by 14-d observation complied with OECD 403 1.61 mg/L	LC_{50} >1.61 mg/L	S-10432
Rabbit (female)	skin irritation	98.11	Single 4-h exposure followed by 8 d observation. OECD 404 0.5 g on 6 cm^2	Non irritant	S-10433
Rabbit (female)	eye irritation	98.11	Single dose followed by 72-h observation complied with OECD 405 100 mg	Non irritant	S-10434
Guinea pig(male, female)	skin sensitisation	98.11	Buehler method. OECD 406	Non sensitizing	S-10435

[1] Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

Table 3. Mutagenicity profile of the technical material based on *in vitro* tests

Species	Test	Purity % Note[1]	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium strains TA 97a, 98, 100, 102, 1535	Bacterial reverse mutation test	97.4	OECD 471 (1997) ≤ 250 µg/plate Levels 1 µg to 5000 µg/plate (at 500, 1000 and 5000 cytotoxicity was observed) Main test at 15.62, 31.25, 62.5, 125 and 250 µg/plate.	negative	IIT-18168

[1] Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

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.
	FAO/WHO	2010	Manual on development and use of FAO and WHO specifications for pesticides. November 2010 Revision of First Edition. FAO Plant Production and Protection Paper.
	Chen, T.	2015	e-mail Prof. Chen, ICAMA, confirming the similarity of confidential data packages on prochloraz Jiangsu Huifeng submitted to ICAMA and FAO
S-10430		2011	Acute oral toxicity study of Prochloraz Technical in rats . Study S-10430. Report R/10430/AOR/11. GLP.
S-10431		2011	Acute dermal toxicity study of Prochloraz Technical in rats . Study S-10431. Report R/10431/ADR/11. GLP.
S-10432		2011	Acute inhalation toxicity study of Prochloraz Technical in rats . Study S-10432. Report R/10432/AIR/11. GLP.
S-10433		2011	Acute Dermal Irritation / Corrosion Study of Prochloraz Technical in New Zealand White Rabbit . Study S-10433. Report R/10433/ADI/11. GLP.
S-10434	A	2011	Acute Eye Irritation I Corrosion Study of Prochloraz Technical in Rabbit . Study S-10434. Report R/10434/AEI/11. GLP. Contract Laboratories,
S-10435		2011	Skin Sensitization Study (Buehler Test) of Prochloraz Technical in Guinea Pigs . Study S-10435. Report R/10435/SS/11. GLP.
HF/TC/140817-1		2014	Study on melt(ing) point of prochloraz TC, GLP.
HF/TC/140817-2		2014	Study of solubility of prochloraz TC, GLP.
IIT-18168		2015	Final report IIT study number 18168 Bacterial reverse mutation test on prochloraz TC, GLP.

PROCHLORAZ

FAO/WHO EVALUATION REPORT 407/2007

Recommendations

The Meeting recommended the following.

(i) The specifications for prochloraz TC and EC, proposed by Makhteshim and as amended, should be adopted by FAO.

(ii) The specifications for prochloraz TK and SC, proposed by Makhteshim and as amended, should be adopted by FAO, subject to acceptable validation and adoption by CIPAC (or equivalent) of an analytical method for determination of the active ingredient content in products that contain prochloraz as its zinc complex.

Appraisal

Data provided by Makhteshim Chemical Works were evaluated in support of proposed new FAO specifications for prochloraz TC, TK, EC and SC. Data were first evaluated by the 2004 JMPS, which required additional information on (i) analytical methods for determination of prochloraz, (ii) identification of the zinc complex of prochloraz and (iii) potentially relevant impurities. The additional information was considered by the 2007 JMPS.

Prochloraz is not under patent.

Prochloraz is a solid of rather low melting point, volatility and water solubility. It is hydrolyzed slowly at pH 9 and very slowly at pH 5 and 7. It is subject to slow photolysis and is subject to thermal decomposition at about 220ºC. It is a weak base, becoming protonated in acidic conditions (pKa 3.8, Tomlin 2000). Prochloraz forms stable complexes with certain metal ions, such as Zn^{2+}.

The Meeting was provided with details of the manufacturing process, 5 batch analysis data, and manufacturing limits for purity and all impurities ≥1 g/kg. Mass balances were high (98.45–99.15%), no unknowns were detected and the minimum prochloraz content of the TC was 970 g/kg. These data were confirmed as identical to those submitted for registration in the UK. The Meeting agreed that none of the impurities occurring ≥1 g/kg should be designated as relevant for the purposes of FAO specifications.

The structure of prochloraz indicates the possibility of dioxin impurity formation (particularly 2,3,7,8-tetrachlorodibenzodioxin or 2,3,7,8-TCDD, the most hazardous of the dioxins) during synthesis of the active ingredient. The Meeting therefore requested data on the dioxin content of prochloraz produced by the proposer. The manufacturer provided evidence showing that dioxins were not detectable (LOQ for 2,3,7,8-TCDD = 0.1 µg/kg of prochloraz) in the products. The Meeting therefore agreed that dioxins should not be designated as relevant impurities in the products of this manufacturer but that an appropriate cautionary note should be inserted into the specifications, alerting users to the possibility that dioxins could occur in the products of other manufacturers, at levels at which they would be considered relevant.

Reversed-phase HPLC-UV methods for the determination of prochloraz in the TC and EC were adopted in 2008 as full CIPAC methods. Various spectroscopic techniques are suitable for confirmation of the identity of prochloraz. The manufacturer provided an ICP-

OES method for identification of the prochloraz-zinc complex in TK and SC, measuring the zinc content and based on the 1:2 stoichometry of the Zn^{2+}:prochloraz complex. An analytical method for the determination of prochloraz in the TK and SC (in which prochloraz is present as the zinc complex) was adopted by CIPAC in 2007, with tentative[1] status only, which is not sufficient to support FAO specifications for these products.

The Meeting considered the proposed specifications for TC, TK, EC and SC, which were broadly in accordance with the requirements of the manual (FAO/WHO 2002, 2006). In addition to the issues already identified above, requiring the insertion of appropriate footnotes, the following issues were considered.

EC and SC. The Meeting questioned the need for control of acidity in the EC and for control of pH (specified limits, 6-8) in the SC, as prochloraz is relatively stable under neutral to acidic conditions. The manufacturer stated that prochloraz is unstable under more extreme conditions and that crystallization (or crystal growth in the SC) can occur under more extreme conditions in the formulations. The Meeting accepted the need for the clauses and limits.

[1] The "Summary of decisions...2008" (document CIPAC/4651/P, accessed at http://www.cipac.org on 10 March 2009) indicates that the method for determination of prochloraz in the TK and SC has "provisional" status, whereas the "Summary of decisions....2007" (document CIPAC/4598/P on the same website) indicates that the method was originally allocated "tentative" status only. The current "tentative" status of the method has been confirmed by CIPAC (CIPAC 2009).

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 407/2007

Uses

Prochloraz is a non-systemic imidazole fungicide, an ergosterol biosynthesis inhibitor with contact and translaminar, protectant and eradicant activity. It is used in agriculture and horticulture against various plant diseases, especially Ascomycetes and Fungi Imperfecti. It is used to control foliar diseases of cereals (*Pseudocercosporella*, *Pyrenophora*, *Rhynchosporium* and *Septoria spp.)*, field crops *(*such as *Alternaria*, *Botrytis*, *Pyrenopeziza* and *Sclerotinia* in oilseed rape, *Ascochyta* and *Botrytis* in legumes, *Pyricularia* in rice), fruit (blossom blight) and vegetables (anthracnose).

Identity of the active ingredient

ISO common name

Prochloraz (E-ISO, (m) F-ISO, BSI, ANSI)

Chemical name(s)

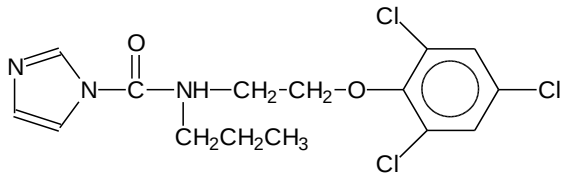
IUPAC: *N*-propyl-*N*-[2-(2,4,6-trichlorophenoxy)ethyl]imidazole-1-carboxamide

CA: *N*-propyl-*N*-[2-(2,4,6-trichlorophenoxy)ethyl]-1*H*-imidazole-1-carboxamide

Synonyms

None

Structural formula



Molecular formula

$C_{15}H_{16}Cl_3N_3O_2$

Relative molecular mass

376.7 g/mol

CAS Registry number

67747-09-5

CIPAC number

407

Identity tests

HPLC retention time; IR, UV, NMR and mass spectra.

Physico-chemical properties of prochloraz

Table 1. Physico-chemical properties of pure prochloraz (a) and prochloraz zinc complex (b)

Parameter	Value(s) and conditions	Purity %	Method	Reference
Vapour pressure	$3.5x10^{-6}$ Pa at 20°C	99.3 (a)	OECD 104, EEC A4 and EPA guideline subdivision D, 63-9	R-7280
	$<8.8 \times 10^{-5}$ Pa at 25°C	99.7 (b)	EC method A4, OECD 104	R-17277
Melting point	48.0-51.0°C	99.3 (a)	EPA guideline 63-5	R-7278
	102.5-105.0°C	99.7 (b)	EC method A1, OECD 102	R-17277
Temperature of decomposition	222°C	98.9(a)	Differential scanning calorimetry	R-17276
Solubility in water	0.0276 g/l at 20°C at pH 5 0.0249 g/l at 20°C at pH 7 0.0236 g/l at 20°C at pH 9 0.0265 g/l at 20°C (purified water)	99.3(a)	CIPAC MT 157, OECD 105, EEC A6, EPA guidelines subdivision D, 63-8	R-7281
Partition coefficient	log P_{OW} = 4.06 at 25°C at pH 7	98.2(a)	EPA guideline 63-11	R-5424
Hydrolysis characteristics	Half-life = 61.7 days at 25°C at pH 9 <20% of prochloraz degraded during 35 days at pH 5 and 7	98.2(a)	EPA guideline 161.1	R-6150
Photolysis characteristics	half-life = 11.4 days at 25°C (artificial light by xenon arc lamp,12 h light/12 h dark)	98.9(a)	EPA guideline 161-2	R-6144
Relative density	1.413	99.3(a)	EC method A3, OECD 109	R-7279
	1.475	99.7(b)		R-17277

Table 2. Chemical composition and properties of technical prochloraz (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 98.45-99.15%, with no un-knowns ≥1 g/kg.
Declared minimum prochloraz 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
Melting temperature range	48.0-51.0°C

Hazard summary

Prochloraz was evaluated by the FAO/WHO JMPR in 1983, 1985, 1987, 1988, 1989, 1990, 1991, 1992 and 2001. The 2001 JMPR confirmed the ADI of 0-0.01 mg/kg bw/d set originally by the 1983 JMPR and set an acute reference dose of 0.1 mg/kg bw (JMPR 2001).

The WHO hazard classification of prochloraz is class III, slightly hazardous (WHO 2002).

Classification and labelling of prochloraz according to the EU council directive (67/548/EEC) is as follows.

Hazard symbols: Xn (harmful), N (dangerous for the environment)
Risk phrases: R22 (harmful if swallowed), R50 (very toxic to aquatic organisms), R53 (may cause long-term effects in the aquatic environment).
Safety phrases: S2 (keep out of reach of children), S60 (this material and its container must be disposed of as hazardous waste), S61 (avoid release to the environment).

Formulations and co-formulated active ingredients

The main formulation types available are emulsifiable concentrates (EC) and aqueous suspension concentrates (SC), used as agricultural fungicides. These formulations are registered and sold in many countries in Europe and South America.

Prochloraz may be co-formulated with other pesticides.

Methods of analysis and testing

Reversed-phase HPLC-UV methods for the determination of prochloraz in the TC and EC were adopted in 2008 as full CIPAC method. IR, UV, NMR and mass spectral techniques are suitable for confirmation of the identity of prochloraz and representative spectra were provided to FAO. Identification of the prochloraz-zinc complex in TK and SC is by means of the manufacturer's in-house ICP-OES method, measuring the zinc content, and is based on the 1:2 stoichometry of the Zn^{2+}:prochloraz complex. An analytical method for the determination of prochloraz in the TK and SC (in which prochloraz is present as the zinc complex) was adopted by CIPAC in 2008, with "tentative" status[1].

The method(s) for determination of impurities are based on reversed-phase HPLC with UV detection at 240 nm and external standardization.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, EPA, EEC, 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 EC and SC formulations, complied with the requirements of the FAO/WHO manual (FAO/WHO 2002, 2006).

Containers and packaging

No special requirements for containers and packaging have been identified.

[1] The "Summary of decisions...2008" (document CIPAC/4651/P, accessed at http://www.cipac.org on 10 March 2009) indicates that the method for determination of prochloraz in the TK and SC has "provisional" status, whereas the "Summary of decisions....2007" (document CIPAC/4598/P on the same website) indicates that the method was originally allocated "tentative" status only. The current "tentative" status of the method has been confirmed by CIPAC (CIPAC 2009).

Expression of the active ingredient

The active ingredient is expressed as prochloraz (in g/kg or g/l at 20 ± 2ºC) whether present as free prochloraz or its zinc complex.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note. The proposer confirmed that most of the toxicological and ecotoxicological data included in the summary below were derived from prochloraz having impurity profiles similar to those referred to in the table above but there are some exceptions. The acute toxicity studies and the short-term toxicity (rat) and teratogenicity (rabbit) studies were conducted with lower purity prochloraz technical (93.4-95.4%) and thus represented worst-case scenarios with respect to impurity hazards.

Table A. Toxicology profile of prochloraz technical material (TC), based on acute toxicity, irritation and sensitization

Species	Test	Duration and conditions	Result	Reference
Rat, Sprague-Dawley (m,f)	Acute oral	Single dose administered as solution in maize oil, followed by 14-d observation. OECD 401. Purity 94.6%	LD_{50} = 1204 mg/kg bw	R-5306
Rat (m,f)	Acute dermal	Single dermal application in place 24 h, 14-d observation. OECD 402. Purity 94.6%	LD_{50} >2000 mg/kg bw	R-5307
Rat (m,f)	Acute inhalation	4-h exposure followed by 14-d observation. Complied with OECD 403. Purity 94.6%	LC_{50} >2.41 mg/l	R-5420
Rabbit	Skin irritation	Single 4-h exposure followed by 8 d observation. OECD 404, EPA FIFRA guideline, subdivision F 81-5. Purity 94.6%	Mild irritant	R-5308
Rabbit	Eye irritation	Single dose followed by 72-h observation. OECD 405, EPA FIFRA guideline subdivision F 81-4. Purity 94.6%	Non irritant	R-5309
Guinea pig	Skin sensitization	Buehler method. OECD 406, EPA FIFRA guideline subdivision F 81-6. Purity 94.6%	Non sensitizing	R-5310

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

Species	Test	Duration and conditions	Result	Reference
Rat (m)	Oral, short-term	13 weeks, dietary administration. OECD 408, EPA FIFRA guidelines, subdivision F 82-1. Purity 93.4%	NOAEL = 50 ppm ≡ 4.4 mg/kg bw/d (m)	R-5312
Rat (m,f)	Carcinogenicity	104 weeks, dietary administration. OECD 456, EPA FIFRA guideline subdivision F 83-5. Purity 97.4%	NOAEL = 40 ppm ≡ 1.7 mg/kg bw/d (m) LOEL =220 ppm ≡ 8.4 mg/kg bw/d(m) Not carcinogenic	R-5924
Mouse (m,f)	Carcinogenicity	78 weeks, dietary administration. OECD 451, EPA FIFRA guideline subdivision F 83-5. Purity 97.4%	NOAEL = 40 ppm ≡ 4.7 mg/kg bw/d (m) LOEL = 220 ppm ≡ 26.3 mg/kg bw/d(m) Not carcinogenic	R-5926
Rat (m,f)	Reproduction	F0 generation,14 weeks; F1 generation, 14 weeks; and F2 generation, 10 weeks; dietary administration. OECD 416, EPA FIFRA guideline subdivision F 83-4, Japanese MAFF. Purity 97.5%	Reproductive NOAEL = 50 ppm (F0, F1, F2) ≡ 3.7 mg/kg bw/d (m F0) LOEL = 150 ppm (F0, F1, F2) ≡ 11.1 mg/kg bw/d (m F0)	R-5928
Rat (f)	Teratogenicity	Gavage administration (day 6 to day 15 of gestation inclusive). EPA FIFRA guideline, subdivision F 83-3 and complied with OECD 414. Purity 97.5%	NOAEL (maternal) = 120 mg/kg/ bw/d NOAEL (foetal) = 30 mg/kg/ bw/d LOEL (foetal) = 60 mg/kg/ bw/d Not teratogenic	R-5930
Rabbit (f)	Teratogenicity	Gavage administration (day 7 to day 19 post-coitum). OECD 414, EPA FIFRA guideline subdivision F 83-3, (1981). Purity 95.4%	NOAEL (maternal) = 40 mg/kg/ bw/d NOAEL (foetal) = 40 mg/kg/ bw/d Not teratogenic	R-5315

No evidence of delayed neurotoxicity observed in acute, sub-chronic and chronic studies.

Table C. Mutagenicity profile of prochloraz technical material (TC), based on *in vitro* and *in vivo* tests

Species	Test	Duration and conditions	Result	Reference
Salmonella typhimurium (TA-1535, TA-100, TA-1538, TA-98 and TA-1537)	Reverse mutation test for bacteria, *in vitro*	2.5-260 µg/plate ±S-9 mix. Complied with OECD 471 (1983). Purity not stated	Negative	R-5400
Human lymphocytes	Cytogenetic test, *in vitro*	5-40 µg/ml, without S-9 10-150 µg/ml, with S-9 OECD 473. Purity 94.6%	Negative Positive Some evidence of clastogenic potential with metabolic activation.	R-5438
Mouse bone marrow cells (m,f)	Micronucleus test, *in vivo*	Doses 12-300 mg/kg OECD 474 (1983). Purity 94.6%	Negative	R-5439
Rat hepatocytes	Unscheduled DNA synthesis, *in vivo*	Doses 40-400 mg/kg. Methods based on: Mirsalis and Butterworth (1980); Mirsalis *et al*. (1982); Ashby *et al*. (1985); Butterworth *et al*. (1987). Complied with OECD 486. Purity 97.9%	Negative	R-6646

Table D. Ecotoxicology profile of prochloraz technical material (TC)

Species	Test	Duration and conditions	Result	Reference
Daphnia magna (water flea)	Acute toxicity	Static, 48-h, 19°C. OECD 202 (1984). Purity 99%	EC_{50} = 0.85 mg/l	R-5934
Oncorhynchus mykiss (rainbow trout)	Acute toxicity	Flow-through, 96-h, 14.9°C. OECD 203 (1984). Purity 99%	LC_{50} = 1.43 mg/l	R-5932
Selenastrum capricornutum (green alga)	Effect on growth	96-h, 20.0-22.8°C. OECD 201. Purity 99%	E_bC_{50} = 0.28 mg/l E_rC_{50} = 1.19 mg/l	R-5931
Eisenia foetida (earthworm)	Acute toxicity	Artificial soil system, 14-d, 20.5-22.0°C. OECD 207. Purity 97.5%	LC_{50} >1000 mg/kg dry soil	R-6352
Apis mellifera (honey bee)	Acute oral and contact toxicity	48-h. Guideline: Laboratory testing for toxicity to honey bees, working document 7/3; MAFF, UK. Purity 97.5%	LD_{50} (oral) = 684.03 µg/bee LD_{50} (contact) = 14.89 µg/bee	R-6211
Anas platyrhynchos (mallard duck)	Acute toxicity	14 days, single oral dose. Guideline: EPA-FIFRA, Subdivision E, No. 71-1. EPA-TOSCA, Subdivision E, wildlife and aquatic organisms, paragraph 797.2175. Purity 97.5%	LD_{50} >2000 mg/kg bw NOEC = 2000 mg/kg bw	R-6010

ANNEX 2

REFERENCES

Makhteshim document number or other reference	Year and title of report or publication details
CIPAC 2009	Confirmation from CIPAC on prochloraz method. E-mail to FAO from CIPAC, dated 3 March 2009.
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, March 2006; WHO, Geneva.
FAO/WHO 2006	Manual on the development and use of FAO and WHO specifications for pesticides, March 2006 revision of the 1st edition. FAO, Rome, March 2006; WHO, Geneva, March 2006 (internet publications).
JMPR 2001	FAO/WHO Joint Meeting on Pesticide Residues. Pesticide residues in food - 2001 evaluations. Part II - Toxicological. World Health Organization, WHO/PCS/02.1, Geneva, 2002.
R-5306	1989. Prochloraz: Acute oral toxicity study in rats.
R-5307	1989. Prochloraz: Acute dermal toxicity in rabbits.
R-5308	1989. Prochloraz: Primary skin irritation in rabbits.
R-5309	1989. Prochloraz: Primary eye irritation in rabbits.
R-5310	1989. Prochloraz: Delayed sensitisation study in guinea pigs.
R-5312	1990. Prochloraz - Toxicity in dietary administration to rats for 13 weeks.
R-5315	1990. Prochloraz: Teratogenicity study in the rabbit.
R-5400	1989. Prochloraz: Assessment of mutagenic potential in histidine auxotrophs of Salmonella typhimurium (The Ames Test).
R-5420	1989. Prochloraz technical: Acute inhalation toxicity study in rats - 4-hour exposure.
R-5424	1989. Prochloraz: Partition coefficient (n-octanol/water).
R-5438	1990. In-Vitro assessment of the clastogenic activity of Prochloraz in cultured human lymphocytes.
R-5439	1990. Prochloraz: Assessment of clastogenic action on bone marrow erythrocytes in the micronucleus test.
R-5924	1993. Mirage - Combined oncogenicity and toxicity study by dietary administration to F-344 rats for 104 weeks.
R-5926	1993. Mirage - Oncogenicity study by dietary administration to CD-1 mice for 78 weeks.
R-5928	1993. Mirage - Reproductive performance study in rats treated continuously through three successive generations.
R-5930	1991. Mirage: Teratology study in the rat.
R-5931	1991. Mirage: Determination of its EC50 to *Selenastrum capricornutum*.
R-5932	1991. Mirage: Acute toxicity to rainbow trout.
R-5934	1991. Mirage: Acute toxicity to Daphnia magna.
R-6010	1991. Acute oral toxicity study in mallard duck with Mirage technical – Limit test.
R-6144	1994. Mirage: Photodegradation in water.
R-6150	1991. Prochloraz: Hydrolysis as a function of pH at 25°C.
R-6211	1991. Laboratory testing for oral and contact toxicity of Mirage technical to honey bees, Apis mellifera L.
R-6352	1991. Acute toxicity (LC50) study of Mirage technical to earthworms.
R-6646	1992. Mirage: Induction of unscheduled DNA synthesis (UDS) in rat hepatocytes.
R-7278	1994. Mirage (pure): Determination of the melting point.
R-7279	1994. Mirage (pure): Determination of the relative density.
R-7280	1994. Mirage (pure): Determination of the vapour pressure.

Makhteshim document number or other reference	Year and title of report or publication details
R-7281	1994. Mirage (pure): Determination of the water solubility.
R-17276	2004. Prochloraz (pure grade) - Boiling temperature.
R-17277	2004. Prochloraz-Zn (pure grade): Physico-Chemical Properties.
Tomlin 2000	Tomlin, C. D. S., 2000. The Pesticide Manual, 12th edition. British Crop Protection Council, Farnham, U.K.
WHO 2002	The WHO recommended classification of pesticides by hazard and guidelines to classification 2000-2002. WHO, Geneva, 2002.