

FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

CHLORPYRIFOS

O,O-diethyl *O*-3,5,6-trichloro-2-pyridyl phosphorothioate



FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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DISCLAIMER¹

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

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¹ This disclaimer applies to all specifications published by FAO.

INTRODUCTION

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

From 2002, the development of FAO specifications follows the **New Procedure**, described in the Manual on Development and Use of FAO and WHO Specifications for Pesticides, 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 pesticide, reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the “FAO/WHO Manual on Pesticide Specifications” and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

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

Specifications bear the date (month and year) of publication of the current version. 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 INTERNET UNDER
(<http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/en/>)

PART ONE

SPECIFICATIONS

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CHLORPYRIFOS

INFORMATION

ISO common name

Chlorpyrifos (E-ISO, BSI, ANSI, ESA)

Synonyms

Chlorpyriphos ([m] F-ISO, JMAF)

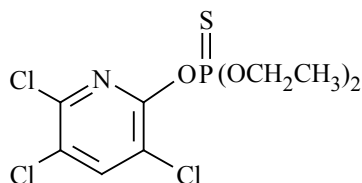
Chlorpyriphos-éthyl ([m] France)

Chemical names

IUPAC O,O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate

CA O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl) phosphorothioate

Structural formula



Molecular formula

C₉H₁₁Cl₃NO₃PS

Relative molecular mass

350.6

CAS Registry number

2912-88-2

CIPAC number

221

Identity tests

HPLC retention time, GC retention time, mass spectrum (from GC-MS)

CHLORPYRIFOS TECHNICAL MATERIAL

FAO Specification 221/TC (October 2004*)

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 (221/2002, 221/2004, 221/2006, 221/2008). 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 (221/2002, 221/2004, 221/2006, 221/2008), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of chlorpyrifos together with related manufacturing impurities and, below its melting point (Note 1), shall be a white to tan coloured crystalline solid, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 Identity tests (221.b/TC/M/2, CIPAC Handbook 1C, p. 2028, 1985) (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 Chlorpyrifos content (221.b/TC/M/3, CIPAC Handbook 1C, p.2028, 1985)

The chlorpyrifos 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

3.1 Sulfotep (O,O,O',O'-tetraethyl dithiopyrophosphate, CAS No. 3689-24-5) (Note 3)

Maximum: 3 g/kg

3.2 Acetone insolubles (MT 27, CIPAC Handbook F, p. 88, 1995)

Maximum retained on a 45 µm test sieve: 5 g/kg

4 Physical properties

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

Maximum acidity: 1 g/kg calculated as H₂SO₄

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

Note 1 The melting point should be in the range, 38-45°C.

Note 2 In addition to HPLC and GC retention times, the mass spectrum (obtained by GC-MS) provides good evidence of identity. The total ion current chromatogram and mass spectrum are shown in Figure 1.

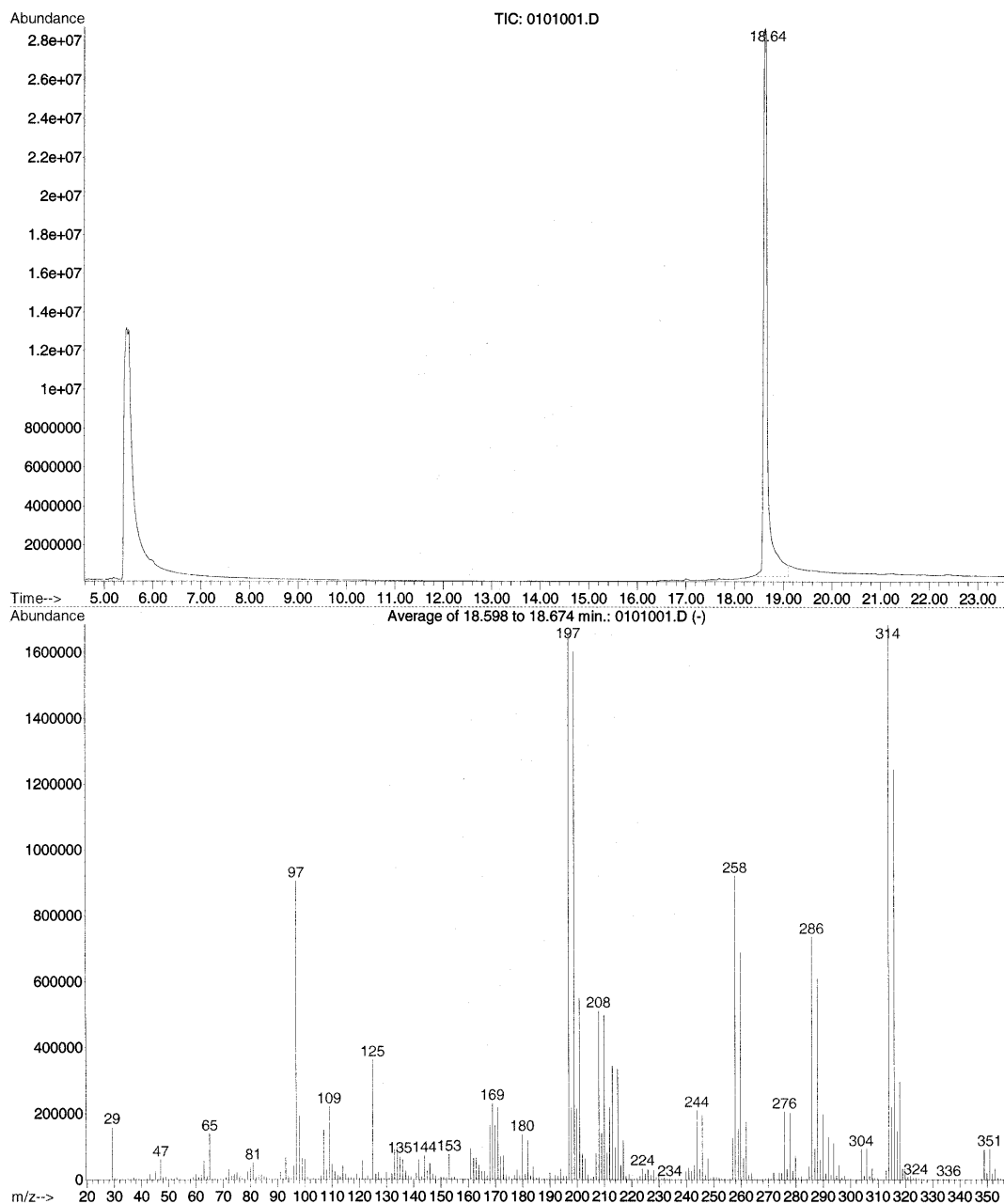


Figure 1. Total ion current chromatogram and mass spectrum of chlorpyrifos

Note 3 The methods for determination of sulfotep in technical and formulated chlorpyrifos are available from the Pesticide Management Group of the FAO Plant Protection Service or can be [downloaded here](#).

CHLORPYRIFOS EMULSIFIABLE CONCENTRATE

FAO Specification 221/EC (October 2004*)

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 (221/2002, 221/2004, 221/2006, 221/2008). It should be applicable to relevant products of these manufacturers, and those of any other formulators who use only TC from the evaluated source. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation reports (221/2002, 221/2004, 221/2006, 221/2008), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of technical chlorpyrifos (complying with the requirements of WHO specification 221/TC (October 2004) dissolved in suitable solvents together with any necessary formulants. It shall be in the form of a stable and homogeneous pale yellow to amber coloured 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 (221.b/EC/M/2, CIPAC Handbook 1C, p. 2031, 1985) (Note 1)

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 Chlorpyrifos content (221.b/EC/M/3, CIPAC Handbook 1C, p. 2031, 1985)

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

Declared content in g/kg or g/l at 20 ± 2°C	Tolerance
Up to 100	± 10% of the declared content
above 100 up to 250	± 6% of the declared content
above 250 up to 500	± 5% of the declared content
<u>Note</u> in each range the upper limit is included	

3 Relevant impurities

3.1 Sulfotep (O,O,O',O'-tetraethyl dithiopyrophosphate, CAS No. 3689-24-5) (Note 3)

Maximum: 3 g/kg (0.3%) of the chlorpyrifos content found under clause 2.2.

* 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/core-themes/theme/pests/jmps/en/>

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 4.5 to 6.5.

4.2 Emulsion stability and re-emulsification (MT 36.1, CIPAC Handbook F, p. 108, 1995) (Note 4)

The formulation, when diluted at $30 \pm 2^\circ\text{C}$ with CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of stability
0 h	Initial emulsification complete
0.5 h	'Cream', maximum: 2ml
2.0 h	'Cream', maximum: 2ml 'Oil', maximum: trace
24 h	Re-emulsification complete
24.5 h	'Cream', maximum: 2ml 'Oil', maximum: trace
<p><u>Note:</u> tests after 24 h are required only where the results at 2 h are in doubt.</p>	

4.3 Persistent foam (MT 47.2, CIPAC Handbook F, p. 152, 1995)

Maximum: 20 ml after 1 minute.

5 Storage stability

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

After storage at $0 \pm 2^\circ\text{C}$ for 7 days, the volume of solid 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 $54 \pm 2^\circ\text{C}$ for 14 days, the determined average active content shall not be lower than 95%, relative to the determined average content found under 2.2 before storage (Note 5), and the formulation shall continue to comply with the clauses for:

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

Note 1 In addition to HPLC and GC retention times, the mass spectrum (obtained by GC-MS) provides good evidence of identity. See Figure 1, attached to the specification for chlorpyrifos TC.

Note 2 In cases of dispute, the analytical results shall be calculated as g/kg.

Note 3 The methods for determination of sulfotep in technical and formulated chlorpyrifos are available from the Pesticide Management Group of the FAO Plant Protection Service or can be [downloaded here](#).

Note 4 Field dilution rates include concentrations below 5% but the MT 36.1 test has been shown to be indicative of performance over the recommended range of dilutions.

Note 5 Samples taken before and after this test should be analyzed concurrently to reduce analytical error.

CHLORPYRIFOS ULTRA LOW VOLUME LIQUID

FAO Specification 221/UL (October 2004*)

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 (221/2002, 221/2004, 221/2006, 221/2008). It should be applicable to relevant products of these manufacturers, and those of any other formulators who use only TC from the evaluated source. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation reports (221/2002, 221/2004, 221/2006, 221/2008), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of technical chlorpyrifos complying with the requirements of FAO specification 221/TC (October 2004), dissolved in suitable solvents together with any other necessary formulants. It shall be in the form of a stable and homogeneous pale yellow to brown coloured liquid, free from visible suspended matter and sediment, to be applied without dilution using appropriate hand-held or aerial ULV application equipment.

2 Active ingredient

2.1 Identity tests (221/UL/(M)/2, CIPAC Handbook K, p. 23, 2003) (Note 1)

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 Chlorpyrifos content (221/UL/(M)/3, CIPAC Handbook K, p. 23, 2003)

The chlorpyrifos content shall be declared (g/kg or g/l at $20 \pm 2^\circ\text{C}$, Note 2) and, when determined, the average measured content shall not differ from that declared by more than the following amounts:

Declared content in g/kg or g/l at $20 \pm 2^\circ\text{C}$	Tolerance
Up to 100	$\pm 10\%$ of the declared content
above 100 up to 250	$\pm 6\%$ of the declared content
above 250 up to 500	$\pm 5\%$ of the declared content
above 500	± 25 g/kg or g/l
Note in each range the upper limit is included	

3 Relevant impurities

3.1 Sulfotep (O,O,O',O'-tetraethyl dithiopyrophosphate, CAS No. 3689-24-5) (Note 3)

Maximum: 3 g/kg (0.3%) of the declared chlorpyrifos content found under clause 2.2.

* 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/core-themes/theme/pests/jmps/en/>

4 Physical properties (Notes 4 and 5)

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

Maximum acidity: 2 g/kg calculated as H₂SO₄

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 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 content shall not be lower than 95%, relative to the determined average content found under 2.2 before storage (Note 6), and the formulation shall continue to comply with the clause for:

- acidity (4.1).

Note 1 In addition to HPLC and GC retention times, the mass spectrum (obtained by GC-MS) provides good evidence of identity. See Figure 1, attached to the specification for chlorpyrifos TC.

Note 2 In cases of dispute, the analytical results shall be calculated as g/kg.

Note 3 The methods for determination of sulfotep in technical and formulated chlorpyrifos are available from the Pesticide Management Group of the FAO Plant Protection Service or can be [downloaded here](#).

Note 4 Viscosity can be critically important for successful application of a UL formulation but the requirements are dependent upon both the formulation and the application technique or equipment. For this reason, no clause is provided for kinematic viscosity.

Note 5 Loss of droplet mass by volatilization can be critical for UL formulations because, if the losses are significant, the proportion of the spray which drifts from the target, and the distance over which the drift occurs, is likely to increase. The volatilization and additional drift that occur in practice are dependent on the initial droplet size spectrum and the height through which droplets fall, the air temperature and wind speed. In addition, a degree of volatilization which may be unacceptable for one type of application may be of little or no consequence in another case. At present, no method is available to allow measurement of loss by volatilization to be related to the potential increase in drift and therefore no clause is provided for volatility.

Note 6 Samples taken before and after this test should be analyzed concurrently to reduce analytical error.

PART TWO

EVALUATION REPORT(S)

CHLORPYRIFOS

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CHLORPYRIFOS

FAO/WHO EVALUATION REPORT 221/2008

Recommendations

The Meeting recommended that:

- (i) the existing FAO specifications for chlorpyrifos TC, EC and UL should be extended to encompass the corresponding products of Gharda Chemicals Limited;
- (ii) the existing WHO specifications for chlorpyrifos TC and EC should be extended to encompass the corresponding products of Gharda Chemicals Limited.

Appraisal

The Meeting considered data and information on chlorpyrifos, submitted by Gharda Chemicals Limited, in support of the extension of the existing (October 2004) FAO specifications for TC, EC and UL and the existing (October 2004) WHO specifications for TC and EC.

The Meeting was provided with data on the physico-chemical properties of pure chlorpyrifos. The purity of chlorpyrifos used to obtain the physico-chemical data was declared to be 98%. Chlorpyrifos is a solid substance with a melting point of 42-44°C. The octanol-water partition coefficient suggests that bioconcentration is high (log Pow = 5.0 at 24.5°C). The vapour pressure is 1×10^{-3} Pa at 25°C.

The Meeting was also provided with confidential information on the manufacturing process, the manufacturing specification and 5-batch analysis data (conducted according to GLP on production scale batch samples) for chlorpyrifos and all detectable impurities. The proposer declared a minimum content of 980 g/kg for chlorpyrifos in the TC. The identity of the impurities at a level > 1 g/kg, not considered relevant, were provided. Mass balances were high with a range from 990 to 995 g/kg.

Sulfotep (*O,O,O',O'*-tetraethyl dithiopyrophosphate) was considered as a relevant impurity, although it was not detected in the five batches analysed (detection limit = 1 g/kg). The manufacturing limit given was 2 g/kg and 3 g/kg was proposed as the specification limit. Assuming that the acute oral LD₅₀ of sulfotep is 5 mg/kg bw, that of chlorpyrifos is 229 mg/kg bw, and that the minimum content of the active ingredient is 970 g/kg, it can be calculated that the RelHaz is 45.80, and the MTIHaz, 2.42. The latter represents an increase by 242% of the acute toxicity of chlorpyrifos at the maximal theoretical sulfotep content in chlorpyrifos. This being in excess of 10%, the impurity is indeed relevant. The maximum limit for the impurity, Imp_{max} is $0.21 \sim 0.2\% = 2$ g/kg (Manual on development and use of FAO and WHO specifications for pesticides). This would be in line with the manufacturing QC limit of 2 g/kg, and in accordance with the proposed specification limit of 3 g/kg.

Acetone insolubles (according to the method MT 27 published in the CIPAC Handbook F) were also declared as relevant impurities with a maximum of 5 g/kg retained on a 45 µm test sieve. No information was provided or identified that would indicate that the other identified impurities are relevant.

As far as impurities are concerned, the reported limits were supported by the 5-batch analysis data submitted by Gharda Chemicals Limited. The 5-batch analysis report (dated of 9 November 2006), conducted according to GLP principles, showed an impurities profile similar to the Dow Agrosiences reference profile and can be considered equivalent.

The toxicological and ecotoxicological studies presented in annex 1 were sufficiently described. Chlorpyrifos was evaluated by the WHO/IPCS and by the FAO/WHO JMPR in 1999. The estimated acceptable daily intake (ADI) for humans was set at 0 to 0.01 mg/kg bw and the acute reference dose (ARfD) at 0.1 mg/kg bw. The WHO/IPCS hazard classification of chlorpyrifos is "Moderately hazardous, Class II". Within the EU, according to the 19th adaptation to technical progress of Council Directive 67/548/EEC, chlorpyrifos is classified as Toxic by swallowing (T, R25), Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (N, R50/53).

Chlorpyrifos manufactured by Gharda Chemicals Limited is approved in Australia. The chemistry and quality control data (manufacturing process, purity and impurities, declaration of composition (specifications), analytical results for five batches, analytical method details with validation data, storage stability, packaging details and toxicology data) submitted by Gharda Chemicals in support of the FAO and WHO specifications for chlorpyrifos are identical to those assessed by the APVMA (Australian Pesticides and Veterinary Medicines Authority) for approval of the new source of chlorpyrifos.

The analytical method for determination of the active ingredient content (including HPLC retention time identity test) was based on the CIPAC method 221.b. Chlorpyrifos was determined by reverse phase HPLC using UV detection at 300 nm and 1,4-dibromonaphthalene as internal standard. The same method was followed for determination of chlorpyrifos in the EC formulation. The methods used for determination of impurities were based on GC using the internal standard calibration and HPLC using the external standard calibration, which were validated as per SANCO/3030/99 rev. 4 working document and US EPA 540/9/82/018 guideline. The method for determination of the relevant impurity sulfotep was based on GC-FID using the external standard calibration. Test methods for determination of physico-chemical properties of technical active ingredient were based on OECD, EPA and EEC guidelines, and for the formulations were CIPAC methods, as indicated in the specifications.

The limits proposed for physical properties of the EC and UL formulations, and the methods for testing them, comply with the requirements of the FAO/WHO manual on pesticides specifications.

**SUPPORTING INFORMATION
FOR
EVALUATION REPORT 221/2008**

Physico-chemical properties of chlorpyrifos

Table 1. Physico-chemical properties of pure chlorpyrifos

Parameter	Value(s) and conditions	Purity %	Method reference	Reference
Vapour pressure	1.0×10^{-3} Pa at 25°C	98%	OECD 104	1 <i>C.CFO.038</i>
Melting point	Melting point = 42-44°C	98%	OECD 102	2 <i>C.CFO.035</i>
Solubility in water	0.39 mg/l at 19.5°C	98%	OECD 105	3 <i>C.CFO.037</i>
Octanol/water partition coefficient	$\log P_{ow} = 5.0$ at 24.5°C	98%	OECD 117	4 <i>C.CFO.039</i>
Photolysis characteristics	(12 h light) Quantum yield : 1.18×10^{-2} $t_{1/2}$ (summer) : 4.2 days $t_{1/2}$ (winter) : 9.7 days	98%	OPPTS 835.2210	5 <i>C.CFO.066</i>
Dissociation characteristics	Practically non dissociative by nature	98%	OECD 112	6 <i>C.CFO.067</i>

Table 2. Chemical composition and properties of chlorpyrifos technical material (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were 99.0-99.5 %.
Declared minimum chlorpyrifos content	980 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	Sulfotep (O,O,O',O'-tetraethyl dithiopyrophosphate, CAS No. 3689-24-5): maximum 3 g/kg
Relevant impurities < 1 g/kg and maximum limits for them	None
Stabilizers or other additives and maximum limits for them	None
Melting range of the TC	42-44°C

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: Gharda Chemicals Limited provided written confirmation that the toxicological data included in the following summary were derived from chlorpyrifos having impurity profiles similar to those referred to in Table 2, above.

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

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Rat (Sprague dawley)	Acute oral	OECD 401	LD ₅₀ = 229 mg/kg bw Purity: not available	7 <i>T.CFO.047</i>
Rat (Sprague dawley)	Acute dermal	OECD 402	LD ₅₀ > 2000 mg/kg bw Purity: not available	8 <i>T.CFO.048</i>
Rat (Sprague dawley)	Acute Inhalation	Gaitonde Committee guidelines	LC ₅₀ = 0.385 mg/L Purity: 99%	9 <i>T.CFO.098</i>
Rabbit, New Zealand white	Skin irritation	OECD 404	Non irritant Purity: not available	0 <i>T.CFO.049</i>
Rabbit, New Zealand white	Eye irritation	OECD 405	Mild irritant Purity: not available	11 <i>T.CFO.045</i>
Guinea pig	Skin sensitisation	OECD 406	Non sensitizer Purity: not available	12 <i>T.CFO.112</i>

Table B. Mutagenicity profile of the technical material based on in vitro and in vivo tests

Species	Test	Conditions and guidelines	Result	Reference
<i>Salomonella typhimurium</i>	Bacterial reverse mutation assay	OECD Guidelines for Testing of Chemicals No. 471 EEC Directive 9/831/EEC, Annex V (Directive 84/449/EEC) US Environmental Protection Agency Method Concentrations up to 5000 µg/plate Purity: 99%	non-mutagenic	13 <i>T.CPO.011</i>
Mice	Chromosomal aberration	OECD guideline 475 Low dose : 3.125 mg/kg bw Medium dose : 6.250 mg/kg bw High dose : 12.50 mg/kg bw Purity: 98%	NOEL = 6.25 mg/kg bw	14 <i>T.CPO.043</i>
Mouse	Micronuclei test	OECD guideline Low dose : 3.124 mg/kg bw Medium dose : 6.250 mg/kg bw High dose: 12.50 mg/kg bw Purity: 98%	Non mutagenic NOEL = 12.50 mg/kg bw	15 <i>T.CPO.042</i>

Table C. Ecotoxicology profile of the technical material

Species	Test	Duration and conditions or guidelines	Result	Reference
<i>Daphnia magna</i> (water flea)	Acute toxicity	48 h flow through observations at 24 and 48 h OECD procedure 202 EEC Methods for determination of ecotoxicity (Annex to Directive 92/69/EEC)	48 h EC ₅₀ = 0.16 µg/l	16 <i>T.CFO.061</i>
<i>Oncorhynchus mykiss</i> (Rainbow trout fish)	Acute toxicity	Under flow through exposure conditions for 96 hrs OECD procedure 203 EEC Methods for determination of ecotoxicity (Annex to Directive 92/69/EEC)	LC ₅₀ = 24 µg/l NOEL = 1.6 µg/l	17 <i>T.CFO.062</i>
<i>Lampito mauriti</i> (earthworm)	Acute toxicity	OECD guideline 207 (soil test method) in sterilized soil for 14 days	LC ₅₀ (14 d) = 78.0 ± 7.40 ppm (soil)	18 <i>T.CFO.051</i>
<i>Apis mellifera</i> (Honey bee)	Acute oral toxicity	Dosed and observed for 24, 48 h at 24-25°C United Kingdom Control of Pesticides Regulation 1986, EPA Pesticide Assessment Guidelines 1989 for Non-target pests EPPO guidelines 1992 for the Efficacy Evaluation of Plant Protection Products Guideline no. 170	LD ₅₀ (48 hrs) = Oral: 0.12 µg/bee	19 <i>T.CFO.054</i>
<i>Apis mellifera</i> (Honey bee)	Acute contact toxicity	Topical application, observed at 24, 48 h at 24-25°C United Kingdom Control of Pesticides Regulation 1986, EPA Pesticide Assessment Guidelines 1989 for Non-target pests EPPO guidelines 1992 for the Efficacy Evaluation of Plant Protection Products Guideline no. 170	LD ₅₀ (48 hrs) = Contact: 0.11 µg/bee	20 <i>T.CFO.054</i>
<i>Colinus virginianus</i> (Bobwhite quail)	Acute oral toxicity	Test levels : 0, 500, 1000, 2000 mg/kg EPA guidelines, Series 71 – Avian and Mammalian Testing	LD ₅₀ = 153 mg/kg bw	21 <i>T.CFO.046</i>

ANNEX 2. REFERENCES

Gharda document number or other references	Year	Title of report or publication details
1	C.CFO.038	1996 Physical & chemical characteristics of Chlorpyrifos Determination – vapour pressure
2	C.CFO.035	1996 Physical & chemical characteristics of Chlorpyrifos Determination – Melting point
3	C.CFO.037	1996 Physical & chemical characteristics of Chlorpyrifos – Solubility in water
4	C.CFO.039	1996 Physical & chemical characteristics of Chlorpyrifos – n-Octanol/Water partition coefficient
5	C.CFO.066	2006 Physical & chemical characteristics of Chlorpyrifos – Direct photo transformation in water
6	C.CFO.067	2006 Physical & chemical characteristics of Chlorpyrifos – Determination of the dissociation constant
7	T.CFO.047	1997 Acute oral toxicity in Wistar rats
8	T.CFO.048	1997 Acute dermal toxicity study in Wistar rats
9	T.CFO.098	1997 Acute inhalation toxicity in Wistar rats
10	T.CFO.049	1997 Acute dermal irritation / corrosion study in New Zealand White Rabbits
11	T.CFO.045	1997 Acute eye irritation/corrosion study in New Zealand white rabbits
12	T.CFO.112	1997 Skin sensitisation in the Guinea pig
13	T.CPO.011	1991 Chlorpyrifos Tech. Bacterial Mutation Assay
14	T.CPO.043	1993 Mutagenicity study : Chromosomal aberration in mouse
15	T.CPO.042	1993 Mutagenicity study: Micronuclei Test in mouse
16	T.CFO.061	1997 Chlorpyrifos Technical : Acute toxicity to <i>Daphnia magna</i>
17	T.CFO.062	1997 Chlorpyrifos Technical : Acute toxicity to Rainbow Trout
18	Pesticide Manual	The Pesticide Manual 13 th Edn. – Chlorpyrifos - Crop Protection Publication
19	T.CFO.051	1993 Chlorpyrifos technical – Acute toxicity study in earthworm (<i>Lampito mauriti</i>)
20	T.CFO.054	1997 Chlorpyrifos Technical –Acute toxicity to honey bees (<i>Apis mellifera</i>)
21	T.CFO.046	1996 Chlorpyrifos technical – Acute toxicity (LD ₅₀) to Bobwhite quail

CHLORPYRIFOS

FAO/WHO EVALUATION REPORT 221/2006

Recommendations

The Meeting recommended that:-

- (i) the existing FAO specifications for chlorpyrifos TC, EC and UL should be extended to encompass the corresponding products of Cheminova A/S;
- (ii) the existing WHO specifications for chlorpyrifos TC and EC should be extended to encompass the corresponding products of Cheminova A/S.

Appraisal

The Meeting considered data on chlorpyrifos, submitted by Cheminova A/S, in support of the extension of existing (October 2004) FAO specifications for TC, EC and UL and existing (October 2004) WHO specifications for TC and EC.

The Meeting was provided with confidential information on the manufacturing process and 5-batch analysis data on the content of active ingredient and impurities with manufacturing limits $\geq 1\text{g/kg}$. Mass balances were very high, 99.6-100.5%, with no reported unknowns. These data, and the corresponding hazard data (see Annex 1), were confirmed as similar in most respects to those submitted by the manufacturer for registration in the USA, although a complete comparison of impurity data was not possible in this case

One of the impurities did not occur in the reference profile and, on this basis, the Cheminova TC did not appear to be equivalent. However, from a comparison of the acute toxicology data, the Meeting agreed that the Cheminova TC is equivalent to the chlorpyrifos upon which the original specification is based. The company provided data confirming that the levels of sulfotep, chlorpyrifos-oxon and "iso-chlorpyrifos" (see FAO/WHO evaluation report 221/2002) did not increase during storage (Cheminova 1998).

The original Cheminova study on inhalation toxicity was difficult to compare with the FAO/WHO reference data, because the highest dose tested was relatively low. The manufacturer had submitted a replacement study of inhalation toxicity to the registration authority in the USA. The US EPA review (USEPA 2004) indicated that the new study supported comparability with the inhalation toxicity of the chlorpyrifos TC upon which the reference FAO/WHO hazard profile was based.

Cheminova confirmed that its chlorpyrifos products comply with the existing FAO and WHO specifications and that the analytical and physical test methods contained therein are applicable.

**SUPPORTING INFORMATION
FOR
EVALUATION REPORT 221/2006**

Physico-chemical properties of chlorpyrifos

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

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were 996-1005 g/kg.
Declared minimum chlorpyrifos content	970 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	Sulfotep (O,O,O',O'-tetraethyl dithiopyrophosphate, CAS No. 3689-24-5): maximum 3 g/kg
Relevant impurities < 1 g/kg and maximum limits for them:	None
Stabilizers or other additives and maximum limits for them:	None
Melting temperature range	Melting point $42.6 \pm 0.1^\circ\text{C}$ (purity: 99.3% w/w) [reference 5 CYF]

Hazard summary

Chlorpyrifos was evaluated by the FAO/WHO JMPR for toxicology in 1972, 1977, 1982, and 1999, and for residues in 1972, 1974, 1975, 1977, 1981, 1982, 1983, 1989, 1995, 2000, and 2004. It is currently under review by the European Commission and the US EPA.

Containers and packaging

To avoid corrosion, containers of iron, steel, tin plate or copper should not be used unless lined with a suitable material.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: Cheminova A/S provided written confirmation that the toxicological data included in the following summary were derived from chlorpyrifos having impurity profiles similar to those referred to in Table 1, above.

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

Species	Test	Duration and conditions or guideline adopted, purity	Result	Reference
Rat, Sprague Dawley (m,f)	Acute oral	FIFRA 81-1; purity 99.3%	LD ₅₀ (m,f) = 320 mg/kg bw (260-393) LD ₅₀ (m) = 276 mg/kg bw (167-455) LD ₅₀ (f) = 350 mg/kg bw (285-429)	8 CYF
Rat, Sprague Dawley (m,f)	Acute dermal	FIFRA 81-2; purity 99.3%	LD ₅₀ >2000 mg/kg	9 CYF
Rat, Sprague Dawley (m,f)	Acute dermal	FIFRA 81-2; purity 98.5%	LD ₅₀ >2000 mg/kg	USEPA 2004
Rat, Sprague Dawley (m,f)	Acute inhalation	FIFRA 81-3; purity 99.3%	MLC (m,f) >36 mg/m ³ (32-40), no deaths.	10 CYF
Rat, Sprague-Dawley (m,f)	Acute inhalation	FIFRA 81-3; purity 97.8%	LC ₅₀ >5.22 mg/l	Cheminova 2004
Rabbit, New Zealand white (sex not stated)	Skin irritation	FIFRA 81-5; purity 99.3%	Mild irritant. No corrosive effects.	11 CYF
Rabbit, New Zealand white (sex not stated)	Eye irritation	FIFRA 81-4; purity 99.3%	Mild irritant (class 4, modified Kay & Calandra classification), all rabbits showed positive effects.	12 CYF
Guinea pig, albino Dunkin-Hartley (f)	Skin sensitization	FIFRA 81-6; purity 99.3%	Non-sensitizer.	13 CYF

ANNEX 2. REFERENCES

Cheminova document number or other reference	Year and title of report or publication details
5 CYF	1994. Chlorpyrifos Technical – Determination of Melting Point.
8 CYF	1994. Chlorpyrifos Technical: Acute Oral Toxicity Test in the Rat.
9 CYF	1994. Chlorpyrifos Technical: Acute Dermal Toxicity (Limit Test) in the Rat.
10 CYF	1994. Chlorpyrifos Technical: Acute Inhalation Toxicity Study Four-Hour Exposure (Nose Only) in the Rat.
11 CYF	1994. Chlorpyrifos Technical: Acute Dermal Irritation Test in the Rabbit.
12 CYF	1994. Chlorpyrifos Technical: Acute Eye Irritation Test in the Rabbit.
13 CYF	1994. Chlorpyrifos Technical: Magnusson & Kligman Maximisation Study in the Guinea Pig.
Cheminova 1998	1998. Chlorpyrifos_Storage_Stability_Study.pdf, sent to FAO 24 March 2007.
Cheminova 2004	2004. Chlorpyrifos_Acute_Inhalation_Study_2004.pdf, sent to FAO 24 March 2007.
USEPA 2004	2004. Data reviews for acute dermal toxicity and acute inhalation toxicity testing. 20060531154740354.pdf sent to FAO 24 March 2007.

CHLORPYRIFOS

EVALUATION REPORT 221/2004

Validation of analytical methods for determination of sulfotep

Explanation

The 2002 JMPS recommended adoption of specifications for chlorpyrifos TC and EC, subject to acceptable validation of the analytical method for determination of the relevant impurity, sulfotep. The specification limit accepted by the Meeting for sulfotep was 3 g/kg of chlorpyrifos.

In 2004, the results of a peer validation, conducted by Dow AgroSciences and Makhteshim Chemical Works, were reported to FAO and WHO (NAFST702). Five batches of TC (from 2 sources), 5 batches of EC (480 g/l) (from 2 sources) and spiked blank formulations were analyzed in two laboratories, using the GC-FID method described in Appendix 1.

A GC-MS method was also validated by Dow AgroSciences, for use as a confirmatory method and for the analysis of formulations which give interference by GC-FID. The formulation samples used for the peer validation (above) were analyzed, together with a UL (300 g/l) formulation which was analyzed as 5 replicates on 2 days. MS detection was by HP 5973 MSD in EI mode, with the ion at m/z 322 used for quantification and the ion at m/z 202 for confirmation.

Results

GC-FID. Linearity, precision and recovery data were similar from both laboratories. Recovery from formulation blanks and chlorpyrifos TC, spiked with sulfotep at 0.3-4.1 g/kg was in the range 81-115%, indicating good accuracy. Linearity over a similar range was good, with r^2 values >0.998 . Results from analysis of the TC and EC samples are given in Table 1. An apparent slight and variable bias between the two laboratories seemed to be within the uncertainty (i.e. accuracy + precision) expected for determinations at the low concentrations involved.

GC-MS. Recovery, linearity, and precision of the GC/MS method were evaluated by Dow AgroSciences for the determination of sulfotep in the TCs and ECs analyzed for peer validation of the GC-FID method. Precision was also assessed for the determination of sulfotep in the Dow AgroSciences 300 UL, because the GC-FID method may give unreliable results due to interference from formulants in this product. The GC-MS method also provides an important means for confirmation of identity and quantity of the impurity.

Recovery at 0.37-1.8 g/kg from the Makhteshim EC and a Dow AgroSciences UL formulation blank was 94.4-100.9% and 93.5-97.0%, respectively, indicating good accuracy. Linearity was also good, with $r^2 >0.9999$. Precision of analysis of the UL formulation analyzed over 2 days was good (RSD 3.2%, $n=10$). In terms of accuracy and precision of analysis of TC and EC samples, the GC-MS and GC-FID methods were very similar (Table 1).

Table 1. Determination of sulfotep in TC and EC formulations (n=5).

Lab	TC 1		TC 2		EC 1		EC 2	
	mean, g/kg	RSD%	mean, g/kg	RSD%	mean, g/kg	RSD%	mean, g/kg	RSD%
GC-FID								
DAS	2.50	11.6	0.14	2.9	1.28	11.7	0.07	1.4
MCW	1.95	9.2	0.11	0.0	1.12	11.6	0.07	14.3
GC-MS								
DAS	2.60	15.0	0.13	3.1	1.15	11.7	0.06	2.5

Recommendation

The Meeting recommended that the GC-FID method should be accepted by FAO and WHO as validated for use in support of the specifications and that the GC-MS method may be used as an alternative, or for confirmatory purposes.

Reference

NAFST702 2004. Collaborative method validation for the analysis of sulfotep in technical product and formulations containing chlorpyrifos.

Note: the methods for determination of sulfotep in technical and formulated chlorpyrifos are available from the Pesticide Management Group of the FAO Plant Protection Service or can be [downloaded here](#).

CHLORPYRIFOS

EVALUATION REPORT 221/2002

Explanation

The data for chlorpyrifos were evaluated for review of existing FAO tentative specifications for TC and EC (AGP: CP/208, 1984) and existing WHO full specifications for TC and EC (WHO/SIT/21.R3 and WHO/SIF/36.R3, 1999).

Chlorpyrifos is not under patent.

The use of chlorpyrifos in public health has been reviewed by WHO (WHO 1997). In addition, chlorpyrifos EC has been successfully evaluated by the WHO Pesticide Evaluation Scheme as a mosquito larvicide (WHO 1980).

Chlorpyrifos was evaluated by the FAO/WHO JMPR in 1972, 1974 (residues only), 1975 (residues only), 1977, 1981 (residues only), 1982, 1983 (residues only), 1995 (residues only), 1999 (periodic review of toxicology) and 2000 (periodic review of residues). At the time of review it was under review by the European Commission and the US EPA.

Draft specifications and supporting data were provided independently by Dow AgroSciences and Makhteshim Chemical Works, in 2002.

Uses

Chlorpyrifos is a non-systemic organophosphorus insecticide, acting as a cholinesterase inhibitor, with contact, stomach and respiratory action. It is used in agriculture, horticulture, viticulture and forestry, in a wide range of crops, and in disease vector (mosquito) control and other public health applications. It is used for control of Coleoptera, Diptera, Homoptera and Lepidoptera in soil or on foliage, household pests (Blattellidae, Muscidae, Isoptera), mosquitoes (larvae and adults), and pests in animal houses.

Identity of the active ingredient

ISO common name

Chlorpyrifos (E-ISO, accepted)

Chemical name(s)

IUPAC: O,O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate

CA: O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl) phosphorothioate

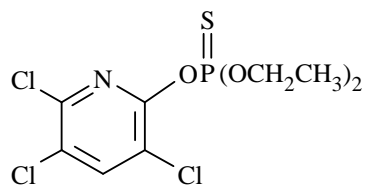
Synonyms

Chlorpyrifos (BSI, ANSI, ESA)

Chlorpyriphos ([m] F-ISO, JMAF)

Chlorpyriphos-éthyl ([m] France)

Structural formula



Molecular formula

C₉H₁₁Cl₃NO₃PS

Relative molecular mass

350.6

CAS Registry number

2912-88-2

CIPAC number

221

Identity tests

HPLC retention time (CIPAC 1C, 1985, 2028-2031), GC-MS.

Physico-chemical properties of pure chlorpyrifos

Table 1. Physico-chemical properties of pure chlorpyrifos

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure	2.546 x 10 ⁻³ Pa (1.91 x 10 ⁻⁵ mm Hg) at 25°C (Dow)	99.8	OECD 104/EPA D (equivalent to EEC A4)
	1.033 x 10 ⁻³ Pa (7.75 x 10 ⁻⁶ mm Hg) at 20°C, by extrapolation (Dow) 6.8 x 10 ⁻⁴ Pa at 25°C, by extrapolation (Makhteshim)	>99	OECD 104, gas saturation
Melting point, boiling point and/or temperature of decomposition	Melting point: 42.0°C (Dow)	99.8	EEC Method A1, OECD 102
	Melting point: 41.0 to 43.2°C (Makhteshim)	>99 *	OECD 102 (Fisher-Johns)
	Boiling point: None observed up to 400°C (Dow) Decomposition temperature: major exotherm over range 201 - 265°C (-190 Joules/g), minor exotherm 340 - 390°C (-82 Joules/g) (Dow)	99.8 99.8	EEC Method A2 EEC Method A1/A2 - DSC
Solubility in water	0.941 mg/l at 20°C (pH unknown) (Dow)	99.8	EEC Method A6/OECD 105
	0.588 mg/l at 20°C (pH not stated) (Makhteshim)	98.2	OECD 105 flask method
Octanol/water partition coefficient	log K _{ow} = 4.7001 at 20°C (Dow)	>98	EEC Method A8
	log P _{ow} = 4.76 at 25°C (Makhteshim)	>99	OECD 107 shake flask method
Hydrolysis characteristics	Half life in buffers at 25°C pH 5: 72 days pH 7: 72 days pH 9: 16 days (Dow)	Mixture of ¹⁴ C and 99.8	EPA Sub. N 161-1
	Half life in buffers at 30°C pH 4.0: 72 days pH 7.0: 40 days pH 9.0: 24 days (Makhteshim)	>99.5 *	EPA test method CS5000
Photolysis characteristics	Direct photo-transformation was observed in buffer solutions and river waters, under both natural and artificial lighting conditions. Approximate 50% conversion after 30-40 days was observed. (Dow)	¹⁴ C and 99.8	EPA Sub. N 161-1
Dissociation characteristics	Does not dissociate. Not determinable by titration, spectrophotometric or conductimetric methods, due to very low water solubility (Dow)	99.8	OECD Guideline 112

* 2004 footnote. The manufacturer stated that these data for purity of chlorpyrifos were incorrect. For melting point the correct value was 98.2% (not >99%) and for hydrolysis rate it was 99.5% (not >99.5%).

Chemical composition and properties of chlorpyrifos technical material (TC)

Table 2. Chemical composition and properties of technical chlorpyrifos

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO and WHO. Mass balances were: (i) 99.0 to 99.5%, with no unknowns detected, although certain impurities were not fully characterized (Dow); (ii) 98.8 to 99.5%, with no unknowns detected, although certain impurities were not fully characterized (Makhteshim).
Declared minimum chlorpyrifos content	970 g/kg.
Relevant impurities ≥ 1 g/kg and maximum limits for them	sulfotep, maximum 3 g/kg.
Relevant impurities < 1 g/kg and maximum limits for them	None.
Stabilizers or other additives and maximum limits for them	None.
Melting or boiling temperature range of the TC and/or TK	38 to 45 °C (Dow). 41.5 to 43.5 (Makhteshim). Decomposition starts at temperatures above 200°C (Dow). Decomposes above 160°C (Makhteshim).

Toxicological summaries

Notes.

- (i) The proposers confirmed that the toxicological and ecotoxicological data included in the summary below were derived from chlorpyrifos having impurity profiles similar to those referred to in the table above.
- (ii) The conclusions expressed in the summary below are those of the proposers, unless otherwise specified.

Table 3. Toxicology profile of the chlorpyrifos technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Duration and conditions or guideline adopted	Result
Male and female rats	Oral	OECD 401	LD ₅₀ = 223 mg/kg bw (Dow)
Rats (Charles River CD)	Oral	OECD 401	LD ₅₀ = 221 mg/kg bw LD ₅₀ = 144 mg/kg bw (Makhteshim)
male			
female			
Male and female rats	Dermal	Meets OECD 402	LD ₅₀ = >2000 mg/kg bw (Dow)
Male and female rabbits	Dermal	OECD 402	LD ₅₀ = >5000 mg/kg bw (Dow)
Male and female rabbits	Dermal	OECD 402, EPA subdivn F 163.81-2	LD ₅₀ = >2000 mg/kg bw (Makhteshim)
NZW rabbits	Inhalation	Meets OECD 403	LC ₅₀ = >200 mg/m ³ (Dow)
Rats	Inhalation	EPA subdivn F 163.81-3, 4 h	LC ₅₀ = >4070 mg/m ³ LC ₅₀ = 2890 mg/m ³ (Makhteshim)
male			
female			

Species	Test	Duration and conditions or guideline adopted	Result
NZW rabbits	Skin irritation	OECD 404	Slight irritation observed which did not persist. Irritancy was less than trigger levels of classification. (Dow)
NZW rabbits	Skin irritation	EPA subdivn F 163.81-5	Mild irritant to the skin (Makhteshim)
NZW rabbits	Eye irritation	OECD 405	Slight irritation observed which did not persist. Irritancy was less than trigger levels of classification (Dow)
NZW rabbits	Eye irritation	EPA subdivn F 163.81-4	Moderate irritant to the eye (Makhteshim)
Guinea pigs	Skin sensitization	OECD 406 and EPA 81-6	Non-sensitizer (Dow)
Guinea pigs	Skin sensitization	EPA subdivn F 163.81-6	Non-sensitizer (Makhteshim)

Table 4. Toxicology profile of the technical material based on repeated administration (sub-acute to chronic)

Note. The data in Table 4 were presented by Dow but additional data on sub-acute to chronic toxicity were also presented to WHO by Makhteshim for the purposes of the 1999 FAO/WHO JMPR evaluation of toxicology.

Species	Test	Duration and conditions or guideline adopted	Result
Rat, F-34	Short term toxicity	13 week, RBC ChE main target organ/adverse effect	NOAEL = 0.1 mg/kg bw/d LOAEL = 1 mg/kg bw/d
Mouse, CD-1	Short term toxicity	13 week, brain ChE, body weight	NOAEL = 0.7mg/kg bw/d, male NOAEL = 1.3 mg/kg bw/d, female LOAEL = 7.1 mg/kg bw/d, male LOAEL = 13.5 mg/kg bw/d, female
Dog, beagle	Short term toxicity	13 week, RBC ChE main target organ	NOAEL = 0.1 mg/kg bw/d LOAEL = 1 mg/kg bw/d
Rat, F-344	Long term toxicity	2 years	NOAEL = 0.1 mg/kg bw/d LOAEL = 1 mg/kg bw/d Not carcinogenic
Mouse, CD-1	Long term toxicity	18 months, RBC ChE]	NOAEL = 0.7mg/kg bw/d, male NOAEL = 0.7 mg/kg bw/d, female LOAEL = 6.1 mg/kg bw/d, male LOAEL = 6.6 mg/kg bw/d, female Not carcinogenic
Dog, beagle	Long term toxicity	1 to 2 years, RBC ChE	NOAEL = 0.1 mg/kg bw/d LOAEL = 1 mg/kg bw/d

Species	Test	Duration and conditions or guideline adopted	Result
Rat, CD	Reproductive toxicity	not stated	NOAEL = 0.1 mg/kg bw/d, dam LOAEL = 1 mg/kg bw/d, dam NOAEL = 1 mg/kg bw/d, litter LOAEL = 10 mg/kg bw/d, litter No reproductive effect
Rat, CD	Teratology	not stated	NOAEL = 0.1 mg/kg bw/d, dam LOAEL = 3 mg/kg bw/d, dam NOAEL = 15 mg/kg bw/d, litter LOAEL = no value given, litter Dam, cholinergic signs & ↓ bw. Litter, ↑ post-implant loss
Rat, F-344	Acute neurotoxicity	not stated	NOAEL = 10 mg/kg bw/d LOAEL = 50 mg/kg bw/d Minimal transient signs of toxicity No neuropathological alterations.
Rat, F-344	Sub-chronic neurotoxicity	not stated	NOAEL = 1 mg/kg bw/d LOAEL = 5 mg/kg bw/d Perineal soiling

The 1999 JMPR concluded that chlorpyrifos is unlikely to pose a carcinogenic risk to humans.

Table 5. Human studies of toxicity

Study	Species	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Main target organ/ adverse effect
Acute oral	Human	1.0	m = - f = 2.0	RBC ChE
Acute dermal	Human	5.0	-	RBC ChE
			5.0 (x20 12h exposures) 25.0 (x3 12h exposures)	Plasma ChE
Sub-acute oral	Human	0.1	-	None

- = not determined.

The 1999 JMPR reaffirmed an ADI of 0-0.01 mg/kg bw. This was on the basis of a NOAEL of 1 mg/kg bw per day for inhibition of brain acetylcholinesterase activity in studies in rats, mice and dogs, using a 100-fold safety factor, and on a NOAEL of 0.1 mg/kg bw per day for inhibition of erythrocyte acetylcholinesterase activity in the study of human subjects exposed for nine days, using a 10-fold safety factor.

In addition, the 1999 JMPR allocated an acute reference dose of 0.1 mg/kg bw. This was on the basis of a study in which human volunteers received a single oral dose of chlorpyrifos, a NOAEL of 1 mg/kg bw for inhibition of erythrocyte acetylcholinesterase activity, and incorporating a safety factor of 10.

Table 6. Mutagenicity profile of the technical material based on *in vitro* and *in vivo* tests

Note. The data in Table 6 were presented by Dow but additional data on mutagenicity were also presented to WHO by Makhteshim for the purposes of the 1999 FAO/WHO JMPR evaluation of toxicology.

Species	Test	Conditions	Result
<i>In vitro</i> tests			
<i>S. cerevisiae</i> D3	Rec assay	Not stated	Negative
<i>B. subtilis</i> H17, M45	Rec-assay	20, 100, 200, 500, 1000 or 2000 µg/plate in DMSO	Negative
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation ^a	10, 50, 100, 500, 1000 or 5000 µg/plate in DMSO	Negative ^a
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation ^a	1, 3.162, 10, 31.62 or 100 µg/plate in DMSO	Negative ^{a c}
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation ^a	30, 100, 300, 3000 or 10,000 µg/plate in DMSO	Negative ^a
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	Reverse mutation	Not stated	Negative
<i>E.coli</i> WP2	Reverse mutation	Not stated	Negative
<i>E coli</i> and <i>Bacillus subtilis</i>	Relative toxicity	Not stated	Negative
Chinese hamster ovary cells	CHO/HGPRT forward mutation ^a	10, 20, 25, 30, 40 or 50 µM	Negative ^a
Chinese hamster ovary cells	CHO/HGPRT forward mutation ^a	5, 10, 25, 50 or 75 µg/ml (-S9; 16 h exposure) 5, 10, 20, 30, 40 or 50 µg/ml (-S9; 16 h exposure) 30, 50, 100, 300 or 1000 µg/ml (+S9) in DMSO	Negative ^{a g}
Human lymphocytes (Laz-007)	Sister Chromatid Exchange ^a	0.02, 0.2, 2 or 20 µg/ml in ethyl alcohol	Negative ^{a h}
Chinese hamster ovary cells	Chromosomal aberration ^a	0.975, 1.47, 2.93, 4.89, 9.75, 14.7, 29.3, 48.9, 97.5 or 147 µg/ml (-S9, 19 h exposure) 1.56, 3.12, 5.2, 10.4, 15.6, 31.2, 52, 104 or 156 µg/ml (-S9, 10 h exposure) 9.75, 14.7, 29.3, 48.9, 97.5, 147 or 293 µg/ml (+S9, 19 h exposure) 1, 1.5, 3, 5, 10, 15, 30, 50 or 100 µg/ml, and 2.95, 4.95, 9.85, 14.8, 29.6, 49.4, 98.5 or 296 µg/ml (+S9, 10 h exposure)	Negative ^{a i j}
Rat hepatocytes	Chromosomal aberration ^a	16.7, 50, 167, 500, 1667 or 5000 µg/ml (harvested after 24 h) and 5, 16.7, 50 or 167 µg/ml (harvested after 24 h and 48h) in DMSO	Negative ^{a k}
Chinese hamster ovary cells	Sister Chromatid Exchange	1, 10 or 100 µg/ml in acetone	Negative

Species	Test	Conditions	Result
Rat hepatocytes in DMSO	Unscheduled DNA synthesis	1, 3.16, 10, 31.6 or 100 µM	Negative
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation ^a	0, 1, 3.16, 10, 31.6 or 100 µg/plate in DMSO	Negative ^a
Chinese hamster ovary cells	CHO/HGPRT forward mutation ^a	0, 3.5, 7, 8.8, 10.5, 14 or 17.5 µg/ml in DMSO	Negative ^{a^l}
Rat lymphocyte	Chromosomal aberration ^a	16.7 to 5000 µg/ml in DMSO	Negative ^{a^m}
Rat hepatocyte	Unscheduled DNA synthesis	1, 3.16, 10, 31.6 or 100 µM in DMSO	Negative
<i>In vivo</i> tests			
Mouse (CD-ICR BR)	Micronucleus ^b (marrow cells)	0, 7, 22 or 70 mg/kg, PO in corn oil	Negative ^b
Chick embryos (Cornell K-strain eggs)	Chromosomal aberration ^b	1.11, 11.1, 111, 1110 or 2220 µg/embryo	Negative ^{bⁿ}
Bovine blastocysts	Chromosomal aberration ^b	Not stated	Negative ^b
Mouse (CD-1 (ICR) BR)	Micronucleus ^b (marrow cells)	90 mg/kg, PO in corn oil	Negative ^b
Mouse (CD-1)	Micronucleus ^b (marrow cells)	0, 7, 22, 70 or 90 mg/kg, PO in corn oil	Negative ^b

Positive control substances were used in all assays and gave expected results.

DMSO = dimethyl sulfoxide

^a Both with and without metabolic activation.

^b With metabolic activation.

^c Cytotoxicity observed at 100µg/plate (TA 100, 1535, 1537, 1538) with precipitation. TA98 test material precipitation in the absence of toxicity.

^d Test material cytotoxic at 10µg/plate and above.

^e Dose-related increases in revertant frequency (2-fold or greater than controls) seen in all tester strains, ± S9. These increases were always lower than positive controls (by 2- to 50-fold) and were not statistically significant.

^f Increase in revertants at all dose levels, -S9, in TA1537 only. No dose-response relationship demonstrated.

^g Test material toxic at 50µg/ml in one assay -S9.

^h At 2 and 20µg/ml, the SCE frequency was statistically significantly different to controls, but was not double the control frequency.

ⁱ -S9: cytotoxic at highest doses. Increase in gaps only at 52µg/ml (10 h exposure). No increases in other aberrations.

^j +S9: cytotoxic at 15µg/ml (10 h incubation). In one 10 h assay, there was a significant increase in cells with aberrations (including gaps) at 3 and 10µg/ml. Incidence of aberrations (excluding gaps) not statistically significant and not dose-dependent. In repeat 10 h assay, no increase in incidence of aberrations.

^k Test material cytotoxic at 500µg/ml and above (-S9) and 167µg/ml and above (+S9) in the first assay. No mitotic index measurable at 50µg/ml (-S9) or 167µg/ml (±S9).

^l Test material precipitated at 10.5, 14.0 and 17.5µg/ml, ±S9.

^m Test material cytotoxic at 50µg/ml and above, ±S9.

ⁿ Increases in mortality at 1110 and 2220µg/embryo.

Chlorpyrifos was not genotoxic in a range of studies *in vitro* and *in vivo*. The 1999 JMPR concluded that chlorpyrifos is not genotoxic.

Table 7. *Ecotoxicology profile of the technical material*

Note. The data in Table 7 were presented by Dow but additional data on ecotoxicology were also presented to WHO by Makhteshim for the purposes of the 1999 FAO/WHO JMPR evaluation of toxicology.

Species	Test	Duration and conditions	Result
House sparrow	Acute oral toxicity	US EPA 71-1	LD ₅₀ = 122 mg/kg
Mallard duck Bobwhite quail	Short term dietary toxicity	Meets OECD 205 Meets OECD 205	LC ₅₀ = 180 ppm LC ₅₀ = 423 ppm
Mallard duck Bobwhite quail	One generation reproductive toxicity	Not stated	NOEC = 25 ppm NOEC = 125 ppm
Roach Ide (Orfe) <i>Daphnia magna</i> Green alga (unspecified) Midge (unspecified) Amphipod (unspecified)	Acute toxicity	96 hours, conditions not stated 96 hours, conditions not stated 48 hours, conditions not stated 72 hours, conditions not stated 10 days, conditions not stated 10 days, conditions not stated	96 h LC ₅₀ 250 µg/l 96 h LC ₅₀ 10 µg/l 48 h LC ₅₀ 1.7 µg/l 72 h EC ₅₀ 580 µg/l 10 d EC ₅₀ 383 µg/kg sed. 10 d EC ₅₀ 399 µg/kg sed
Rainbow trout <i>Daphnia magna</i>	Chronic toxicity	21 days, conditions not stated 21 days, conditions not stated	21 d LC ₅₀ ca 2 µg/l NOEC 0.51 µg/l 21 d LC ₅₀ 0.06 µg/l NOEC 0.056 µg/l
Fathead minnow	Two-generation life-cycle	Not stated	NOEC 0.57 µg/l
Honey bees	Acute toxicity	Not stated	Oral LD ₅₀ 0.36 µg/bee Contact LD ₅₀ 0.07 µg/bee
Coccinellidae Carabidae Staphylinidae Tenebrionidae Neuroptera Spiders Hymenoptera	Topical application	Not stated	ca 0.3 µg/adult, 0.1 µg/larvae "Harmful" (IOBC) "Harmful" (IOBC) 96 h ED ₅₀ ca 60 µg/kg bw ca 0.02 µg/adult, 0.05 µg/larvae EC ₁₀₀ 720 ppm residue EC ₉₀ 10 ppm residue
Earthworms (unspecified) Technical 48%EC	Acute toxicity	14 days, conditions not stated 14 days, conditions not stated	14 d LC ₅₀ 210 ppm 14 d LC ₅₀ 313 ppm

Species	Test	Duration and conditions	Result
Soil micro-organisms			
Effects of (unspecified) formulation on:			
Dehydrogenase activity		Not stated	Unaffected at 1.5 x field rate, transient inhibition at 5 x field rate
Respiration		Not stated	Unaffected at 5 x field rate
Nitrogen turnover		Not stated	Mainly unaffected at 5 x field rate

Chlorpyrifos is not persistent in soil and leaching is not significant. Therefore there is negligible risk to following crops or of groundwater contamination. Volatilization is a significant dissipative process in the environment although, once in the vapour phase, chlorpyrifos is short-lived. Transport to surface water *via* spray drift poses a risk to aquatic species, although the duration of exposure is brief because chlorpyrifos dissipates in microbially active natural water systems with a half-life of less than one week. The compound will also tend to migrate to sediment.

Health risks for avian and mammalian species following the consumption of treated vegetation and contaminated insects are considered to be low. The slightly higher long-term risk indicated for insectivorous species and birds grazing on treated grassland is not likely to arise due to:-

- (i) the high acute toxicity of chlorpyrifos to insects, preventing residue build-up in this food source;
- (ii) the generally low persistence of chlorpyrifos in the environment; and
- (iii) the rapid decline of residues in species forming the diet.

Aquatic organisms (fish and invertebrates) are potentially at risk, especially in the event of a direct overspray to static water bodies. However the introduction of buffer zones appropriate to each crop should ensure that aqueous concentrations remain below the environmentally acceptable concentration (EAC) of 1 µg/L, even in the event of multiple applications. Although chlorpyrifos is fat-soluble, the rates of biotransformation and excretion of metabolites largely mitigate bioconcentration. The risks to algal species, earthworms, soil micro-organisms and sewage bacteria are considered to be low, even in worst-case scenarios, without taking into consideration the rapid dissipation processes that occur in the environment.

Chlorpyrifos is extremely toxic to honeybees and beneficial insects. However, it has no growth inhibitory activity and the effects of treatment are relatively short-lived. Most beneficial insect populations recover quite rapidly and label restrictions on the time of application are intended to minimise the risks to honeybees.

Data from a number of field studies confirm that effects on earthworm population fecundity and viability are minimal at field use rates.

Soil microbiological processes are generally unaffected by field use of chlorpyrifos.

Chlorpyrifos was evaluated by the WHO/PCS and by the FAO/WHO JMPR in 1999. The estimated acceptable daily intake (ADI) for humans was set at 0 to 0.01 mg/kg bw and the acute reference dose (acute RfD) at 0.1 mg/kg bw. The WHO/PCS hazard classification of chlorpyrifos is "Moderately hazardous, Class II".

Formulations and co-formulated active ingredients

The main formulation types available are EC, CS and UL. Other formulation types are produced (GR, WP, WG, DP) for various markets. UL formulations are used principally for locust control.

Formulations of the same type but intended for use in agriculture or public health are not identical and should not be used interchangeably, but they share basic quality standards and thus product quality can be controlled through common specifications.

Chlorpyrifos may be formulated alone or co-formulated with other active ingredients, such as pyrethroid insecticides.

Chlorpyrifos formulations are registered and sold in many countries throughout the world.

Methods of analysis and testing

The analytical method for the active ingredient (including the HPLC retention time identity test) is a full CIPAC method (CIPAC 1C). Chlorpyrifos is determined by internal standard reversed-phase LC, using UV detection at 300 nm. The internal standard used is 1,4 dibromonaphthalene.

Extension of the CIPAC method to UL formulations was adopted as provisional by CIPAC in 2002, following submission of validation data by Dow. Validation data for extension of the CIPAC method to CS formulations were not provided. Validated methods for the determination of “free” chlorpyrifos and its “release rate” in the CS formulations were not available.

An alternative analytical method for chlorpyrifos, based on capillary GC-FID and external standardization is used routinely by Makhteshim. A variant of this, which employed octadecane as an internal standard, was also used and supported by validation data (Makhteshim report R-8197, 1995). Although these methods appear to be practical alternatives to the HPLC method, they have not been validated by collaborative study and the HPLC method must therefore be considered to be the referee method for support of the specifications.

The methods for determination of impurities were based on LC-UV or GC-FID, utilised according to the nature of the impurity.

The method of analysis for the relevant impurity, sulfotep, is based on GC-FID analysis with external standardization but has not yet been peer-validated*.

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

* The method was peer validated in 2004, see evaluation report 221/2004.

Physical properties

The limits proposed for physical properties of the EC and UL formulations, and the methods for testing them, comply with the requirements of the FAO Manual (5th edition).

No methods or limits were provided for “free” chlorpyrifos, “release rate” and “freeze/thaw stability” of CS formulations.

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as chlorpyrifos, in g/kg (or alternatively for liquid formulated products, in g/l). In cases of dispute, the content is expressed as g/kg.

Appraisal

Chlorpyrifos is an active ingredient for which tentative FAO and full WHO specifications were accepted in 1984 and 1999, respectively. Review of the specifications was proposed independently by three companies. Chlorpyrifos is not subject to patent and has been widely used in agriculture and certain vector control and public health applications for many years.

Chlorpyrifos is a slightly volatile, non-systemic organophosphorus insecticide of low water-solubility, classified as fat-soluble by the FAO/WHO JMPR. Although hydrolysis and photolysis in solution is slow, it is of short persistence in animals, plants, soil and water and therefore bioaccumulation is unlikely.

The proposed minimum purity of the TC, 970 g/kg, is significantly higher than that of the 1984 FAO tentative specification, which was 940 ± 20 g/kg (in effect a minimum of 920 g/kg) and that of the 1999 WHO full specification, which was for a minimum of 920 g/kg.

Confidential information on the manufacturing processes and impurity profiles was provided by the two proposers. The impurity data presented by Dow and Makhteshim were essentially the same as those presented by the companies to the UK authorities for the purposes of registration.

The content of the impurity, sulfotep, was not limited by the 1984 FAO tentative specification and the 1999 WHO full specification. This compound has higher acute toxicity than chlorpyrifos, by oral, dermal and inhalation routes. The data from one proposer indicated that it can exceed 1 g/kg in the TC in current production, whereas data from the other proposer indicated that it does not (<0.8 g/kg). The meeting agreed that sulfotep is a relevant impurity.

Chlorpyrifos is a phosphorothionate and other compounds of this type are known to have the potential to isomerize in storage, to form a potentially more toxic S-alkyl isomer. A manufacturing limit of 5 g/kg for “iso-chlorpyrifos” (O,S-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate) was based on a hypothetical 100% yield from the maximum limit for the precursor impurity in the raw materials used to manufacture chlorpyrifos. Dow provided data for iso-chlorpyrifos to show that, although it increased in concentration during storage of chlorpyrifos in the presence of air and at very high temperatures (90-110°C), no increase was detectable during

10 days at 60°C. The higher temperatures are such that they can never be attained in storage practice and are unrealistically extreme as a test of accelerated storage stability. It is clear that *iso*-chlorpyrifos is unlikely to increase in concentration during the CIPAC test at 54°C for 14 days and, for practical purposes, this is normally considered to be the most stringent test of storage stability. No acute toxicity data were available for *iso*-chlorpyrifos. Dow considered that its toxicity would be comparable to that of chlorpyrifos itself. The opinion of WHO/PCS was that *iso*-chlorpyrifos could be more toxic than chlorpyrifos but that it was unlikely that a significant increase in overall toxicity would occur even if *iso*-chlorpyrifos occurred at the highest concentration theoretically achievable (which is not attained in practice). Given the evidence that the concentration of *iso*-chlorpyrifos is normally <1 g/kg and does not increase during storage, the meeting concluded that it should not be regarded as a relevant impurity.

Phosphorothionates also generally have a tendency to undergo air oxidation during storage, to form the corresponding oxons. The oxons are usually more potent inhibitors of acetylcholinesterase, although they are not necessarily more toxic, because they may also be metabolized more rapidly. As in the case of *iso*-chlorpyrifos, a manufacturing limit of 2 g/kg for “chlorpyrifos oxon” (O,O-diethyl O-3,5,6-trichloro-2-pyridyl phosphate) was based on a hypothetical 100% yield from the maximum limit for the precursor impurity in the raw materials used to manufacture chlorpyrifos. Dow provided data to show that chlorpyrifos oxon can increase in concentration during storage of chlorpyrifos in the presence of air at very high temperatures (90-110°C) and it seems possible that, at these very high temperatures, a free radical mechanism is initiated. In contrast, no increase in the concentration of chlorpyrifos oxon was detectable during 10 days storage at 60°C and thus it is unlikely in practice that its concentration would increase during storage, or during the CIPAC test at 54°C for 14 days. Dow determined the acute oral LD₅₀ of chlorpyrifos oxon to be 300 mg/kg bw, indicating that the oxon is not more toxic than chlorpyrifos. On the basis of this evidence, the meeting concluded that chlorpyrifos oxon is not a relevant impurity.

On the basis of the most complete series of related data for toxicology, ecotoxicology and stability, the purity and impurity data presented by Dow were considered by the meeting to form the reference profile. The meeting concluded that the Makhteshim TC was equivalent to that of Dow.

The analytical method for chlorpyrifos is a full CIPAC method and an extension of the method to UL was adopted as provisional by CIPAC in 2002. The analytical method for the relevant impurity, sulfotep, has not yet been peer-validated.

The proposed specification for TC was in accordance with the requirements of the FAO Manual. A limit for water was specified in the previous FAO and WHO specifications but, because the water content is limited by its low affinity for chlorpyrifos, the clause is not included in the new specification.

The proposed specifications for EC and UL were also in accordance with the requirements of the Manual. The limit for acidity in the UL specification is higher than of the corresponding clause for the TC, due to the formulants. As it has been demonstrated that the concentration of sulfotep does not increase during storage, it is not necessary to determine its concentration after the test of stability at elevated temperature.

The meeting considered the problems of specifying kinematic viscosity and volatility in chlorpyrifos UL formulations, though recognising that the issues also applied to UL formulations of other pesticides. The appropriate kinematic viscosity is very dependent upon the application equipment used and therefore this parameter, though important, cannot be considered in isolation within the specification. The meeting concluded that the clause for kinematic viscosity should be removed from the specification but that its importance would be recognised by retention of a footnote to the specification. The meeting also considered the specification of volatility. The impact of evaporation, mainly of solvent, from spray droplets inevitably increases the potential for spray drift and increases both the risks of deposition beyond the target area and lower than expected deposition on the target. However, loss by evaporation does not depend solely on the volatility of the solvent and drift does not depend solely upon droplet size. To a greater or lesser extent, both are also dependent upon air temperature, air movement, initial droplet size, and the sedimentation distance. So, for example, under otherwise identical conditions, loss by volatilization may be more important for an aerial application than for an equivalent ground-based application, because of the difference in the height of fall and the difference in air movement as the ground is approached. The meeting concluded that manufacturers should be urged to develop a meaningful general test for volatility, together with supporting data to enable the results of the test to be interpreted for a range of applications. In the absence of the test and supporting information, the meeting considered that it would be inappropriate and potentially misleading to include a clause and limit for volatility in specifications for UL formulations.

The meeting considered the need for inclusion in the specifications of a note cautioning against misuse, in that a specification applying to both agricultural and public health products should not be construed as a recommendation that an agricultural product could be used equally for public health purposes, or *vice versa*. Concern was expressed that some manufacturers charge much more for public health products that are notionally similar to those used in agriculture. The meeting acknowledged the issue but concluded that pesticides must be used in accordance with the label recommendations. The meeting agreed that the standard disclaimer, which prefaces all specifications, is sufficient to make this clear to those who use specifications.

Recommendations

The meeting recommended that the proposed specifications for TC and EC should be adopted by FAO and WHO, and that the proposed specification for UL should also be adopted by FAO, subject to satisfactory peer validation of the method for determination of the relevant impurity, sulfotep* (TC, EC, UL).

The meeting also recommended that suitable test methods and limits for clauses for active ingredient content; the relevant impurity, free active ingredient content; release rate; and freeze/thaw stability should be developed to support development of a specification for CS formulations of chlorpyrifos.

* The method was peer validated in 2004, see evaluation report 221/2004.

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