

WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

DIMETHOATE

O,O-dimethyl *S*-methylcarbamoylmethyl
phosphorodithioate



**World Health
Organization**

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Disclaimer¹

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* 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. 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.

* Footnote: The publications are available on the Internet under (<http://www.who.int/whopes/quality/en/>).

PART ONE
SPECIFICATIONS

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WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

DIMETHOATE

INFORMATION

ISO common name

Dimethoate

Synonyms

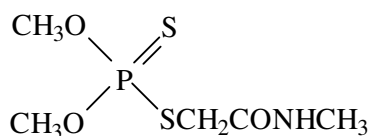
EI 12880, L 395, BAS 152, OMS 94, OMS 111, ENT 24 650, chemathoate, cygon, fosfamid, cekuthoate, daphene, devignon, dimet, dimethogen, trimetion

Chemical names

IUPAC O,O-dimethyl S-methylcarbamoylmethyl phosphorodithioate,
2-dimethoxyphosphinothioylthio-N-methylacetamide

CA O,O-dimethyl S-[2-(methylamino)-2-oxoethyl] phosphorodithioate

Structural formula



Molecular formula

C₅H₁₂NO₃PS₂

Relative molecular mass

229.3 g/mol

CAS Registry number

60-51-5

CIPAC number

59

EEC number

200-480-3

Identity tests

HPLC retention time (CIPAC E, p. 69); IR spectrum in CCl₄ or CS₂ solution (CIPAC H, p. 155).

DIMETHOATE TECHNICAL MATERIAL

WHO specification 59/TC (April 2006*)

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 (59/2001, 59/2004). 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 (59/2001, 59/2004) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of dimethoate together with related manufacturing impurities and shall be a white solid, having a mercaptanic odour, free from visible extraneous matter and added modifying agents.

2 Active ingredient

- 2.1 **Identity tests** (59/TC/M3/2, CIPAC Handbook E, p.69, 1993 or 59/TC/(M2)/2, CIPAC Handbook H, p.154, 1998)

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 **Dimethoate content** (59/TC/M3/3-, CIPAC Handbook E, p. 69, 1993)

The dimethoate content shall be declared (not less than 950 g/kg) and, when determined, the mean measured content shall not be lower than the declared minimum content.

3 Relevant impurities

- 3.1 **Omethoate** (CAS No. 1113-02-6, CAS name *O,O*-dimethyl *S*-[2-(methylamino)-2-oxoethyl] phosphorothioate) (Note 1)

Maximum: 2 g/kg.

- 3.2 **Isodimethoate** (CAS No. 3344-11-4, CAS name phosphorodithioic acid, *O,S*-dimethyl *S*-[2-(methylamino)-2-oxoethyl] ester) (Note 1)

Maximum: 3 g/kg.

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

Maximum: 2 g/kg.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: <http://www.who.int/whopes/quality/en/>.

4 Physical properties

4.1 Acidity (MT 31.1, CIPAC Handbook F, p.96, 1995)

Maximum acidity: 10 g/kg calculated as H₂SO₄.

Note 1 The analytical method for determination of omethoate and isodimethoate is given in Appendix 1 to the evaluations in Part 2 of this publication.

DIMETHOATE EMULSIFIABLE CONCENTRATE

WHO specification 59/EC (June 2012*)

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 (59/2001, 59/2004, 59/2011). 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 (59/2001, 59/2004, 59/2011) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of technical dimethoate, complying with the requirements of WHO Specification 59/TC (April 2006) dissolved in suitable solvents, together with any other necessary formulants or stabilizers if present. 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** (59/EC/(M3)/2, CIPAC Handbook E, p.71, 1993 or 59/EC/(M2)/2, CIPAC Handbook H, p.161, 1998)

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 **Dimethoate content** (59/EC/(M3)/3, CIPAC Handbook E, p.71, 1993)

The dimethoate content shall be declared (g/kg or g/l at $20 \pm 2^\circ\text{C}$, Note 1) and, when determined, the mean measured content shall not differ from that declared by more than the following tolerances:

Declared content in g/kg or g/l at $20 \pm 2^\circ\text{C}$	Permitted tolerances
above 250 up to 500	+10 or -5% of the declared content
above 500	+40 or -20 g/kg or g/l
Note: in the lower range the upper limit is included	

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: <http://www.who.int/whopes/quality/en/>.

3 Relevant impurities

- 3.1 **Omethoate** (CAS No.1113-02-6, CAS name *O,O*-dimethyl *S*-[2-(methylamino)-2-oxoethyl] phosphorothioate) (Note 2)

Maximum: 0.4% of the dimethoate content found under 2.2, above.

- 3.2 **Isodimethoate** (CAS No.3344-11-4, CAS name phosphorodithioic acid, *O,S*-dimethyl *S*-[2-(methylamino)-2-oxoethyl] ester) (Note 2)

Maximum: 7% of the dimethoate content found under 2.2, above.

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

Maximum: 2 g/kg.

4 Physical properties

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

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, MT 36.3
0 h	Initial emulsification complete
0.5 h	'Cream' maximum: 1 ml
2.0 h	'Cream' maximum: 2 ml 'Free oil' maximum: 0.5 ml
24 h (Note 4)	Re-emulsification complete
24.5 h (Note 4)	'Cream' maximum: 4 ml 'Free oil' maximum: 0.5 ml

- 4.2 **Persistent foam** (MT 47.2, CIPAC Handbook F, p. 152, 1995) (Note 5)

Maximum: 40 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 $0 \pm 2^\circ\text{C}$ for 7 days, the volume of solid and/or liquid which separates shall not be more than 0.3 ml.

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

After storage at $54 \pm 2^\circ\text{C}$ for 14 days, the determined average active ingredient content must not be lower than 90% relative to the determined average content found before storage (Note 6) for products with active ingredient content ≤ 400 g/kg, or not lower than 85% relative to the determined average content found before storage (Note 6) for products > 400 g/kg active ingredient content, and the formulation shall continue to comply with the clauses for:

- omethoate (3.1);
- isodimethoate (3.2);
- emulsion stability and re-emulsification (4.1).

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- Note 1 If the buyer requires both g/kg and g/l at 20°C, then in case of dispute, the analytical result shall be calculated as g/kg.
- Note 2 The analytical method for determination of omethoate and isodimethoate is given in Appendix 1 to the evaluations in Part 2 of this publication.
- Note 3 This test will normally only be carried out after the heat stability test, clause 5.2.
- Note 4 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. In applying MT 36.3, tests at 24/24.5 h are required only where results at 2 h are in doubt.
- Note 5 The test should be carried out at the highest application concentration in CIPAC standard water A.
- Note 6 Samples of the formulation taken before and after the storage stability test should be analysed concurrently after the test in order to reduce the analytical error.

PART TWO

EVALUATION REPORTS

DIMETHOATE

		Page
2001	FAO evaluation report based on submission of data from Cheminova, Denmark, Isagro, Italy, and BASF, Germany (TC, TK, EC).	13
2004	FAO/WHO evaluation report based on submission of information from Cheminova, Denmark (TC, EC)	24
2011	FAO/WHO evaluation report based on submission of information from the Dimethoate Task Force (TK, EC)	29
Appendix 1	Method for determination of omethoate and isodimethoate in dimethoate TC, TK and EC	31

WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

DIMETHOATE FAO EVALUATION REPORT 59/2001

Explanation

Dimethoate was scheduled as existing FAO specifications to be reviewed in 2000/2001 under the new procedure (FAO 1999).

FAO has existing specifications for dimethoate technical material (FAO Specification 59/TC/S (1990)), dustable powder (DP), (FAO Specification 59/DP/S (1990)), wettable powder (WP) (FAO Specification 59/WP/S (1990)), soluble concentrate (SL), (FAO Specification 59/SL/S (1990)), and dimethoate emulsifiable concentrate (EC), (FAO Specification 59/EC/S (1990)).

Dimethoate was evaluated for toxicology by the FAO/WHO JMPR in 1963, 1965, 1967, 1984 and 1987 and an ADI of 0-0.01 mg/kg b.w. for dimethoate was allocated. The ADI was changed, after a subsequent JMPR toxicology review in 1996, to 0-0.002 mg/kg b.w. (sum of dimethoate and omethoate, expressed as dimethoate, although it was noted that omethoate was considerably more toxic). The 1996 Meeting noted that a re-evaluation of the toxicity of dimethoate might be required if the periodic review of its residue chemistry showed omethoate to be a major part of the residue.

Dimethoate was evaluated for residues by the JMPR in 1965-1967, 1970, 1973, 1977, 1978, 1983, 1984, 1986-1988 and 1990. Dimethoate was scheduled by the 1992 CCPR for a periodic review of its residue chemistry by the 1993 JMPR. The schedule was changed subsequently and the 1996 CCPR scheduled dimethoate and omethoate for periodic review in 1998. A general review of organophosphorus pesticides (WHO 1986) also included information on dimethoate.

Data were submitted by members of the Dimethoate Task Force (DTF: Cheminova A/S, Denmark, BASF, Germany and Isagro, Italy) in 1999 and 2000. The draft TC and TK specifications were submitted by Cheminova A/S, whereas the draft EC specification was submitted jointly by the DTF.

Uses

Dimethoate formulations are used to control a wide range of Acari, Aphididae, Aleyrodidae, Coccidae, Coleoptera, Collembola, Diptera, Lepidoptera, Pseudococcidae and Thysanoptera in cereals, citrus, coffee, cotton, fruit, grapes, olives, pastures, beetroot, potatoes, pulses, tea, tobacco, and vegetables. They are also used for control of flies in animal houses. Dimethoate is a systemic insecticide and acaricide, with contact and stomach action. It acts as a cholinesterase inhibitor (Tomlin 1997).

Identity

ISO common name

Dimethoate (BSI, E-ISO, (m) F-ISO, ANSI, ESA, JMAF)

Synonyms

EI 12880, L 395, BAS 152, OMS 94, OMS 111, ENT 24 650, chemathoate, cygon, fosfamid, cekuthoate, daphene, devignon, dimet, dimethogen, trimetion

Chemical names

IUPAC: O,O-dimethyl S-methylcarbamoylmethyl phosphorodithioate, 2-dimethoxyphosphinothioylthio-N-methylacetamide

CA: O,O-dimethyl S-[2-(methylamino)-2-oxoethyl] phosphorodithioate

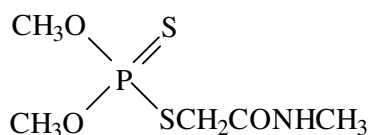
CAS Registry No.

60-51-5

CIPAC No.

59

Structural formula



Molecular formula

C₅H₁₂NO₃PS₂

Molecular weight

229.3 g/mol

Identity tests

HPLC retention time (CIPAC E, p. 69); IR spectrum in CCl₄ or CS₂ solution (CIPAC H, p. 155).

Physical and chemical properties

Table 1. Physicochemical properties of pure dimethoate

Characteristic	Purity	Value	Reference and/or method
Vapour pressure	98.0%	1.85×10 ⁻⁶ mm Hg at 25°C 1.21×10 ⁻⁵ mm Hg at 35°C	Teeter, D. 1988
Melting point	technical	45-47°C	Cheminova Agro, no formal report
	not stated	49°C	Tomlin 1997
Boiling point	not stated	117°C at 0.1 mm Hg	Tomlin 1997
Decomposition temperature	not stated	rapid at >80°C	Cheminova Agro, no formal report
Solubility in water	90%	39.8 g/l at 25°C after 4 h equilibration	Mangels, G. 1987

Characteristic	Purity	Value	Reference and/or method
Octanol:water partition coefficient	98.0%	log K _{OW} = 0.704	Mangels, G. 1987 (FIFRA D-63-11 method)
Hydrolysis	radiochemical purity >98%	estimated half-life at 25 ± 1°C for 30 days: pH 5 = 156 days pH 7 = 68 days pH 9 = 4.4 days. At pH 5 and 7 major degradation products were <i>O</i> -desmethyldimethoate and <i>O,O</i> -dimethylphosphorothioic acid. At pH 9 major degradation product was <i>O</i> -desmethyldimethoate.	Hawkins, D.R. <i>et al.</i> 1986
Photolysis	radiochemical purity >99%	No significant photolysis of [<i>O</i> -methyl- ¹⁴ C]dimethoate in buffer solution at pH 5, exposed to 15 days continuous artificial sunlight.	Hawkins, D.R. <i>et al.</i> 1986

Table 2. Chemical composition and properties of dimethoate 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. Mass balances were 99.7 ± 0.5% to 100.4 ± 0.7% with total impurities accounting for 0.64-1.19%.
Declared minimum dimethoate content:	950 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them:	Omethoate, 2 g/kg Isodimethoate, 3 g/kg Water, 2 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	Melting point: 45-47°C

Hazard summary

Notes.

(i) The proposers provided written confirmation that the toxicological and ecotoxicological data included in the summary below were derived from dimethoate 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. Most of the information presented below is a summary of the proposers' data previously evaluated in detail by the FAO/WHO JMPR (JMPR 1996 and 1998).

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

Species	Test	Duration and conditions	Result
Rat, sex not stated	Acute oral toxicity	Not stated, purity not stated	LD ₅₀ = 310 mg/kg bw
Rat, sex not stated	Acute dermal toxicity	Not stated, purity not stated	LD ₅₀ >7000 mg/kg bw
Rabbit, sex not stated	Dermal irritation	Not stated, purity not stated	Slightly irritating

Species	Test	Duration and conditions	Result
Rabbit, sex not stated	Eye irritation	Not stated, purity not stated	Slightly irritating
Human, sex not stated	Dermal sensitization	Not stated, purity not stated	Positive

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

Species	Test	Duration and conditions	Result
Short-term toxicity (1-26 weeks)			
Rabbit, sex not stated	Dermal	Repeated dosing, 21 days	NOAEL = 1000 mg/kg bw per day (highest dose tested)
Rat	Oral	Repeated dosing, reproductive toxicity, actual duration not stated	NOAEL = 1.2 mg/kg bw per day, reproductive toxicity NOAEL = 0.08 mg/kg bw per day, parental toxicity
Rat	Oral	Repeated dosing, developmental toxicity, actual duration not stated	NOAEL = 6 mg/kg bw per day, maternal toxicity. No evidence of embryotoxicity or teratogenicity at 40 mg/kg bw per day (highest dose tested)
Rabbit	Oral	Repeated dosing, developmental toxicity, actual duration not stated	NOAEL = 10 mg/kg bw per day, maternal toxicity. No evidence of embryotoxicity or teratogenicity at 40 mg/kg bw per day (highest dose tested)
Long-term toxicity and carcinogenicity (1 year)			
Rat, sex not stated	Oral	Repeated dosing, toxicity and carcinogenicity	NOAEL = 0.04 mg/kg bw per day, cholinesterase inhibition. No evidence of carcinogenicity.

Table 5. Mutagenicity profile of dimethoate technical material based on *in vivo* tests.

Species	Test	Conditions	Result
Mouse (m, f)	Micronucleus test, <i>in vivo</i>	Oral dosing, purity 97.3%	Negative
Mouse (m, f)	Dominant lethal mutation study, <i>in vivo</i>	Oral dosing, purity 96.89%	Negative

Table 6. Ecotoxicology profile of dimethoate technical material

Species	Test	Duration and conditions	Result	Reference ¹
Carp	Not stated	96 h, conditions not stated	LC ₅₀ = 694 mg/l	Bathe, R. 1982
Rainbow trout	Not stated	96 h, conditions not stated	LC ₅₀ = 30.2 mg/l	Bathe, R. 1982

¹ Source of data submitted to FAO.

Species	Test	Duration and conditions	Result	Reference ¹
<i>Daphnia magna</i>	Not stated	24 h, conditions not stated, dimethoate purity 95%	EC ₅₀ = 4.7 mg/l	Ellgehouse, H. 1983
<i>Daphnia magna</i>	Not stated	21 days, conditions not stated, dimethoate purity 99%	EC ₅₀ = 0.04-0.1 mg/l	Wüthrich, V. 1990
Ring-necked pheasant	Acute oral	Duration and conditions not stated	LD ₅₀ = 20 mg/kg bw	Hudson, R.H. <i>et al.</i> 1984
Mallard duck (m)	Acute oral	Duration and conditions not stated	LD ₅₀ = 41.7 mg/kg bw	Hudson, R.H. <i>et al.</i> 1984
Mallard duck (f)	Acute oral	Duration and conditions not stated	LD ₅₀ = 63.5 mg/kg bw	Hudson, R.H. <i>et al.</i> 1984
Sparrow	Acute oral	Duration and conditions not stated	LD ₅₀ = 22 mg/kg bw	USDA 1979
Red-winged blackbird	Acute oral	Duration and conditions not stated	LD ₅₀ = 6.6-17.8 mg/kg bw	Schafer, E.W. <i>et al.</i> 1983
Starling	Acute oral	Duration and conditions not stated	LD ₅₀ = 31.6 mg/kg bw	Schafer, E.W. <i>et al.</i> 1983
Blackbird	Acute oral	Duration and conditions not stated	LD ₅₀ = 26 mg/kg bw	USDA 1979
Honey bee	Contact	Duration and conditions not stated	LD ₅₀ = 0.12 µg/bee	Stevenson, J.H. 1978
Honey bee	Oral	Duration and conditions not stated	LD ₅₀ = 0.15 µg/bee	Stevenson, J.H. 1978

The FAO/WHO JMPR has evaluated the residues and toxicology of dimethoate several times.

The JMPR (JMPR 1998) considered the environmental fate of dimethoate in studies of confined rotational crops, degradation, dissipation and mobility in soil, adsorption and desorption, photodegradation on soil, and aquatic dissipation. The JMPR concluded that inadvertent residues in rotational crops would not be significant, that the low residue levels consisted mainly of polar metabolites and that dimethoate and omethoate concentrations under field conditions would be below 0.01 mg/kg, a typical lower limit of detection. The JMPR considered that knowledge of plant metabolism was incomplete.

The JMPR (JMPR 1996) concluded that the metabolism of dimethoate and omethoate in animals was adequately understood. Dimethoate was rapidly and extensively absorbed from the gut and rapidly excreted. There was no accumulation in fat tissue. In rats and humans, up to 90% of radiolabel was found in the urine within 24 h. The report of a study with methylcarbamoyl-labelled dimethoate indicated that up to 18% of the administered label was excreted in expired air. Four metabolites with anticholinesterase activity were identified in rats and humans. One was omethoate, which was hydrolyzed to a thiocarboxyl product, the main metabolite in rats and humans.

JMPR consideration of the acute oral toxicity of dimethoate led to LD₅₀ values of about 310 mg/kg bw in rats, 150 mg/kg bw in mice, and 55 mg/kg bw in hens. The signs of toxicity were those typical of cholinesterase inhibition. In short-term and long-term studies at dietary concentrations of 75 ppm or above, there were minor reductions in body-weight gain and food consumption. Apart from the inhibition of

cholinesterase activity, dimethoate had no effect on food consumption, the blood or urine. The liver weights of animals treated at the higher doses tended to be lower than those of the control groups but there were no microscopic changes and the effect was considered unlikely to be of toxicological significance. Investigations of toxicity at higher doses were limited by cholinesterase inhibition. NOAELs were thus generally based on reductions in acetylcholinesterase activity in the brain or erythrocytes. On the basis of minimal reductions in acetylcholinesterase activity of 10-20%, the NOAEL in a 12-month study in dogs at doses of 0, 5, 20, or 125 ppm was 5 ppm, equal to 0.2 mg/kg b.w per day; in rats the NOAEL in a life-span study at doses of 0, 1, 5, 25, or 100 ppm was 1 ppm, equal to 0.04 mg/kg bow per day. In mice , a NOAEL was not identified, as cholinesterase activity was depressed at all doses after 52 weeks of treatment in a life-span study at doses of 0, 25, 100, or 200 ppm.

The JMPR considered that long-term studies of toxicity and carcinogenicity in mice (at 0, 25, 100, or 200 ppm) and rats (at 0, 5, 25, or 100 ppm) showed that dimethoate is not carcinogenic to rodents. The NOAEL for reproductive toxicity appeared to be 15 ppm (equal to 1.2 mg/kg b.w. per day), and that for parental toxicity was 1 ppm (equal to 0.08 mg/kg b.w per day on the basis of cholinesterase inhibition), but the JMPR noted that reproductive performance may have been affected at lower doses. In a multi-generation study in mice, there was no overt effect on reproductive capacity. Studies of developmental toxicity in rats and rabbits provided no evidence of a teratogenic effect, although maternal toxicity was observed at the high dose in rats and rabbits. The JMPR concluded that although *in-vitro* studies indicate that dimethoate has mutagenic potential, this potential does not appear to be expressed *in vivo*.

The JMPR noted that undiluted dimethoate formulations were irritating to the eye in rabbits but skin irritation was minimal and confined to slight, transient erythema.

The JMPR allocated an ADI of 0-0.002 mg/kg b.w. (sum of dimethoate and omethoate).

The WHO EHC review (WHO 1986) noted low risk to farm animals, moderate toxicity for birds, fish and aquatics, and very high toxicity for honey bees. The review concluded that, when used under proper conditions, exposure of the human population through air, food or water is negligible.

The WHO hazard classification of dimethoate is "Class II, moderately hazardous" (WHO 2002). The UN classification is: toxic, (Class 6.1). The US EPA classification is: (formulation) II. The EC classification is: risk Xn (R21/22). The signs of toxicity are those typical of cholinesterase inhibition.

Formulations

The main formulation types of dimethoate are EC, with some WP, UL and GR. Dimethoate is co-formulated with many other active ingredients. The most common trade names are Danadim, Bi58, Perfekthion, Rogor, Roxion, Cekutoate, Champ, Chimigor, Diadhan, Dicentra, Dimezyl, Efdacon, Robgor, Romethoate and Tara 909.

DTF dimethoate products are registered and sold in the following countries.

TK (Cheminova A/S): Australia and Canada.

EC (BASF): Algeria, Argentina, Australia, Bangladesh, Belarus, Belgium, Belize, Bolivia, Brazil, Chile, Denmark, Ecuador, France, Germany, Ghana, Greece, Guatemala, Honduras, Hong Kong, Hungary, India, Indonesia, Italy, Korea Republic of, Croatia, Morocco, Malaysia, Mozambique, Netherlands, Nicaragua, Nigeria, Norway, Pakistan, Paraguay, Philippines, Portugal, Qatar, Romania, Saudi Arabia, Senegal, Slovenia, Spain, Taiwan, Thailand, Tunisia, Ukraine, UK, USA, Venezuela.

EC (Cheminova A/S): Australia, Belgium, Bolivia, Cuba, Denmark, Finland, Germany, Ghana, Hungary, India, Italy, Kenya, Mexico, Pakistan, Poland, Saudi Arabia, Slovakia, Spain, Sudan, United Arab Emirates, UK.

EC (Isagro): United Arab Emirates, Bangladesh, Croatia, Cuba, Egypt, France, Germany, Greece, Hungary, India, Ireland, Jordan, Malaysia, Malta, Morocco, Pakistan, Saudi Arabia, Spain, Switzerland, Taiwan, Tanzania, Thailand, Turkey, UK.

Methods of analysis and testing

Determination of active ingredient content

Two full CIPAC methods are available for the determination of dimethoate in TC, TK and EC. One method (CIPAC Handbook E) utilises reversed-phase HPLC (C-8 column with acetonitrile/water as mobile phase) and UV detection at 210 nm with external standardization. The other method (CIPAC Handbook H) utilises GC on an OV-17 column and FID, with dibutyl phthalate internal standard. The HPLC Method in Handbook E is the referee method.

Two methods used by Cheminova are broadly similar. One utilises GC on an HP-17 column, FID and *n*-eicosane internal standard. The other method utilises reversed-phase HPLC (C-18 column eluted with acetonitrile/water/acetic acid) and UV detection at 220 nm with external standardization.

Determination of relevant impurities

A full CIPAC method (CIPAC Handbook H) for the determination of omethoate in technical dimethoate utilises GC on an OV-225 and FPD (phosphorus mode) with external standardization. The manufacturers indicated that the CIPAC method has limitations for the determination of omethoate (Lystbæk, 2002a) and it was not validated for determination of isodimethoate.

The manufacturers proposed that Cheminova method AM 443 should be used. The method is based upon reversed-phase HPLC (C-18 column eluted with acetonitrile/water/phosphate buffer pH 2.5) and UV detection at 210 nm with external standardization (Appendix 1). The method was successfully subjected to independent laboratory validation for analysis of dimethoate TC, TK and EC (summarized in Bura 2001) and proved suitable for the determination of omethoate, isodimethoate (and certain other impurities) as required by the specifications. Linearity ($r=0.99999$), accuracy (97.9-105.5% recovery), precision (CV=1.6-1.9%), limit of detection (0.02% dimethoate) were good.

Water, as a relevant impurity, is determined by CIPAC methods.

Physical properties

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

Containers and packaging

No special requirements.

Expression of active ingredient

The active ingredient is expressed as dimethoate.

Appraisal

The existing FAO specifications for dimethoate TC, DP, WP, SL and EC, published in 1991, were reviewed by the Meeting. Revised specifications and the supporting data for dimethoate were provided by members of the Dimethoate Task Force (BASF AG, Cheminova A/S and Isagro S.p.A). The supporting data provided in summary only in the tables given above were stated to be the same as those evaluated in detail for toxicology by the FAO/WHO JMPR.

Dimethoate is sparingly soluble in water, relatively stable in acid to neutral conditions (pH 2-7) but is hydrolyzed in alkaline conditions (pH 9). It is not subject to photolysis by sunlight but is readily decomposed on heating in air.

The Meeting was provided with information on the manufacturing process, 5-batch analysis data for all impurities ≥ 1 g/kg and their manufacturing limits (1-15 g/kg) in the TC (the TK is dimethoate TC dissolved in xylene/cyclohexanone). Mass balances were high in the 5-batch data. The impurities and their maximum limits in the manufacturing specification were not identical to the dimethoate impurity profile provided to the Hungarian authorities in support of registration. Cheminova explained that the current manufacturing specification (as provided to FAO) is based on a 1992 product chemistry study which, in error, was not submitted to Hungary in 1996 for the re-registration.

The Meeting was informed that dimethoate TC and TK formulated by members of the DTF is produced by Cheminova and therefore no determination of equivalence was required.

Clauses for dimethoate content in the existing and proposed FAO specifications were similar, with a minimum of 950 g/kg, and the Meeting accepted the proposed limit. The existing FAO specification for EC allowed for an overage in the dimethoate content (+10 and -5% at up to 400 g/kg or +40 and -20g g/kg at >400 g/kg), because of the relative instability of dimethoate. In error, the initial DTF proposal for EC formulations incorporated the standard tolerances given in the Manual (FAO 1999) but DTF members made it clear that this was not appropriate for countries with hot climates. The Meeting agreed to maintain the existing (overage) tolerances but to apply them to the standard concentration ranges (which made no significant change to the tolerance values).

The degradation of dimethoate during storage of the EC is concentration-dependent and therefore the proposed limit after 14 days at 54°C for ECs containing >400 g/kg (or g/l) is 85% of the initial concentration, whereas that for ECs <400 g/kg is 90%.

Cheminova and BASF provided data (summarized in Bura, 2001) supporting these limits and they were accepted by the Meeting.

Existing FAO specifications included clauses to limit the content of omethoate but the DTF and the Meeting agreed that isodimethoate (CAS No. 3344-11-4) should also be considered relevant. Although both impurities occur only at low levels in DTF products, omethoate is of much higher acute toxicity (by oral, dermal and inhalation routes) than dimethoate, whereas isodimethoate (in contrast with certain the *S*-alkyl isomers produced by certain other organophosphorus compounds) is apparently only slightly more toxic than dimethoate.

Omethoate was originally considered by DTF to be formed only during manufacture, not during storage, and this was reflected in proposed limits for TK and EC that were equivalent to that proposed for the TC. Initially, the DTF did not propose clauses for omethoate in TK and EC and questioned whether it was necessary to limit this impurity in them, because they are produced by simple dilution of the TC. However, a DTF member provided data (Lystbæk 2002b) which showed that omethoate increases during storage of TK or EC and requested that the proposed limit should be changed from 0.2% to 0.4% of the dimethoate content. The Meeting accepted the revised limit and considered it essential insert a clause to control omethoate concentration in these products. Although isodimethoate is only slightly more toxic than dimethoate, the Meeting considered that its concentration should be controlled. The rate of isodimethoate formation is slow at low temperatures but the reaction cannot be prevented and the potential for isomerization in storage is reflected in the higher limits for isodimethoate in the TK and EC specifications. In the opinion of WHO/PCS, the proposed limits were acceptable and the Meeting agreed to adopt them.

The DTF proposed that water and acetone insolubles should be considered relevant impurities in the TC and TK. The proposers explained that control of water content is critical for the stability of dimethoate and for preparation of satisfactory ECs and the Meeting accepted this clause. The proposers declared that acetone insolubles are never detected in their products and the Meeting agreed that the clause was not necessary in the specifications.

In addition to the changes to clauses for active ingredient and relevant impurities, the existing specifications were amended according to the requirements of the new Manual (FAO 1999) and the following changes agreed to the specifications.

The proposed clause for emulsion stability and re-emulsification in the existing FAO specification for EC had limits for 6 h and 6.5 h, instead of the standard 24 h and 24.5 h requirements given in the Manual (FAO 1999). The DTF stated that this was because dimethoate hydrolyses rather rapidly in water. BASF provided evidence of 2 and 12% degradation after 24 h at pH 6 and 8, respectively. However, test data on emulsion stability remained acceptable after 24/24.5 h and the Meeting agreed the standard timings should be retained because the clause defines the stability of the emulsion and not the active ingredient. The Meeting agreed that the usual footnote on testing at 24/24.5 h should be amplified to warn users that the test does not imply that dimethoate emulsions may be left for a day before application.

In contrast with the requirements of the Manual (FAO 1999), neither the existing FAO specification for EC, nor that initially proposed by DTF, contained a clause for

persistent foam. DTF agreed with the inclusion of the persistent foam test in the specification and provided the requested analytical data.

The Meeting and DTF agreed to include the odour characteristics in the description clauses of the TC and TK specification.

The members of the DTF declared that the materials produced and commercialised by them comply with the specifications, as amended.

Methods for determination of dimethoate content are full CIPAC methods (59/TC/M3 and 59/EC/M3). However, Cheminova uses a modified validated method (VAM 010-01), because a minor impurity (occurring at about 0.3 g/kg of dimethoate) interferes with the dimethoate peak when using the CIPAC method. This level of interference is below that which can be distinguished analytically and the company declared that there is no difference in results when analysing their products with the two methods.

A full CIPAC method is available for the determination of omethoate in dimethoate TC but it had not been validated for determination of isodimethoate, nor for analysis of TK or EC. In proposing the draft specifications, DTF recommended the use of Cheminova AM443 (HPLC method) and it was stated that the CIPAC method has limitations even for the determination of omethoate in the TC. The internally-validated Cheminova method was additionally validated in two independent laboratories for the determination of omethoate and isodimethoate in TC. TK and EC and is suitable for use in support of the proposed specifications. The method is described in Appendix 1.

The JMPR allocated an ADI of 0-0.002 mg/kg b.w. (sum of dimethoate and omethoate), based on a full package of toxicology data including short-term and chronic testing on rats, rabbits, dogs and mice (JMPR 1996). Dimethoate showed no evidence of carcinogenicity, teratogenicity, embryotoxicity or reproductive effects in animals, although maternal toxicity was observed at the high doses in rats and rabbits. The JMPR concluded that although *in-vitro* studies indicate that dimethoate has mutagenic potential, this potential does not appear to be expressed *in vivo*. Undiluted dimethoate formulations were irritating to the eye in rabbits but skin irritation was minimal and confined to slight, transient erythema.

The WHO EHC review noted low risk to farm animals, moderate toxicity for birds, fish and aquatic animals, and very high toxicity for honey bees, but that exposure of humans should be negligible when dimethoate is used correctly.

WHO classified dimethoate as moderately hazardous (Class II) and the UN , USEPA and EC hazard/risk classifications are broadly similar.

Recommendations

The Meeting recommended that existing FAO specifications for dimethoate TC, DP, WP, SL and EC should be withdrawn and that the specifications for dimethoate TC, TK and EC, proposed by DTF and amended as described above, should be adopted by FAO.

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WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

DIMETHOATE FAO/WHO EVALUATION REPORT 59/2004

Explanation

Revised FAO specifications* for dimethoate TC, TK and EC were recommended for adoption, following evaluation under the new procedure in 2000 and 2001 (FAO evaluation 59/2001), although the original FAO specifications* (developed under the old procedure in 1990) remained in force at the time of the 2004 Meeting. The revised FAO specifications recommended in 2000/2001 applied to the companies of the Dimethoate Task Force (DTF: BASF, Cheminova and Isagro). Existing WHO specifications* for dimethoate TC and EC were adopted under the old procedure in 1999. The existing WHO and revised FAO specifications were considered, with a view to harmonizing them without recourse to a complete re-evaluation of the supporting data under the new procedure.

In 2003, BASF and Cheminova declared that the dimethoate TC utilized for preparation of ECs for use in public health is identical to that utilized for preparation of TKs and ECs intended for agricultural uses. Isagro declared that it produces dimethoate for use only in public health and that the products are fully compliant with the FAO specifications. Dimethoate TK is not intended for use in public health.

Appraisal

Results of a new 5-batch analysis, together with a slightly revised manufacturing specification, were presented by Cheminova to FAO on 5 March 2002 (Lystbæk 2004a). The company stated that the data were identical to those submitted to the UK Pesticide Safety Directorate (as rapporteur member state), as part of the EU Annex I dossier in 2002, to comply with current EU guidance documents for validation of analytical methods. No significant changes in manufacturing processes had occurred since the 1992 5-batch analysis and this was reflected in the results of the new 5-batch analysis. A few minor adjustments (within FAO equivalence criteria) had been made to the new manufacturing specification, based upon the 5-batch analysis and experience from quality control analysis since 1992 (Lystbæk 2005a). The Meeting agreed that, because the toxicological and ecotoxicological data referred to the 1992 manufacturing specification, this earlier profile should be used as the reference profile for the purpose of future equivalence determinations.

As the dimethoate TC produced by the three companies is identical for both public health and agricultural applications, the Meeting agreed that it was only necessary to consider the differences between the revised FAO specifications and the existing WHO specifications for TC and EC.

* In this report, "revised FAO specification" refers to an unpublished specification recommended for adoption by FAO in 2001 but not in force at the time of this review; "original FAO specification" refers to a published 1990 FAO specification in force at the time of this review; "existing WHO specification" refers to a published 1999 WHO specification in force at the time of this review.

TC specification

Description clause

The description clause in the existing WHO specification allowed for white, yellow or grey crystals, whereas the revised FAO specification allowed only white. The revised FAO specification described the odour of dimethoate as mercaptanic, whereas the existing WHO specification did not mention odour. The Meeting agreed that the description of the revised FAO specification should apply.

Dimethoate content clause

The minimum content of dimethoate in the revised FAO specification was 950 g/kg, whereas that in the existing WHO specification was 930 g/kg. The maximum content of omethoate was 2 g/kg in the revised FAO specification but 5 g/kg in the existing WHO specification. The Meeting agreed that, as the Dimethoate Task Force (DTF) manufacturers currently adhered to the revised FAO specification, the more stringent value should be applied.

Isodimethoate content clause

The maximum content of isodimethoate was 3 g/kg in the revised FAO specification but 5 g/kg in the existing WHO specification. The Meeting agreed that, as the DTF currently adhered to the revised FAO specification, the more stringent value should be applied.

Insolubles and acidity clauses

The existing WHO specification included clauses for acetone insolubles and acidity, which did not appear in the revised FAO specification. The Meeting noted that these clauses were not required for materials currently produced by the DTF.

EC specification

Dimethoate content clause

The revised FAO and existing WHO specifications allowed for an overage in dimethoate content but the revised FAO specification tolerance limits for formulations >500 g/kg were +40 and -20 g/kg, whereas those of the existing WHO specification were +50 and -25 g/kg. Both were non-standard ranges and the Meeting agreed that the more stringent revised FAO specification tolerance should apply.

Omethoate content clause

The existing WHO specification had no clause to limit omethoate, whereas it was limited to 0.4% of dimethoate in the revised FAO specification. The Meeting agreed that omethoate should be controlled.

Isodimethoate content clause

The clause controlling isodimethoate in the existing WHO specification allowed for up to 0.5% of the dimethoate before storage at 54°C for 14 days and 4% after storage. The corresponding revised FAO specification allowed up to 7% before or after and was therefore less stringent. Because the revised FAO specification limit was based on more recent data, and because isomerization inevitably occurs during the storage test (and therefore different limits effectively apply before and after the test), and because the higher limit is still well below that at which a discernible increase in risks could be expected to occur, the Meeting agreed that the higher limit is acceptable. Partly corresponding to the increase in isodimethoate during storage,

the revised FAO specification allowed for losses of dimethoate (10-15%), whereas the existing WHO specification allowed for no loss. The Meeting noted that degradation of dimethoate occurs even under the best practical storage conditions and agreed that the revised FAO specification limits should apply.

Emulsion stability clause

In the clause for emulsion stability, limits for 0.5 and 2 h standing time were provided in all specifications. The limits for separation of the emulsion at 2 h differed (i.e. existing WHO specification, 2 ml cream and/or oil; original and revised FAO specifications, 2 ml cream and 0.5 ml oil). The difference between the limits was relatively small but, as the separation of oil is the more serious condition, the Meeting agreed that the revised FAO specification limits at 2 h should be adopted.

The revised FAO specification included limits for stability at 24 and 24.5 h (the original FAO specification had limits at 6 and 6.5 h) but the existing WHO specification had no limits beyond 2 h. For the 2001 review, the DTF had proposed new limits for 24 and 24.5 h but in 2004, limits were proposed for 6 and 6.5 h. The Meeting agreed that, although results at 2 h are usually definitive, a longer standing time must be specified to allow doubtful cases to be resolved. However the use of tests at the non-standard times of 6 and 6.5 h required justification, as did the questionable limits required at 24.5 h (4 ml cream and 0.5 ml free oil). The manufacturer was asked to explain why dimethoate emulsions at 24.5 h are relatively unstable (after complete re-emulsification at 24 h) compared with the initial 0.5 h (1 ml cream).

Experimental data were provided by Cheminova to show that dimethoate, in the form of a 5% emulsion of a 400 g/l EC in CIPAC standard waters A and D, is not significantly degraded at 30°C over a period of 24 h (Bjorholm 2005). Over this period, the change in isodimethoate concentration relative to dimethoate was barely measurable, increasing from 0.2-0.3% to ≤0.4%.

Experimental data were also provided by Cheminova to show that the emulsion is not destabilized after 24 h as a consequence of a slow partition of dimethoate from the oil phase into the aqueous phase, over this period (Lystbæk 2005b). A 400 g/l formulation of the "EC" was prepared, without emulsifiers, and 5 ml (about 2 g dimethoate) was mixed with 95 ml deionized water in 100 ml glass bottles (8 replicates). The mixtures were continuously rotated at 22°C and duplicates were analyzed after 0.5, 2, 6 and 24 h. Oil and water phases were separated by centrifugation and analyzed separately by GC. The results showed that equilibrium had been established within 0.5 h, with concentrations of dimethoate in the aqueous and oil phases of 1.5% and 31% w/w respectively (corresponding to approximately 70% of dimethoate in the aqueous phase and 30% in the oil phase, Lystbæk 2005c), and this distribution remained unchanged after 2, 6 and 24 h.

Therefore, in the absence of any discernible problem related to the unresolved issue of emulsion stability at 24.5 h, and in the absence of any reported problems in using dimethoate ECs in the field over many years, the Meeting and manufacturer agreed that tests of emulsion stability should be conducted at 24 and 24.5 h and that limits of 4 ml cream and 0.5 ml free oil at 24.5 h are appropriate.

Waters for testing emulsion stability

For the tests of emulsion stability, the original and revised FAO specifications required the use of CIPAC standard waters (waters A and D in the latter case),

whereas the existing WHO specification referenced WHO standard waters. CIPAC standard water D and the WHO hard water are of identical measured hardness (342 mg/l measured as calcium carbonate) but the Ca⁺⁺:Mg⁺⁺ ratio is 4:1 and 6.6:1, respectively. CIPAC standard water A and WHO soft water differ slightly in measured hardness (20 and 34.2 mg/l, respectively) and the Ca⁺⁺:Mg⁺⁺ ratio is 1:1 and 6.6:1, respectively. The Meeting considered that the differences are unlikely to produce a significant difference in results and that, because products of the DTF are known to comply with the revised FAO specifications, CIPAC standard waters should be specified, as indicated in the manual (FAO/WHO 2002).

Water for testing persistent foam

For determination of persistent foam, the existing WHO specification required the use of WHO standard soft water. The revised FAO specification did not indicate which water should be used but referenced CIPAC Handbook F, which indicates that, unless otherwise specified, CIPAC water C should be used. In preparing the 5th edition of the FAO manual (FAO 1999), FAO previously decided to restrict tests of physical properties to CIPAC standard waters A and D. The Meeting agreed that CIPAC water A should be specified for the test of persistent foam and that this should be clarified as a general requirement when the FAO/WHO manual is updated.

Flash point and packaging clauses

The WHO specification included clauses for flash point and packaging but these are not incorporated into specifications under the new procedure of FAO and WHO.

Recommendations

The Meeting recommended that:

- (i) the original FAO specifications* for dimethoate TC, DP, WP, SL and EC should be withdrawn;
- (ii) the existing WHO specifications* for dimethoate TC and EC should be withdrawn;
- (iii) the revised FAO specifications* for dimethoate TC, TK and EC should be adopted by FAO and those for the TC and EC (but not the TK) should be adopted by WHO;
- (iv) the wording of the FAO/WHO manual (FAO/WHO 2002) should be amended to state that CIPAC standard water A should be used for the determination of persistent foam.

* "Revised FAO specifications" refers to unpublished specifications recommended for adoption by FAO in 2001 but not in force at the time of this review; "original FAO specifications" refers to published 1990 FAO specifications in force at the time of this review; "existing WHO specifications" refers to published 1999 WHO specifications in force at the time of this review.

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WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

DIMETHOATE FAO/WHO EVALUATION REPORT 59/2011

Recommendations

The Meeting recommended the following:

- (i) The acidity clause in the existing FAO specification for dimethoate TK and in the FAO and WHO specifications for dimethoate EC should be deleted.
- (ii) The emulsion stability clause of the existing dimethoate FAO and WHO EC specifications should be revised to refer to CIPAC method MT 36.3 instead of MT 36.1.1.
- (iii) The limit in the persistent foam clause of the existing dimethoate FAO and WHO EC specifications should be increased to a maximum of 40 mL instead of 25 mL of foam after 1 minute.

Appraisal

The Meeting considered data and information submitted by the Dimethoate Task Force (DTF) in support of revision of the existing dimethoate TK and EC FAO and WHO specifications. The DTF currently consists of BASF SE and Cheminova A/S. Isagro S.p.a. withdrew from Dimethoate Task Force following Cheminova's acquisition of their Dimethoate business in May 2010.

Dimethoate has been evaluated and reviewed by the European Commission as part of the EU review of existing active substances for inclusion in Annex I of the Council Directive 91/414/EEC. It has been included in Annex I (inclusion directive 07/25/EC of 1-10-2007) with a minimum purity 950 g/kg.

The Meeting was informed that Cheminova A/S is the sole producer of dimethoate TC and that the DTF produces a variety of EC formulations (stabilized, non-stabilized, coloured, non-coloured). In the case of stabilized formulations the DTF wishes to keep the identity of the stabilizer confidential.

TK, EC: The existing FAO specification for dimethoate TK and FAO/WHO specifications for dimethoate EC included clauses with limit for acidity as a simple parameter for measuring the decomposition of the active ingredient. Dimethoate decomposes during storage in the abovementioned formulations to form omethoate and isodimethoate which are considered as relevant impurities. For that reason existing FAO and WHO specifications include clauses to limit the content of both omethoate and isodimethoate.

A DTF member (Cheminova A/S) informed the Meeting that they produce new stabilized TK and EC formulations in order to minimize the decomposition of the active ingredient and the formation of the two relevant impurities omethoate and isodimethoate. For that reason the DTF member (Cheminova A/S) proposed the deletion of the acidity clause from the existing FAO and WHO specifications of TK

and EC as acidity is no longer a suitable quality parameter. The proposer provided data and showed that in these new stabilized TK and EC products, in which a stabilizer is added, the stabilizer contributes to the acidity and this contribution (the stabilizer forms free acids under test conditions used for determination of acidity and therefore leads to erroneous test results) is unrelated to quality parameters. In the same data a reduced degradation rate of dimethoate was demonstrated for the stabilized formulations in comparison to the non-stabilized one.

The additional evidence now suggests that an acidity specification is not necessary for measuring the decomposition of the active ingredient. The Meeting agreed to delete the acidity clause for dimethoate TK and EC formulations and to amend the TK and EC specifications accordingly.

EC: The existing FAO and WHO specifications include a clause for emulsion stability and re-emulsification according to CIPAC MT 36.1.1. The DTF proposed to change the reference testing method to CIPAC MT 36.3 instead of CIPAC MT 36.1.1 as new coloured dimethoate EC formulations failed to comply with the existing FAO specifications probably due to the high use rate concentration of 5% evaluated in the CIPAC MT 36.1.1. The actual CIPAC method to determine emulsion stability and re-emulsification, CIPAC MT 36.3, is based on the evaluation of a minimum and a maximum use rate concentration of the tested formulation and is therefore considered to be more suitable. The Meeting agreed that the emulsion stability is more appropriate to be tested in the use concentrations. For that reason the Meeting accepted this change and agreed that the method reference should be corrected.

With respect to the limit of persistent foam in EC formulations the DTF proposes to change its value from 25 ml to 40 ml after 1 minute. The Meeting noted that the value of 25 mL is too low taking into account that the DTF produces a wide range of products (stabilized, unstabilized, coloured, non-coloured), some of them possibly leading to higher volumes of persistent foam using the CIPAC method MT 47.2. Considering also that the recommended limit of 60 mL is too high, the meeting agreed that the proposed value of 40 mL is more appropriate.

Appendix 1

Method for determination of omethoate and isodimethoate in dimethoate TC, TK and EC

(Adapted from Cheminova method AM443.2 version 4, dated 20 February 2002)

Principle

The impurities are determined by reversed-phase HPLC, with UV detection and quantification by external standardization.

Chemicals

Acetonitrile, HPLC grade (solvent B)

Phosphoric acid, analytical reagent grade

Potassium dihydrogen phosphate, analytical reagent grade

Water, HPLC grade

Phosphate buffer, pH 2.5. Dissolve 11.32 g of H₃PO₄ and 32.86 g of KH₂PO₄ in 1000 ml of HPLC grade water

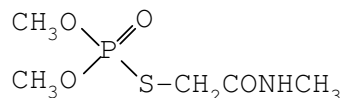
Solvent A, mix 9 volumes of water with 1 volume of phosphate buffer

Solvent for reference standard solutions, mix 9 volumes of solvent A with 1 volume of acetonitrile (solvent B)

Omethoate reference standard, highest purity available

CAS No. 1113-02-6

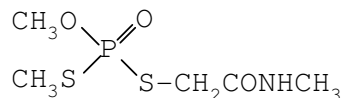
CAS name *O,O*-dimethyl *S*-[2-(methylamino)-2-oxoethyl]
phosphorothioate



Isodimethoate reference standard, highest purity available

CAS No. 3344-11-4

CAS name phosphorodithioic acid, *O,S*-dimethyl *S*-[2-(methylamino)-2-oxoethyl] ester



Reference solutions. Prepare 1% solutions of each reference material by weighing accurately approximately 0.1 g (a₁, a₂ g) into tared sample bottles (capable of holding at least 14 ml) with screw caps. Add 10 ml of acetonitrile, weigh again (b₁, b₂ g) and mix well (stock solutions). Weigh accurately 100 µl omethoate stock solution and 500 µl isodimethoate stock solution (c₁, c₂ g) into a tared sample bottle with screw cap, add 9 ml of 10% acetonitrile/90% solvent A, weigh again (d g) and mix well (Solution 1, approximate concentrations: omethoate 0.1 mg/ml, isodimethoate 0.5 mg/ml).

Weigh 7 ml Solution 1 (e g) into a tared sample bottle, add 7 ml of 10% acetonitrile/90% solvent A, weigh it (f g) and mix well (Solution 2, approximate concentrations: omethoate 0.05 mg/ml, isodimethoate 0.25 mg/ml).

Weigh 2 ml Solution 2 into a tared sample bottle, add 2 ml of 10% acetonitrile/90% solvent A, weigh it and mix well (Solution 3, approximate concentrations: omethoate 0.025 mg/ml, isodimethoate 0.1 mg/ml).

Weigh 1 ml Solution 2 into a tared sample bottle, add 9 ml of 10% acetonitrile/90% solvent A, weigh it and mix well (Solution 4, approximate concentrations: omethoate 0.0025 mg/ml, isodimethoate 0.01 mg/ml).

Solutions 1, 2, 3 and 4 are injected into the liquid chromatograph.

Equipment and typical operating conditions

Sample bottles, screw-capped, to hold a minimum of 14 ml.

Liquid chromatograph, Hewlett Packard HP 1100 or equivalent, equipped with binary eluent delivery system, column oven, auto-sampler, photodiode array detector and data handling system.

Analytical column, Phenomenex Spherclone ODS2 or equivalent, 5 µm, 120 mm x 4.6 mm.

Guard column, Phenomenex Spherclone ODS2 or equivalent, 5 µm, 50 mm x 4.6 mm.

<i>Gradient programme:</i>	min	% B
	0	15
	12	75
	17	75
	18	15
Stop time	18	
Post time	5	

<i>Flow programme</i>	min	ml/min
	0	0.75
	12	0.75
	12.5	2.0

Oven temperature, 50°C

Typical retention times, omethoate 3.7 min, isodimethoate 4.8 min, dimethoate 7.7 min.

Signals, monitor 210 and 215 nm (10 nm bandwidth) for the analytes, 550 nm (80 nm bandwidth) for the reference. Acquire spectrum from 190 to 400 nm in 2 nm steps and use spectra for checking peak purity, if required.

Detector slit width, 4 nm

Injection volume, 15 µl reference solutions

Integration, peak area

Calibration, single-point calibration measured on solution 2.

System suitability check

Repeatability. Inject reference solution 2 at least three times or until the peak areas of omethoate and isodimethoate from successive injections differ by no more than 5.0%, relative.

Linearity. Inject reference Solutions 1, 3, 4 and 2 and measure peak areas. Calculate the response factors, r_i for omethoate and isodimethoate. The linearity is acceptable if the response factors from Solution 1, 2, 3 and 4 do not differ more from their average by more than $\pm 5.0\%$, relative. Alternatively, calculate the linear regression coefficient (r^2). Acceptable linearity for $r^2 > 0.98$.

Carry over. Inject blank solvent after reference Solution 2 in the linearity check and measure the peak areas of omethoate and isodimethoate. "Carry over" from the previous injection is acceptable if the peak areas of omethoate and isodimethoate in the blank solvent are $\leq 2.0\%$ of the peak areas measured in reference Solution 2.

Method

Preparation of test solutions:

TC. Weigh accurately approximately 0.3 g (g g) into a tared 12 ml sample bottle with screw cap. Add 10 ml 10% acetonitrile/90% solvent A, weigh again (h g) and mix well. This solution is injected into the HPLC.

TK. Weigh accurately sufficient to give 300 mg dimethoate (g g) into a tared 12 ml sample bottle with screw cap. Add 10 ml 10% acetonitrile/90% solvent A, weigh again (h g) and mix well. This solution is injected into the HPLC. Dilute the test solution appropriately, if the peak area of one impurity exceeds the peak area obtained from reference Solution 1.

EC. Weigh accurately approximately 0.5 g (g g) into a tared 12 ml sample bottle with screw cap. Add 10 ml 10% acetonitrile/90% solvent A, weigh again (h g) and mix well. If the solution appears turbid, it may be centrifuged before analysis but injection of the turbid solution should not cause problems, as the chromatographic run is ended with a washing step. Dilute the test solution appropriately, if the peak area of one impurity exceeds the peak area obtained from reference Solution 1.

HPLC analysis:

The following injection sequence is used:

Solution 2, T₁, T₂, T₃, T₄, T₅, T₆, T₇, T₈ Solution 2, T₉.....T₁₆, Solution 2, T₁₇.....,etc.

Where T = test solutions 1, 2, 3,.....n

Always end the sequence with reference solution 2. N.B. only one injection from each vial.

Calculations

For either impurity, calculate the average response factor, r_f, from reference Solution 2 data:

$$r_f = \frac{(\% \text{ impurity in reference material}) \times a \times c \times e}{(\text{average peak area from impurity in reference solution 2}) \times b \times d \times f}$$

Calculate the weight per cent of the impurity as follows:

$$\% \text{ w/w of impurity} = \frac{(\text{peak area of impurity in test solution}) \times h \times r_f}{g}$$