WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

PIRIMIPHOS-METHYL

O-2-diethylamino-6-methylpyrimidin-4-yl-
O,O-dimethyl phosphorothioate

World Health Organization

TABLE OF CONTENTS

DISCLAIMER[1]

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

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

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

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

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

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

---

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

INTRODUCTION

WHO establishes and publishes specifications[1] for technical material and related formulations of public health pesticides with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 2002, the development of WHO specifications follows the **New Procedure**, described in the Manual for Development and Use of FAO and WHO Specifications for Pesticides. This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by WHO and the experts of the "FAO/WHO Joint Meeting on Pesticide Specifications" (JMPS).

WHO Specifications now only apply to products for which the technical materials have been evaluated. Consequently, from the year 2002 onwards the publication of WHO specifications under the **New Procedure** has changed. Every specification consists now of two parts, namely the specifications and the evaluation report(s):

Part One: The Specification of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the above-mentioned manual.

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

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

Specifications bear the date (month and year) of publication of the current version. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

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

PART ONE: SPECIFICATIONS

PIRIMIPHOS-METHYL

Page

Pirimiphos-Methyl Information

ISO common names

pirimiphos-methyl (E-ISO, BSI, ANSI, ESA)

pirimiphos-méthyl ((m) F-ISO)

Synonyms

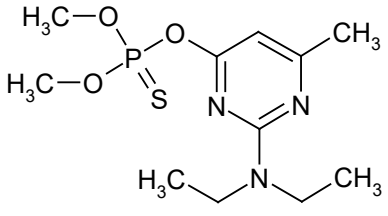
none

Chemical names

IUPAC *O*-2-diethylamino-6-methylpyrimidin-4-yl-*O*,*O*-dimethyl phosphorothioate

CA *O*-[2-(diethylamino)-6-methyl-4-pyrimidinyl] *O*,*O*-dimethyl phosphorothioate

Structural formula



Empirical formula

$C_{11}H_{20}N_3O_3PS$

Relative molecular mass

305.3

CAS Registry number

29232-93-7

CIPAC number

239

Identity tests

UV, IR, NMR and mass spectra. In UV, molar extinction coefficients (ε M^{-1} cm^{-1}) in methanol are: 220 nm, 3.39 x 10^3; 247 nm, 2.24x 10^4; 301 nm, 3.69 x 10^3.

Pirimiphos-Methyl Technical Material

WHO Specification 239/TC (December 2023∗)

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 reports (239/2004, 239/2014, 239/2016, 239/2023). It should be applicable to TC produced by this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for TC produced by other manufacturers. The evaluation reports (239/2004, 239/2014, 239/2016, 239/2023), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of pirimiphos-methyl together with related manufacturing impurities and shall be a clear or faintly turbid, mobile, red-brown liquid at temperatures above 18°C, free from visible extraneous matter and added modifying agents, except stabilizers (Note 1).

2 Active ingredient

2.1 **Identity tests** (239/TC/M/2, CIPAC Handbook O, p.113, 2017)
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 **Pirimiphos-methyl content** (239/TC/M/3,CIPAC Handbook O, p.113, 2017)
The pirimiphos-methyl content shall be declared (not less than 880 g/kg, Note 2) and, when determined, the average measured content shall not be lower than the declared minimum content.

3 Relevant impurities (239/TC/M/5, CIPAC Handbook O, p.118, 2017)

3.1 ***O,O*-dimethyl phosphorochloridothioate** (DMPCT, R305032, CAS No. 2524-03-0)
Maximum: 5 g/kg.

3.2 ***O,O,S*-trimethyl phosphorodithioate** (MeOOSPS, R305910, CAS No. 2953-29-9)
Maximum: 5 g/kg.

3.3 ***O,O,S*-trimethyl phosphorothioate** (MeOOSPO, R348532, CAS No. 152-20-5)
Maximum: 5 g/kg.

3.4 ***O,O,O*-trimethyl phosphorothioate** (MeOOOPS, R065249, CAS No. 152-18-1)
Maximum: 5 g/kg.

3.5 **Water** (MT 30.6, CIPAC Handbook P, p.222, 2021)
Maximum: 2 g/kg.

4 Physical properties

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

4.1 **Acidity** (MT 191, CIPAC Handbook L, p.143, 2006)
Maximum acidity: 3 g/kg calculated as H_2SO_4.

Note 1 Stabilizers are added to the technical material to prevent degradation in storage. For public health applications, odour suppressants are also added to minimize the formation of volatile sulfur compounds. The identity and concentrations of stabilizers are not part of the WHO specification but, if required, the manufacturer should be contacted for details and the appropriate methods of analysis.

Note 2 The declared value takes into account the addition of stabilizers.

Pirimiphos-Methyl Emulsifiable Concentrate

WHO Specification 239/EC (December 2023*)

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 reports (239/2004, 239/2014, 239/2016). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated sources. 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 reports (239/2004, 239/2014, 239/2016), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of technical pirimiphos-methyl, complying with the requirements of WHO specification 239/TC (April 2022), 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** (239/EC/M/2, CIPAC Handbook O, p.124, 2017)
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 **Pirimiphos-methyl content** (239/EC/M/3, CIPAC Handbook O, p.124, 2017)
The pirimiphos-methyl 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 tolerances.

Declared content in g/kg or g/l at 20 ± 2°C	Tolerance
above 100 up to 250	± 6% of the declared content
above 250 up to 500	± 5% of the declared content
Note. In each range the upper limit is included	

3 Relevant impurities (239/TC/M/5, CIPAC Handbook O, p.118, 2017)

3.1 ***O,O*-dimethyl phosphorochloridothioate** (DMPCT, R305032, CAS No. 2524-03-0)
Maximum: 0.5% of the pirimiphos-methyl content found under 2.2.

3.2 ***O,O,S*-trimethyl phosphorodithioate** (MeOOSPS, R305910, CAS No. 2953-29-9)
Maximum: 0.5% of the pirimiphos-methyl content found under 2.2.

3.3 ***O,O,S*-trimethyl phosphorothioate** (MeOOSPO, R348532, CAS No. 152-20-5)
Maximum: 0.5% of the pirimiphos-methyl content found under 2.2.

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

3.4 ***O,O,O*-trimethyl phosphorothioate** (MeOOOPS, R065249, CAS No. 152-18-1)
Maximum: 0.5% of the pirimiphos-methyl content found under 2.2.

3.5 **Water** (MT 30.6, CIPAC Handbook P, p.2022, 2021)
Maximum: 5 g/kg.

4 Physical properties

4.1 **Acidity** (MT 191, CIPAC Handbook L, p.143, 2006)
Maximum acidity: 1 g/kg calculated as H_2SO_4.

4.2 **Emulsion stability and re-emulsification** (MT 36.3, CIPAC Handbook K, p.137, 2003) (Notes 2 & 3)
The formulation, when diluted at 30 ± 2°C 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: 0.1 ml
2 h	'Cream', maximum: 0.1 ml 'Free oil': nil
24 h	Re-emulsification complete
24.5 h	'Cream', maximum: 2 ml 'Free oil', maximum: 2 ml
Note: in applying MT 36.3, tests after 24 h are required only where results at 2 h are in doubt.	

4.3 **Persistent foam** (MT 47.3, CIPAC Handbook O, p.177, 2017) (Note 4)
Maximum: 60 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 46.4, CIPAC Handbook P, p.232, 2021)
After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 95%, relative to the determined average content found before storage (Note 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 This test will normally only be carried out after the heat stability test 5.2.

Note 3 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 4 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 at 25 ± 5°C.

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.

Pirimiphos-Methyl Capsule Suspension

WHO Specification 239/CS (December 2023*)

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 (239/2014, 239/2016, 239/2021). It should be applicable to relevant products of 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 the products of other manufacturers, irrespective of the source of TC. The evaluation reports (239/2014, 239/2016, 231/2021), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of a suspension of micro-capsules (Note 1) containing technical pirimiphos-methyl, complying with the requirements of WHO specification 239/TC (April 2022), in an aqueous phase, together with suitable formulants. After agitation, the material shall appear homogeneous (Note 2) and suitable for further dilution in water.

2 Active ingredient

2.1 **Identity tests** (239/CS/M/2, CIPAC Handbook O, p.125, 2017)
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 **Pirimiphos-methyl content**

2.2.1 **Total content** (239/CS/M/3, CIPAC Handbook O, p.125, 2017)
The pirimiphos-methyl content shall be declared (300 g/l at 20 ± 2ºC, Note 3) and, when determined, the average content measured shall not differ from that declared by more than ± 5%.

2.2.2 **Free (non encapsulated) content** (MT 189.2, CIPAC Handbook O, p.193, 2017)
The free pirimiphos-methyl average content measured shall not exceed 4% of the determined total content.

2.2.3 **Release rate** (MT 190.2, CIPAC Handbook O, p.199, 2017)
The release of pirimiphos-methyl measured from the capsules after 15 min shall be 35 to 65% of the total pirimiphos-methyl content found under 2.2.1.

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

3 **Relevant impurities** (239/TC/M/5, CIPAC Handbook O, p.118, 2017)

3.1 ***O,O*-dimethyl phosphorochloridothioate** (DMPCT, R305032, CAS No. 2524-03-0)
Maximum: 0.5% of the pirimiphos-methyl content found under 2.2.1.

3.2 ***O,O,S*-trimethyl phosphorodithioate** (MeOOSPS, R305910, CAS No. 2953-29-9)
Maximum: 0.5% of the pirimiphos-methyl content found under 2.2.1.

3.3 ***O,O,S*-trimethyl phosphorothioate** (MeOOSPO, R348532, CAS No. 152-20-5)
Maximum: 0.5% of the pirimiphos-methyl content found under 2.2.1.

3.4 ***O,O,O*-trimethyl phosphorothioate** (MeOOOPS, R065249, CAS No. 152-18-1)
Maximum: 0.5% of the pirimiphos-methyl content found under 2.2.1.

4 **Physical properties**

4.1 **pH range** (MT 75.3, CIPAC Handbook J, p.131, 2000)
The pH of a 1% aqueous dispersion shall be 3.5 to 8.0.

4.2 **Pourability** (MT 148.1, CIPAC Handbook J, p.133, 2000) (Note 4)
Maximum "residue": 8%.

4.3 **Spontaneity of dispersion** (MT 160, CIPAC Handbook F, p.391, 1995) (Note 5)
Spontaneity of dispersion: minimum 80% after 5 min in CIPAC Standard Water D at 30 ± 2°C.

4.4 **Suspensibility** (MT 184.1, CIPAC Handbook P, p.245, 2021) (Notes 5 & 6)
Suspensibility: minimum 75% after 30 min in CIPAC Standard Water D at 30 ± 2°C.

4.5 **Wet sieve test** (MT 185, CIPAC Handbook K, p.149, 2003)
Maximum: 1% of the formulation shall be retained on a 75 µm test sieve.

4.6 **Persistent foam** (MT 47.3, CIPAC Handbook O, p.177, 2017 (Note 7)
Maximum: 10 ml after 1 min.

5 **Storage stability**

5.1 **Freeze/thaw stability** (Note 8)
After undergoing 4 freeze/thaw cycles between 20 ± 2°C and -3 ± 2°C in 18-hour freeze/6-hour thaw cycles, and following homogenization, the formulation shall continue to comply with the clauses for:
- free (non-encapsulated) pirimiphos-methyl content (2.2.2)
- pH range (4.1),
- pourability (4.2),
- spontaneity of dispersion (4.3),
- suspensibility (4.4),
- wet sieve test (4.5).

5.2 **Stability at elevated temperature** (MT 46.4, CIPAC Handbook P, p.232, 2021)
After storage at 54 ± 2°C for 14 days, the determined average total active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 9), and the formulation shall continue to comply with the clauses for:

- free (non-encapsulated) pirimiphos-methyl content (2.2.2),
- relevant impurities (3),
- pH range (4.1),
- pourability (4.2),
- spontaneity of dispersion (4.3),
- suspensibility (4.4),
- wet sieve test (4.5).

Note 1 The typical particle size distribution of pirimiphos-methyl CS formulation is loosely related to quality aspects. It is provided for information purposes as follows:
d(0.1) typically > 2 µm
d(0.5) typically in the range 8 to 13 µm
d(0.9) typically < 30 µm

Note 2 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 formulation quality, the commercial container must be inspected carefully. On standing, capsule suspensions usually develop a concentration gradient from the top to the bottom of the container. This may even result in the appearance of a clear liquid on the top and/or of sediment on the bottom. 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. After this procedure, the container should not contain a sticky layer of non-dispersed matter at the bottom. A suitable and simple method of checking for a non-dispersed sticky layer "cake" is by probing with a glass rod or similar device adapted to the size and shape of the container.

Note 3 Unless homogenization is carried out carefully, it is possible for the sample to become aerated. This can lead to errors in the determination of the mass per millilitre, and in calculation of the active ingredient content (in g/l), if methods other than OECD 109 or MT 3.3 are used. 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 The value specified is above the normally accepted limit for pourability, but it is not perceived to be an issue under actual conditions of use. The small pack size (1 litre) combined with the clear instructions on the bottle, to shake prior to opening followed by rinsing, will reduce the residue to an acceptably low limit.

Note 5 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, the simpler gravimetric method may be used on a routine basis provided that it has been shown to give equal results to those of the chemical assay method. In case of dispute, the chemical method shall be the referee method.

Note 6 Where several concentrations are recommended, the formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in the method MT 184.1.

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 at 25 ± 5°C.

Note 8 After manufacture and during shipping it is often impossible for buyer or seller to guarantee that the formulation has not been exposed to freezing temperatures. As freezing of an aqueous capsule suspension may result in undesirable, irreversible changes, including (but not limited to) capsule failure caused by crystallization of the active ingredient, the ability of the formulation to successfully withstand repeated freezing and thawing is an important property. To avoid such undesirable changes, pirimiphos-methyl CS formulations for use in public health must not be allowed to freeze, which occurs at about –5ºC.

Note 9 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

PIRIMIPHOS-METHYL

PIRIMIPHOS-METHYL

FAO/WHO Evaluation Report 239/2023

Recommendations

The Meeting recommended the following:

(i) The new site identified by Syngenta for the production of pirimiphos-methyl TC should be accepted as equivalent to the current production of pirimiphos-methyl TC by Syngenta.

Appraisal

The Meeting considered data and supporting information submitted by Syngenta Crop Protection AG between October 2021 and November 2023 in support of the proposed inclusion of a new manufacturing site for the production of the established Syngenta pirimiphos-methyl TC. Syngenta submitted information so as to present the substantial similarity of the manufacturing process and resulting batch production at the new site as compared to the production based on which the compliance with the FAO/WHO specification was established.

The production at the new site relies upon a similar manufacturing process and the same internal manufacturing limits as the original site.

The Meeting concluded that the pirimiphos-methyl TC from the new site identified by Syngenta should be considered as equivalent to the reference profile supporting the existing FAO/WHO specification 239/TC.

Additional actions recommended by the Meeting

The Meeting recommended to refer, in the TC, EC (FAO/WHO) and/or CS (WHO) specifications, the CIPAC methods for pirimiphos-methyl identity and content, free content, release rate, relevant impurities and persistent foam, as appropriate and as they are published in the CIPAC Handbook O. The relevant footnotes relating to the pre-published CIPAC methods should be withdrawn.

The Meeting also recommended updating the FAO/WHO TC and EC specifications and the WHO CS specification to align them with the most recent versions of the specification templates in the Manual, in particular with the latest versions of CIPAC methods. They include:

- the replacement of method for water content MT 30.5 by MT 30.6 as published in CIPAC Handbook P for the TC;
- the replacement of method for suspensibility MT 184 by MT 184.1 as published in CIPAC Handbook P for the CS;
- the replacement of method for accelerated storage stability MT 46.3 by MT 46.4 as published in CIPAC Handbook P; and
- the update of some footnotes.

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

Annex 1: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
CHMU170694	Stefan Ehmele	2017	Pirimiphos-methyl - Analysis of Five Representative Batches. GLP Testing Facility WMU, Syngenta Crop Protection AG, Switzerland
CHMU230627	Karine Heintz	2023	Pirimiphos-Methyl - Analysis of Three Representative Batches produced at Hunan Haili Chemical Industry Co. Ltd., China. GLP Testing Facility WMU, Syngenta Crop Protection AG, Switzerland

PIRIMIPHOS-METHYL

FAO/WHO Evaluation Report 239/2016

Recommendations

The Meeting recommended that:

(i) The impurity *iso*-pirimiphos-methyl in pirimiphos-methyl TC, EC and CS should no longer be considered as relevant.
(ii) The published WHO specifications for pirimiphos-methyl TC, EC and CS should be revised to reflect the non-relevance of the impurity *iso*-pirimiphos-methyl.
(iii) The published FAO specifications for pirimiphos-methyl TC and EC should be revised to reflect the non-relevance of the impurity *iso*-pirimiphos-methyl and editorially revised and brought in line with the WHO specifications for TC and EC.

Appraisal

The data for pirimiphos-methyl TC, EC and CS were evaluated by JMPS in 2004 and 2014. Several impurities were identified as relevant - *O,O*-dimethyl phosphorochloridothioate (DMPCT), *O,O,S*-trimethyl phosphorodithioate (MeOOSPS), *O,O,S*-trimethyl phosphorothioate (MeOOSPO), *O,O,O*-trimethyl phosphorothioate (MeOOOPS), *O*-2-diethylamino-6-methylpyrimidin-4-yl-*O,S*-dimethyl phosphorothioate, *iso*-pirimiphos-methyl (R37292), and water, with limits of 5 g/kg each in the TC, and 2 g/kg for water.

In the absence of specific toxicological data on *iso*-pirimiphos-methyl (R37292) at time of evaluation, the conclusion on the relevance of that impurity was based on an analogy: R37292 was considered to be a relevant impurity by comparing the acute toxicity of thiono- (P=S; pirimiphos-methyl-like) and oxono- (P=O; R37292-like) analogues of other organophosphates, which indicated a ratio of acute toxicity hazard in the range of 3:1 to 20:1 (Gallo and Lawryk (1991)). The higher acute toxicity of P=O analogues reported by Gallo and Lawryk is consistent with the fact that conversion of the P=S moiety to P=O is a key step in formation of the active cholinesterase inhibiting moiety in vivo. The maximum limit of 5 g/kg was considered an appropriate level for R37292 by the WHO/PCS secretariat as this would have no impact on the overall toxicity of pirimiphos-methyl, even if the impurity was twenty times more toxic than parent pirimiphos-methyl (the very upper end of Gallo and Lawryk's range).

However, Syngenta submitted in May 2016 some specific studies that had been generated in the 1970's by a predecessor company (ICI) using a limited amount of *iso*-pirimiphos-methyl (Laboratory Report, 1970, R37292). The study was conducted in 1970, prior to the introduction of standard protocols and GLP, nevertheless the report contains sufficient information to provide new evidence of the toxicology of *iso*-pirimiphos-methyl.

In an acute oral range finding test, female rats received a single oral dose of *iso*-pirimiphos-methyl in the dosing vehicle propylene glycol at a constant concentration of 50 mg/ml. The dose volume was adjusted to achieve doses of 100, 400, 1600 or 2000 mg/kg bodyweight and the animals were observed for 14 days.

There were no treatment related mortalities. Females administered 1600 mg/kg or 2000 mg/kg R37292 showed clinical signs of toxicity (incontinence and subdued behaviour) for the first 24hours post dose, the signs of incontinence persisted for up to 3 days post dose for the single female given 2000 mg/kg. At all other dose levels and time points there were no signs of clinical toxicity.

The data indicates that *iso*-pirimiphos-methyl is not 20 times more toxic than pirimiphos-methyl, since single doses up to 2000 mg/kg were well tolerated in rats, indicating it is of lower acute toxicity than pirimiphos-methyl which has an LD50 of 1414 mg/kg. The data thereby infers R37292 has indeed a lower activity as a cholinesterase inhibitor than pirimiphos-methyl.

The Meeting therefore concluded that the assumption on a higher toxicity of *iso*-pirimiphos-methyl in comparison to pirimiphos-methyl is no longer valid and that the impurity *iso*-pirimiphos-methyl should no longer be considered as relevant. The WHO specifications for TC, EC and CS should be revised accordingly and the FAO specifications for TC and EC should be brought in line with those of WHO.

The Meeting also recommended:

- to withdraw the reference to the analytical method for the determination of relevant impurities in pirimiphos-methyl TC and EC by ^{31}P NMR (Syngenta analytical method SD-876/2).
- to refer in the specifications for TC and EC to the new analytical methods adopted by CIPAC for pirimiphos-methyl and relevant impurities identity and content.
- to update the CIPAC physical-chemical methods where necessary (e.g. acidity: MT 191 instead of MT 31, emulsion stability: MT 36.3 instead of 36.1.1, persistent foam: MT 47.3 instead of MT 47.2).

Annex 1: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
	Gallo M.A and Lawryk, N.J.1991	1991	Organic phosphorus pesticides. In: Handbook of pesticide toxicology, volume 2, Classes of pesticides. Hayes W.J. Jr & Laws E.R. Jr, eds. Academic Press, Inc., San Diego. pp. 917-957.
K-CA 5.8.2 / 08, Laboratory Report, 1970	ICI	1970	Range finding test. Laboratory Report No.AR2923 issue date 11 February 1970. Unpublished. (Syngenta File No. R37292_10000)

PIRIMIPHOS-METHYL

FAO/WHO Evaluation Report 239/2014

Recommendations

The Meeting recommended that the specification for pirimiphos-methyl capsule suspension (CS), proposed by Syngenta, and as amended, should be adopted by WHO.

Appraisal

The data submitted were broadly in accordance with the requirements of the 2010 revision of the FAO/WHO Manual and supported the draft specification for new WHO specification for pirimiphos-methyl CS formulation.

Pirimiphos-methyl is a phosphorothioate insecticide with a WHOPES recommendation as larvicide and for space and indoor residual spraying (IRS) for an EC formulation published in 2006. As with other organophosphorous insecticides, pirimiphos-methyl has limited chemical/biochemical stability. This is reflected in the aqueous hydrolysis: half-live at pH 5 is 7 days and photolysis half live is less than one day. The use of pirimiphos-methyl in indoor residual spraying using an EC formulation is therefore somewhat limited as the residual activity is rather short for practical purposes (2 months). Microencapsulation is intended to ensure a controlled, slow release of the active ingredient in IRS for vector control while protecting the bulk of the active ingredient from premature degradation. On the other hand, the microencapsulation has to strike a critical balance between sufficient release rate of the active ingredient to ensure efficacy and to avoid an excessive release leading to insufficient residual activity. The product was successfully evaluated by WHOPES in 2013 who recommended it for indoor residual spraying for malaria control (WHO 2013).

Active ingredient identity, content and non-encapsulated (free) active ingredient and release rate

The 2006 WHO specification for pirimiphos-methyl covers a TC and an EC formulation. The analytical methods to support identity and content determination were based on a CIPAC method published in Handbook 1C. Briefly, pirimiphos-methyl is determined in the technical material and formulations like EC, DP and HN by packed column gas chromatography with flame ionization detection and *n*-octacosane as internal standard. CS formulations were not included because they were hardly in practical use at that time (late 1970, early 1980). As CIPAC recently has identified this method as "no longer supported", an extension of the analytical method was not possible. For that reason, the proposer decided to initiate a collaborative study for a new analytical method based on capillary gas chromatography covering TC, EC and CS formulations. The method and results of the study were presented at the 2011 CIPAC Meeting in Beijing and are in the meantime adopted as full CIPAC Methods.

The distinction between "free" and encapsulated active ingredient is an important parameter for encapsulation quality. The maximum proposed limit for non-encapsulated pirimiphos-methyl is 4 %, and the method to determine the free active

ingredient is a new compound-specific CIPAC MT 189.2 presented and adopted at the 2011 CIPAC Meeting. Briefly, the water diluted CS formulation is exposed in a glass bottle to a rolling movement with a water immiscible solvent (*iso*-hexane), which does not affect the capsule walls, so the ratio of the non-encapsulated ("free") active ingredient to the encapsulated one can be determined by capillary GC.

The release rate is determined in a similar way as with other microencapsulated insecticides like lambda-cyhalothrin: the water diluted CS formulation is again exposed to a rolling movement, this time with a mixture of ethanol and iso-hexane. After a certain time period (15 min), the amount of pirimiphos-methyl in the organic phase is determined by capillary GC. The experiment is intended to broadly mimic the diffusion process of pirimiphos-methyl through the capsule walls in a two-phase solvent system: the aqueous phase together with ethanol which enhances the diffusion by a higher solubility of the poorly water soluble active ingredient which in turn is extracted into the *iso*-hexane phase. The limit in the clause for the release rate does therefore not reflect a "real life" situation but is a useful model for e.g. distinguishing a fast release capsule system from a slow release system as in use for public health applications. The Meeting noted that such a release rate and its method need to be tailor made for the active ingredient and its intended uses and accepted the clause and its limits.

By-products of manufacture and storage

The WHO specification for the TC (2006) identifies several by-products of manufacture and storage as relevant impurities. These are summarized as follows (all with a maximum limit of 5 g/kg)

- *O,O*-dimethyl phosphorochloridothioate (DMPCT, R305032, CAS No. 2524-03-0)
- *O,O,S*-trimethyl phosphorodithioate (MeOOSPS, R305910, CAS No. 2953-29-9)
- *O,O,S*-trimethyl phosphorothioate (MeOOSPO, R348532, CAS No. 152-20-5)
- *O,O,O*-trimethyl phosphorothioate (MeOOOPS, R065249, CAS No. 152-18-1)
- *O*-2-diethylamino-6-methylpyrimidin-4-yl-*O,S*-dimethyl phosphorothioate (R037292, *iso*-pirimiphos-methyl, CAS No. 76471-79-9)

and water with a maximum of 2 g/kg.

FAOIn the 2006 specification, an analytical method based on quantitative ^{31}P NMR for the 5 relevant phosphorous-containing impurities is provided. This NMR method apparently can no longer be used with the CS formulation. The reason for that is the incompatibility of ^{31}P-NMR with the solvent system used for liberating the active ingredient with the associated impurities from the microcapsules. For that reason, a new method based on capillary GC with flame ionization detection and mass spectrometry detection was developed and peer validated under the auspices of CIPAC. The method and the results of the peer validation were presented at the 2011 CIPAC Meeting in Beijing and adopted by CIPAC. The Meeting noted that the conditions used to form the capsules may lead to a transesterification of pirimiphos-methyl to *iso*-pirimiphos-methyl, as the limit of this relevant impurity is increased from 5 g/kg in the TC to 0.8 % of the pirimiphos-methyl content in the CS formulation.

The Meeting discussed the necessity and possible consequences of the higher limit for *iso*-pirimiphos-methyl (0.8 %) in CS-formulation compared to 5 g/kg in TC and EC formulation. The proposer provided data which showed an increase of *iso*-pirimiphos-methyl during the encapsulation process and, subsequently, a decay of this relevant impurity during storage of the product (Syngenta, 2011). Therefore, the

Meeting concluded that, in this particular case, the somewhat higher limit of 0.8 % in CS-formulations of *iso*-pirimiphos-methyl is considered acceptable.

Physical-chemical properties

Whereas most of the clauses in the physical-chemical properties section are quite straightforward and essentially comply with the Manual (FAO/WHO, second revision 2010), some properties may merit further consideration. These are:

pH range. In the TC specification, water is specified with a maximum limit of 2 g/kg and acidity with a maximum limit of 3 g/kg expressed as sulfuric acid. The continuous phase in the pirimiphos-methyl CS specification is water, and the active ingredient seems to be somewhat protected against hydrolytic attack mediated by water through the encapsulation. Nevertheless, the capsule walls necessarily have a certain permeability also for water and a pH range of 3.5 to 8.0 should ensure the stability of the active ingredient containing a stabilizer and hence limit its hydrolytic degradation. The Meeting agreed with this justification.

Pourability. The proposed limit of 8 % was considered as excessively high by the Meeting and was questioned. The company explained that the rheological properties of the CS formulation lead to a rather high limit, which was not expected to lead to problems under practical use conditions as the rinsed residue was low. The company explained that indoor residual spraying is done with a pressurized knapsack sprayer, where the entire content of a bottle holding approximately 833 ml of the formulation is poured into water, rinsed and mixed. The Meeting accepted this explanation.

Particle size distribution. As with the pH range, the necessity of this clause has to be justified. With a CS formulation intended to have slow release properties, the size and thickness of the capsule wall is instrumental for determining the diffusion of pirimiphos-methyl through the capsule walls and also to the adherence properties in indoor residual spraying. The majority of the capsules have a diameter of less than 30 µm. The method chosen is the CIPAC MT 187. The Meeting concluded that particle size distribution being kept but should be presented in a footnote of the specification.

Viscosity. The draft specification contained a clause for viscosity measured with the revised CIPAC MT 192. The Meeting questioned the need for a viscosity clause, which is not a requirement in the CS specification guideline. Viscosity is actually indirectly controlled by clauses like pourability and spontaneity of dispersion. The company agreed to remove the viscosity clause.

The Meeting agreed also:
- to withdraw the Appendix 1 on the analytical method for the determination of relevant impurities in pirimiphos-methyl TK and EC by ^{31}P NMR (Syngenta analytical method SD-876/2);
- to refer in the specifications for TC and EC the new analytical methods adopted by CIPAC for pirimiphos-methyl and relevant impurities identity and content;
- to update in the specification for pirimiphos-methyl EC the CIPAC methods for emulsion stability and re-emulsification (MT 36.3 instead of 36.1.1) and persistent foam (MT 47.3 instead of MT 47.2) to be in line with the current CIPAC methods.

Annex 1: References

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
	Baker Simon	2011	WHO Specification 239/CS (pirimiphos-methyl). Proposed specification limit change for *iso*-pirimiphos-methyl within Pirimiphos-methyl 300 CS formulation. Letter of Syngenta Crop Protection to WHO, May 06, 2011.
	WHO	2013	Report of the Sixteenth WHOPES Working Group Meeting, WHO/HQ, Geneva, 22-30 July 2013. WHO, Geneva, document ISBN 978 92 4 150630 4 and WHO/HTM/NTD/WHOPES/2013.6

PIRIMIPHOS-METHYL

FAO/WHO Evaluation Report 239/2004

Recommendations

The Meeting recommended the following.

(i) Existing FAO specifications for pirimiphos-methyl TC and EC should be withdrawn.
(ii) Existing WHO specifications for pirimiphos-methyl TC, EC and WP should be withdrawn.
(iii) The proposed specifications for pirimiphos-methyl TC and EC, as amended, should be adopted by FAO and WHO.

Appraisal

The data for pirimiphos-methyl were evaluated for the review of existing WHO specifications for TC, EC and WP (WHO/SIT/30.R1, WHO/SIF/52.R1 and WHO/SIF/53.R1, 1999) and existing FAO specifications for TC and EC (239/a/TC/S and 239/a/EC/S, 1988). Proposed specifications for pirimiphos-methyl TC and EC, and the supporting data were submitted by Syngenta Crop Protection AG, in 2003. The data submitted were in accordance with the requirements of the manual (FAO/WHO, 2002) and supported the draft specifications.

Pirimiphos-methyl is no longer patent protected.

Pirimiphos-methyl is slightly volatile, has low solubility in water and is readily soluble in organic solvents. In aqueous solution, hydrolysis is pH dependent, being fairly rapid at pH 4, very slow at pH 7 and slow at pH 9. Photolysis is very rapid. Pirimiphos-methyl is weakly basic, with pKa of 4.3.

The Meeting was provided with commercially confidential information on the manufacturing process and 5-batch analysis data on all impurities present at or above 1 g/kg. Mass balances were high: 99.6-100.2%. The data were declared to be identical to those submitted to for registration in the EU, the USA and rest of the world. These data, and those for physico-chemical, toxicological and ecotoxicological properties, were confirmed as being identical to those submitted for registration in the UK (although there were certain differences in interpretation, as noted in the hazard summary, above).

The manufacturer proposed that *O,O*-dimethyl phosphorochloridothioate (DMPCT, R305032), *O,O,S*-trimethyl phosphorodithioate (MeOOSPS-triester, R305910), *O,O,S*-trimethyl phosphorothioate (MeOOSPO-triester, R348532) and water should be considered as relevant impurities. The Meeting also considered two other impurities, *O,O,O*-trimethyl phosphorothioate (R065249, CAS No. 152-18-1) and *O*-2-diethylamino-6-methylpyrimidin-4-yl-*O,S*-dimethyl phosphorothioate (R037292, "*iso*-pirimiphos-methyl" CAS No. 76471-79-9), as potentially relevant and (with the exception of water) sought the advice of WHO/PCS on all of the relevant impurity candidates.

The manufacturer provided summaries of two series of acute and sub-acute toxicity data on DMPCT (Table 1). The studies were conducted in 1971, prior to the introduction of standard protocols and GLP but, because the data from the two

series correlate well, the manufacturer considered them to provide good evidence of the toxicology of DMPCT.

Table 1. Acute and sub-acute toxicity of DMPCT from studies conducted in 1971

Test and duration	Manufacturer and study report No.	
	Stauffer Chemical Co., T-1707 (1971)	ICI IHRL, HO/IH/T/894
	Result (species)	
Acute oral	LD_{50} = 1260 mg/kg (rat)	LD_{50} = 1300 mg/kg (rat)
Acute dermal	LD_{50} = 2150 mg/kg (rabbit)	LD_{50} = 330–650 mg/kg (rat)
Acute inhalation (4hr)	LD_{50} equivalent to 0.57 mg/l (rat)	-
Skin irritation	Severe (rabbit)	Irritant, (rat)
Eye irritation	Severe to corrosive (rabbit)	Severe (rabbit)
Skin sensitization	-	Sensitizer (Stevens protocol), (Guinea pig)
14-day sub-acute oral	-	3/14 animals died. On day 7 there was a 40% decrease in plasma and RBC cholinesterase. Ulceration in fore-stomachs (rat)
21-day sub-acute inhalation (6 h/day, 5 days a week for 3 weeks)	-	Evidence of cholinesterase inhibition down to 20 ppm; evidence of pulmonary inflammation down to 5 ppm. NOEL = 1 ppm (rat)

DMPCT is irritant to skin and eyes and has properties not shared by the active ingredient, including skin sensitization. The manufacturer confirmed that the batch of pirimiphos-methyl used for some important longer-term toxicological studies (oncogenicity in mouse; rat multi-generation; rabbit developmental study) contained 3.2 g/kg DMPCT. Thus the manufacturer concluded that the toxicological significance of DMPCT as an impurity had been adequately tested in longer term studies.

WHO/PCS secretariat considered the evidence on DMPCT (WHO/PCS 2005). It concluded that DMPCT has acute oral toxicity similar to that of pirimiphos-methyl but that, in contrast to pirimiphos-methyl, it is strongly irritating and may be a skin sensitizer. On this basis, it should therefore be considered a relevant impurity. WHO/PCS secretariat also considered the proposed maximum limit of 5 g/kg for DMPCT. It noted that GHS guidelines (GHS 2003) do not require mixtures to be labelled as skin or eye irritants if they containing less than 10 g/kg of an irritating component. On this basis, the proposed maximum of 5 g/kg would be acceptable as the specification limit for DMPCT in pirimiphos-methyl. However, GHS guidelines indicate two limits for skin sensitizers, 10 g/kg and 1 g/kg, without a clear indication of which should apply in any particular case. The proposed limit of 5 g/kg is thus between the two GHS guideline limits. WHO/PCS secretariat concluded that, the proposed limit was borderline but acceptable. The Meeting agreed with the WHO/PCS conclusions and noted that the concentration of DMPCT would not increase during storage.

MeOOOPS, MeOOSPO, and MeOOSPS are all more toxic than pirimiphos-methyl (LD_{50} = 562, 47, 628 and 1400 mg/kg bw, respectively) and therefore WHO/PCS secretariat was of the opinion that these three triester impurities should be considered relevant. The manufacturing specification for each of the triesters was <5

g/kg. At or below this level, they were not expected to contribute significantly to the overall toxicity of the pirimiphos-methyl. The most toxic of them, MeOOSPO, only slightly exceeded the 10% threshold for calculated increase in overall hazard (the criterion usually applied by the JMPS) and WHO/PCS secretariat recommended that the 5/kg limit was appropriate for all three triesters. The Meeting agreed.

The LD_{50} of *iso*-pirimiphos-methyl was not known but the ratio of the acute toxicity hazards of P=O and P=S analogues of many organophosphorus compounds is in the range 3:1 to 20:1 (Gallo & Lawryk 1991). Considering the TC only, a minimum active ingredient content of 880 g/kg implies a theoretical maximum concentration of iso-pirimiphos-methyl of 120 g/kg. If iso-pirimiphos-methyl is only 3x as hazardous as pirimiphos methyl (i.e. at the lower end of Gallo & Lawryk's range), the calculated overall hazard of a mixture containing it at 120 g/kg would be about 40% more than that for the active ingredient, which exceeds the 10% threshold used by the JMPS to determine relevance. On this basis, WHO/PCS secretariat considered that the impurity should be designated as relevant and the Meeting agreed.

The original manufacturing specification for *iso*-pirimiphos-methyl was 15 g/kg. If this limit was applied in FAO/WHO specifications, and if iso-pirimiphos-methyl is actually 20x as toxic as pirimiphos-methyl (the upper end of Gallo & Lawryk's range), the calculated overall increase in hazard would be 30%, implying that the 15 g/kg limit may be unacceptable. The measured concentration of *iso*-pirimiphos-methyl in pirimiphos-methyl TC was 2.8-3.9 g/kg, in the 5 batches tested. A 5 g/kg limit implies a maximum calculated contribution of 10% to the overall hazard. As this did not exceed the threshold, no additional data were required to support a limit of 5 g/kg and it was recommended as appropriate by WHO/PCS secretariat. The Meeting agreed.

In principle, the concentration of *iso*-pirimiphos-methyl in pirimiphos-methyl could increase during storage, especially at elevated temperature. The manufacturer stated that epoxidized soybean oil is added as a stabilizer to inhibit the isomerization reaction. As it is technically difficult to determine that sufficient stabilizer is present, the Meeting agreed that the clause for storage at elevated temperature, in formulation specifications, should include a requirement for continued compliance with the clause for *iso*-pirimiphos-methyl.

The stabilizer also inhibits degradation of pirimiphos-methyl to volatile sulfur compounds, responsible for offensive odours. These compounds may also be produced during manufacture and, for this reason, an odour suppressant is normally added to products for use in public health. The identity and concentration of the stabilizers were stated to be not critical and the Meeting agreed that it was not appropriate to include them in the specifications.

The manufacturer stated that water must be regarded as a relevant impurity in order to: minimize degradation of pirimiphos-methyl, especially if the level of stabilizer drops for any reason during storage; enable production of a satisfactory EC; and minimize the development of offensive odours. The Meeting agreed that water should be considered a relevant impurity in the TC and EC.

The Meeting considered the existing and proposed specifications.

TC. The Meeting welcomed the proposed minimum content of active ingredient (880 g/kg), which was higher than that of the existing FAO and WHO specifications (860 g/kg). With the exception of water, for which the proposed limit was unchanged,

no relevant impurities were identified in the existing specification, although the existing WHO specification indicated that stabilizers were added to inhibit the formation of *iso*-pirimiphos-methyl.

EC. The proposed specification was broadly similar to the existing FAO and WHO specifications, though it no longer specified products >500 g/kg and included clauses for the relevant impurities. Proposed limits for emulsion stability were identical to those of the existing FAO specification but better than those of the existing WHO specification (which, in principle, could have permitted the separation of 2 ml oil). The proposed clause for storage stability allowed 5% degradation during the test, whereas the existing specifications required continued compliance with the clause for active ingredient content.

Analytical methods for determination of pirimiphos-methyl in the TC and EC are full CIPAC methods (CIPAC 239a/TC/M/3; 239a/EC/M/3). The analytical method for determination of the five organophosphorus relevant impurities in the TC and EC, which is based on ^{31}P NMR, has been peer validated. Values for RSD_r were 1.9-6.0% and those for RSD_R were 7.1-22%. Given that DMPCT is readily hydrolyzed, and that *iso*-pirimiphos-methyl formation from pirimiphos-methyl is temperature/time dependent, and that sample storage/treatment conditions and times were not identical in the 3 laboratories, the high RSD_R values (22 and 17%, respectively) for these two impurities may have incorporated differences in their true concentrations. The Meeting accepted that the method for determination of relevant impurities is fit for purpose.

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

Supporting Information
for
Evaluation Report 239/2004

Uses

Pirimiphos-methyl is a broad-spectrum organophosphorus insecticide and acaricide, with both contact and fumigant action. In plants, it penetrates leaf tissue and exhibits translaminar action but is of short persistence. When applied to stored agricultural commodities (such as grain and nuts) or to the fabric of buildings, it provides longer-lasting pest control. It is also effective for space treatment and as a mosquito larvicide. Pirimiphos-methyl is used for controlling a wide range of chewing, sucking and boring insects and mites in warehouses, stored grain, animal houses, domestic and industrial premises; various mites on vegetables, ornamentals, bulb flowers, sugar cane, maize, sorghum, rice, citrus and other fruit, olives, vines, alfalfa, cereals; and for controlling certain glasshouse pests (especially whiteflies, thrips, mealybugs, aphids, and mites).

Identity

ISO common names:

pirimiphos-methyl (E-ISO, BSI, ANSI, ESA)

pirimiphos-méthyl ((m) F-ISO)

Synonyms:

none

Chemical name(s):

IUPAC:

O-2-diethylamino-6-methylpyrimidin-4-yl-*O*,*O*-dimethyl phosphorothioate

CA:

O-[2-(diethylamino)-6-methyl-4-pyrimidinyl] *O*,*O*-dimethyl phosphorothioate

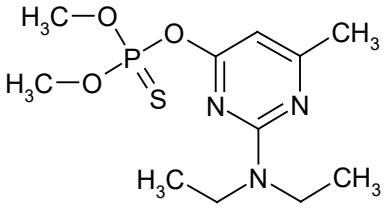
CAS Registry number:

29232-93-7

CIPAC number:

239

Structural formula:



Molecular formula:

$C_{11}H_{20}N_3O_3PS$

Relative molecular mass:

305.3

Identity tests:

UV, IR, NMR and mass spectra. In UV, molar extinction coefficients (ε M^{-1} cm^{-1}) in methanol are: 220 nm, 3.39 x 10^3; 247 nm, 2.24x 10^4; 301 nm, 3.69 x 10^3.

Physical and chemical properties

Table 2. Physical and chemical properties of pure pirimiphos-methyl

Parameter	Value(s) and conditions	Purity %	Method reference	Reference
Vapour pressure	2.0 x 10^{-6} kPa at 20ºC	99.0%	EEC A4	PP511/0055
Melting point, boiling point and/or temperature of decomposition	Freezing point: 20.8ºC (294ºK) Boiling point cannot be determined as pirimiphos-methyl decomposes on heating, at approximately 120ºC	99.0%	EEC A1	PP511/0055 PP511/0057
Solubility in water	10 mg/l in unbuffered water at 20ºC 11mg/l at pH 5 at 20 deg C 10 mg/l at pH 7 at 20 deg C 9.7 mg/l at pH 9	99.0%	CIPAC MT157.1	PP511/0055
Octanol/water partition coefficient	At 20ºC, K_{ow} log P = 4.2 in unbuffered water 3.9 at pH4 4.2 at pH 5 and 7	99.0%	EEC A8	PP511/0055
Hydrolysis characteristics	DT_{50} at 25ºC: 2, 7, 117 and 75 days at pH 4, 5, 7 and 9, respectively. Two degradation compounds identified: 2-diethylamino-6-methylpyrimidin-4-ol, and *O*-(2-diethylamino-6-methylpyrimidin-4-yl) *O*-methylphosphorothioate.	99.0%	EEC C7	PP511/0494
Photolysis characteristics	Estimated DT_{50} = 0.46 and 0.47 h at pH 5 and 7, respectively. Test solutions continuously irradiated using a xenon arc lamp, filtered for spectral distribution similar to natural sunlight. Samples were irradiated for up to the equivalent of approximately 4.12 hours Florida summer sunlight, at 25ºC. The major degradate, 2-diethylamino-6-methylpyrimidin-4-ol, reached 63% of applied radioactivity at the end of the study. *S*-2-diethylamino-6-methylpyrimidin-4-yl-*O,O*-dimethylphosphorothioate was formed up to 14.5% during the study, but degraded rapidly to final levels of 2.8% and 3.3% of applied radioactivity at pH 5 and 7, respectively. An unknown product reach levels of 12.1% and 9.5% of applied radioactivity at pH 5 and 7 but degraded quickly (DT_{50} approx. 2 h] and therefore was not characterized.	97.0%	EPA FIFRA Subdiv. N, Guidelines 161-2 and 161-3	PP511/0497
Dissociation characteristics	pKa = 4.30 at 20ºC	93.0%	OECD 112	PP511/0055

Table 3. Chemical composition and properties of technical pirimiphos-methyl (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by WHO and FAO. Mass balances were 99.6 – 100.2% and no unidentified impurities were reported.
Declared minimum pirimiphos-methyl content	880 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	*O,O*-dimethylphosphorochloridothioate (DMPCT, R305032, CAS RN 2524-03-0), 5 g/kg *O,O,S*-trimethylphosphorodithioate (R305910, CAS RN 2953-29-9), 5 g/kg *O,O,S*-trimethylphosphorothioate (R348532, CAS RN 152-20-5), 5 g/kg *O,O,O*-trimethylphosphorothioate (R065249, CAS RN 152-18-1), 5 g/kg *O*-2-diethylamino-6-methylpyrimidin-4-yl-*O,S*-dimethylphosphorothioate (R037292, "*iso*-pirimiphos-methyl" CAS No. 76471-79-9), 5 g/kg Water, 2 g/kg.
Relevant impurities < 1 g/kg and maximum limits for them:	None.
Stabilisers or other additives and maximum limits for them:	Epoxidized soybean oil is added as stabilizer – maximum limit 44g/kg. Odour suppressants are also added for public health applications.
Melting temperature range	16-22ºC (freezing point range)

Background information on toxicology/ecotoxicology

The toxicology of pirimiphos-methyl was evaluated by the FAO/WHO JMPR in 1974, 1976 and 1992, the 1992 JMPR establishing an acceptable daily intake (ADI) of 0.00-0.03 mg/kg bodyweight (JMPR, 1992b). The only biochemical effect consistently noted in acute, short-term and long-term, or chronic toxicity tests was inhibition of cholinesterase. The JMPR concluded that pirimiphos-methyl is not genotoxic. Residues of pirimiphos-methyl were considered by the JMPR in 1974, 1976, 1977, 1979, 1983, 1985, 1994 and 2003. In assessing short-term intake of residues, the 2003 JMPR noted that an acute reference dose (acute RfD) may be required for pirimiphos-methyl but had not been established (JMPR, 1992a).

The European Commission is currently reviewing pirimiphos-methyl under the EU Directive 91/414.

A review of pirimiphos-methyl conducted as part of the UK routine review programme and considered by the Advisory Committee on Pesticides in 1997 produced the following conclusions (PSD 2003). The ADI is 0-0.005 mg/kg bw/day and pirimiphos-methyl is of relatively low acute toxicity by oral, dermal and inhalation routes and, though a weak irritant to skin and eyes, it is not classifiable as an irritant or a skin sensitizer under EU criteria. Pirimiphos-methyl should be regarded as: not carcinogenic to rat or mouse; not teratogenic to rat or rabbit; not a reprotoxin and has no effect on reproduction in rats; not considered to be non-genotoxic; and there was no evidence of delayed neurotoxicity. Pirimiphos methyl should be categorized under EC criteria as R50 (very toxic to aquatic organisms) and, as it is not readily biodegradable it should also be categorised as R53 (may cause long-term adverse effects in the aquatic environment).

The WHO classification of pirimiphos-methyl is class III, slightly hazardous (WHO 2002)

Formulations

The main formulation types available are emulsifiable concentrates (EC) and these are registered and sold in many countries throughout the world for both for agricultural and public health uses.

Methods of analysis and testing

The analytical method for the active ingredient (including identity tests) is a full CIPAC method (CIPAC 1C). Pirimiphos-methyl is determined by GC with FID and internal standardization with n-octadecane.

The method for determination of the relevant impurities (except water) is based on ^{31}P NMR and was peer-validated in three laboratories (Syngenta 2005).

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, EPA and EU, 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 formulations, comply with the requirements of the Manual (FAO/WHO, 2002).

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as pirimiphos-methyl.

Annex 1: Hazard Summary Provided by the Proposer

Note: The proposer provided written confirmation that the toxicological and ecotoxicological data included in the following summary were derived from pirimiphos-methyl having impurity profiles similar to those referred to in Table 3, above.

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

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Rat, male and female	Oral	91.7	OECD 401	LD_{50} = 1414 mg/kg bw	PP511/0132
Rat, male and female	Inhalation	90.6	OECD 403	LC_{50} >5.04 mg/m^3 [>4.7 mg/l*]	PP511/0129
Rat, male and female	Dermal	91.7	OECD 402	LD_{50} >2000 mg/kg bw	PP511/0133
Rabbit, male and female	Skin irritancy	91.7	OECD 404	Slight irritant [slight but not classifiable*]	PP511/0134
Rabbit, male and female	Eye irritancy	91.7	OECD 405	Mild irritant [mild but not classifiable*]	PP511/0135
Guinea pig	Skin sensitization	91.7	OECD 406	Mild sensitizer [mild but not classifiable*]	PP511/0136

* Conclusions of the UK Pesticide Safety Directorate (PSD 2003).

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

Species	Study type	Purity %	Result	Reference
Rat	90-day toxicity	93.1	NOAEL: 8 ppm (2.8-3.6 mg/kg/day). Based on reduction in plasma, erythrocyte and brain cholinesterase activity.	PP511/0141
Dog	90-day toxicity	99.0	NOAEL: 0.5 mg/kg/day. Based on reduction in plasma and erythrocyte (but not brain) cholinesterase activity.	PP511/0146
Rat	2-year toxicity and carcinogenicity	86.8%	Not carcinogenic NOAEL = 10 ppm (0.4 mg/kg bw/d), based on depression of brain cholinesterase activity (>10%) at 50 and 300 ppm. [NOAEL for carcinogenicity = 50 ppm (2.1 mg/kg bw/d) based on equivocal increased incidence of rare pancreatic and brain tumours at 300 ppm (12.6 mg/kg bw/d)*. Manufacturer proposed carcinogenicity NOAEL = 10 ppm, considering the tumours to be unrelated to treatment.]	PP511/0559
Mouse	78 week carcinogenicity	89.8%	Not carcinogenic NOAEL: 50 ppm, based on reduction in plasma, erythrocyte and brain cholinesterase activity. [NOAEL for carcinogenicity is >300ppm (>57 mg/kg bw/day), the highest dose tested. Significant inhibition of brain and erythrocyte cholinesterase activity was seen at the lowest dose level of 50 ppm(9 mg/kg bw/day), therefore an overall NOAEL cannot be determined*.]	PP511/0149
Rat	2-generation reproduction	86.7%	Not a reprotoxin NOAEL >160 ppm	PP511/0155
Rat	Teratogenicity, maternal and developmental toxicity	88.5%	Not teratogenic Fetotoxicity NOAEL: 15 mg/kg/day	PP511/0645

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

Species	Study type	Purity %	Result	Reference
Rabbit	Teratogenicity, maternal and developmental toxicity	86.7%	Not teratogenic No effects on developmental parameters NOAEL: 48 mg/kg/day. [Alterations in the pelvis seen at 48 mg/kg bw/d are uncommon and considered to be an indication of fetotoxicity, not teratogenicity. NOAELs for teratogenicity and fetotoxicity are thus 48 mg/kg bw/d and 24 mg/kg bw/d respectively*.]	PP511/0153

* Conclusions of the UK Pesticide Safety Directorate (PSD 2003).

Table C. Mutagenicity profile of pirimiphos-methyl technical material based on *in vitro* and *in vivo* tests

Species	Study Type	Purity %	Results	Reference
S. typhimurium	Ames reverse mutation	88.9	negative	PP511/0671
Mouse lymphoma cells	L5178Y mammalian cell gene mutation	90.7	negative	PP511/0158
Hyman lymphocytes	*In vitro* clastogenicity	90.7	negative	PP511/0159
Chinese hamster lung fibroblasts	Sister chromatid exchange	90.7	equivocal	PP511/0160
Hamster kidney fibroblasts	Mammalian cell transformation	Not stated	negative	PP511/0663
Rat hepatocytes	*In vivo* UDS	93.5	negative	PP511/0161
Mouse	Dominant lethal	Not reported	negative	PP511/0156

Pirimiphos-methyl was observed to induce small increases in sister chromatid exchange in Chinese hamster fibroblasts but such minor increases were not thought to be of any toxicological significance. Evidence from *the in vitro* studies therefore suggests that pirimiphos-methyl is not genotoxic. Data from *in vivo* studies were unequivocally negative, in that pirimiphos-methyl did not induce DNA repair in the rat liver nor elicit a dominant lethal response in mice.

Table D. Ecotoxicology profile of pirimiphos-methyl technical material

Species	Test	Duration and conditions	Results	Reference
Daphnia magna (water flea)	Immobilization	48 h, EEC method C2, purity not recorded	EC_{50} = 0.21 μg/l	PP511/0528
Oncorhynchus mykiss (rainbow trout)	Mortality	96 h, EEC method C1, purity not recorded	LC_{50} = 0.2 mg/l	PP511/0520
Selenastrum capricornutum (green alga)	Growth	96 h based on OECD 201, purity 91%	EC_{50} >1000 μg/l	PP511/0533
Bobwhite quail	Acute oral	GLP, single dose 14 day oral, purity 89.8%	LD_{50} = 40 mg/kg bw	PP511/0516
Bobwhite quail	Dietary	GLP, 5-day treatment, 3-day observation, purity 89.3%	LC_{50} = 304 mg/kg diet.	PP511/0515
Hen	Reproduction	28 days, pre-GLP, purity not recorded	NOAEL = 40 mg/kg diet.	PP511/0517

Annex 2: References

Syngenta document No. or other reference	Year and title or publication details
CIPAC 1C	Collaborative International Pesticides Analytical Council (CIPAC). Handbook 1C, p.2192, 1985, Harpenden, U.K.
FAO/WHO, 2002	Manual on development and use of FAO and WHO specifications for pesticides. First edition. FAO Plant Production and Protection Paper 173. Food and Agriculture Organization of the United Nations, Rome, 2002
Gallo & Lawryk 1991	Gallo M.A. & Lawryk N.J., 1991. Organic phosphorus pesticides. In: Handbook of pesticide toxicology, volume 2, Classes of pesticides. Hayes W.J. Jr & Laws E.R. Jr, eds. Academic Press, Inc., San Diego. pp. 917-957.
GHS 2003	Globally Harmonized System of Classification and Labelling of Chemicals, United Nations, New York and Geneva, 2003, http://www.unece.org/trans/danger/publi/ghs/ghs_rev00/english
JMPR, 1992a	FAO/WHO Joint Meeting on Pesticide Residues. Pesticide residues in food – 1992 evaluations. Part I – Residues. FAO Plant Production and Protection Paper 116, 1993 (http://www.inchem.org/documents/jmpr/jmpmono/v074pr32.htm)
JMPR, 1992b	FAO/WHO Joint Meeting on Pesticide Residues. Pesticide residues in food – 1992 evaluations. Part II – Toxicology. World Health Organization, WHO/PCS/93.34 (http://www.inchem.org/documents/jmpr/jmpmono/v092pr16.htm)
PP511/0055	1997, Pirimiphos-methyl: Physical and Chemical Properties of Pure Material.
PP511/0057	1998, Pirimiphos-methyl: Physical and Chemical Properties of Technical Material.
PP511/0129	1990. Pirimiphos-methyl: 4hr Acute Inhalation Toxicity Study in the Rat.
PP511/0132	1999. Pirimiphos-methyl: Acute Oral Toxicity Study in Rats.
PP511/0133	1999. Pirimiphos-methyl: Acute Dermal Toxicity Study in Rats.
PP511/0134	1999. Pirimiphos-methyl: Skin Irritation Study in Rabbits.
PP511/0135	1999. Pirimiphos-methyl: Eye Irritation Study in Rabbits.
PP511/0136	1999. Pirimiphos-methyl: Skin Sensitisation Study in Guinea Pigs.
PP511/0141	1970. Pirimiphos-methyl: 90-Day Oral Toxicity in Rats.
PP511/0146	1973. Pirimiphos-methyl: Oral Toxicity Study in Beagle Dogs (Repeated Daily Dosage for 2 Years).
PP511/0149	1996. Pirimiphos-methyl: 78 Week Carcinogenicity in Mice With Administration By Diet.
PP511/0153	1994. Pirimiphos-methyl: Developmental Toxicity Study in Rabbits.
PP511/0155	1995. Pirimiphos-methyl: Two Generation Reproduction Study in Rats.
PP511/0156	1975. Dominant Lethal Study in Mice of Pirimiphos-methyl.
PP511/0158	1986. Pirimiphos-methyl: Assessment of Mutagenic Potential Using L5178Y Mouse Lymphoma Cells.
PP511/0159	1986. Pirimiphos-methyl: A Cytogenetic Study in Human Lymphocytes In Vitro.
PP511/0160	1986. Pirimiphos-methyl: An In Vitro Sister Chromatid Exchange Study in Chinese Hamster Lung Fibroblasts.
PP511/0161	1998. Pirimiphos-methyl: In Vivo Rat Liver Unschedulled DNA Synthesis Assay.
PP511/0494	1996, Pirimiphos-methyl: Aqueous Hydrolysis in pH4, 5, 7 and 9 solutions at 25ºC.
PP511/0497	1999, Pirimiphos-methyl: Aqueous Photolysis at pH5 and 7 at 25ºC.
PP511/0515	1990. Pirimiphos-Methyl Technical: Dietary Toxicity (LC50) to the Bobwhite Quail.
PP511/0516	1994. Pirimiphos-Methyl: An Acute Oral Toxicity Study with the Northern Bobwhite.
PP511/0517	1975. Egg Production and Hatchability Following Inclusion of Pirimiphos-Methyl at Various Levels in the Diet of the Laying Hen.
PP511/0520	1973. Pirimiphos-Methyl: Acute Toxicity to Rainbow Trout (Salmo gairdneri) and to Common Carp (Cyprinus carpio).

Syngenta document No. or other reference	Year and title or publication details
PP511/0528	1976. Pirimiphos-methyl: Acute toxicity to common carp (Cyprinus carpio) in a 96-hour flow-through test.
PP511/0533	1989. Pirimiphos-methyl: Determination of Toxicity to the Green Alga (Selenastrum capricornutum).
PP511/0559	1974. Pirimiphos-methyl: 2yr Feeding Study in the Rat.
PP511/0645	1985. Pirimiphos-methyl: Teratogenicity Study in the Rat.
PP511/0663	1983. An Examination of Pirimiphos-methyl Using the Mammalian Cell Transformation Test.
PP511/0671	1984. Pirimiphos-methyl: An Evaluation in the Salmonella Mutagenicity Assay.
PSD 2003	FAO/WHO specification for pirimiphos-methyl. Letter of 22.12.2003. Approvals Committee Branch, Pesticides Safety Directorate, UK.
Syngenta 2005	2005. Pirimiphos-methyl: peer review of analytical method SD-876/2 for the determination of five impurities in pirimiphos-methyl technical material and EC formulations.
WHO 2003	WHO specifications and evaluations of public health pesticides. Malathion. Available at: http://www.who.int/whopes/quality/en/Malathion_july04.pdf
WHO/PCS 2005	Relevant impurities of pirimiphos-methyl, Chemical safety information, WHO/PCS, AAi/ATr/JTe/TMe, 12 January 2005.