

# WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

## TEMEPHOS

*O,O,O',O'*-tetramethyl *O,O'*-thiodi-*p*-phenylene  
bis(phosphorothioate)



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## Disclaimer<sup>1</sup>

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.

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<sup>1</sup> 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 Specifications of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the “FAO/WHO Manual on Pesticide Specifications.”

**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 “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.

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 [\(http://www.who.int/whopes/quality/en/\)](http://www.who.int/whopes/quality/en/).

**PART ONE**  
**SPECIFICATIONS**

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TEMEPHOS

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# WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

## TEMEPHOS

### INFORMATION

#### ISO common name

Temephos (BSI, draft E-ISO)

*Synonyms* AC 52 160 (Cyanamid)

BAS 317 I (BASF)

OMS 786; ENT 27 165

#### Chemical names

*IUPAC:* *O,O,O',O'*-tetramethyl *O,O'*-thiodi-*p*-phenylene bis(phosphorothioate)

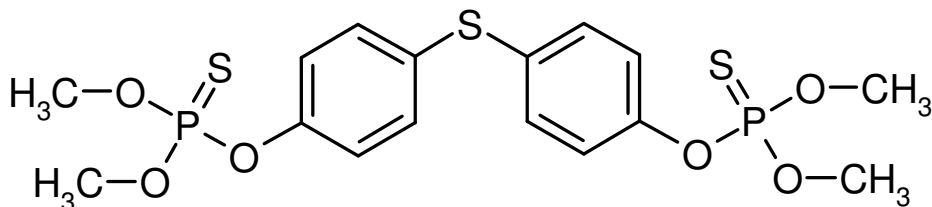
*O,O,O',O'*-tetramethyl *O,O'*-thiodi-*p*-phenylene diphosphorothioate

*O*-[4-({4-[(dimethoxyphosphorothioyl)oxy]phenyl}thio)phenyl] *O,O*-dimethyl thiophosphate.

*CA:* phosphoric acid, *O,O'*-(thiodi-1,4-phenylene) *O,O,O',O'*-tetramethyl ester

*O,O'*-(thiodi-4,1-phenylene) bis(*O,O*-dimethyl phosphorothioate)

#### Structural formula



#### Empirical formula

C<sub>16</sub>H<sub>20</sub>O<sub>6</sub>P<sub>2</sub>S<sub>3</sub>

#### Relative molecular mass

466.5

#### CAS Registry number

[3383-96-8]

#### CIPAC number

340

#### Identity tests

HPLC retention time, IR spectrum, TLC.

# WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

## TEMEPHOS TECHNICAL MATERIAL

WHO specification 340/TC (September 2008\*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose name are listed in the evaluation reports (340/2005, 340/2010). 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 (340/2005, 340/2010), as PART TWO, forms an integral part of this publication.*

### 1 Description

The material shall consist of temephos together with related manufacturing impurities and shall be a yellow to brown viscous liquid, free from visible extraneous matter and added modifying agents.

### 2 Active ingredient

#### 2.1 Identity tests (340/TC/M/2, CIPAC Handbook 1C, p.2230, 1985)

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 Temephos content (340/TC/M/3, CIPAC Handbook 1C, p.2230, 1985)

The temephos content shall be declared (not less than 925 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

### 3 Relevant impurities

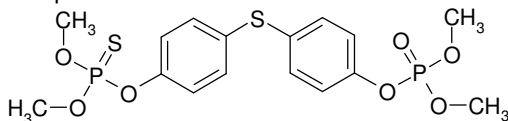
#### 3.1 "Temephos-oxon"<sup>1</sup>, 4-({4-[(dimethoxyphosphorothioyl)oxy]phenyl}thio)phenyl dimethyl phosphate or CL 52828

The "temephos-oxon" content shall not exceed 3 g/kg.

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\* 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/>.

<sup>1</sup> "Temephos-oxon" is a name of convenience for the compound having the following structure:

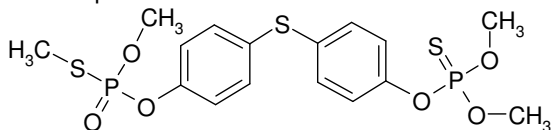


3.2 “*iso-Temephos*”<sup>1</sup>, O-{4-[(4-{[methoxy(methylthio)phosphoryl]oxy}phenyl)thio]phenyl} O,O-dimethyl thiophosphate or CL 78791

The “*iso-temephos*” content shall not exceed 13 g/kg.

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<sup>1</sup> “*iso-Temephos*” is a name of convenience for the compound having the following structure:



# WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

## TEMEPHOS GRANULES

WHO specification 340/GR (September 2008\*)

*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 (340/2005, 340/2010). It should be applicable to relevant products of these manufacturers, and those of any other formulators who use only TC from the evaluated sources. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation reports (340/2005, 340/2010), as PART TWO, forms an integral part of this publication.*

### 1 Description

The material shall consist of silica sand grains bearing technical temephos, complying with the requirements of WHO specification 340/TC (September 2008), together with other necessary formulants. It shall be dry, free flowing, nearly dust-free, and free from visible extraneous matter and hard lumps.

### 2 Active ingredient

#### 2.1 Identity tests (340/GR/M/2, CIPAC Handbook 1C, p.2233, 1985)

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 Temephos content (340/GR/M/3, CIPAC Handbook 1C, p.2233, 1985)

The temephos content shall be declared (10 g/kg) and, when determined, the average measured content shall not differ from that declared by more than  $\pm 25\%$ .

### 3 Relevant impurities

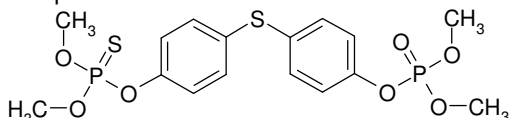
#### 3.1 "Temephos oxon"<sup>1</sup>, 4-({4-[(dimethoxyphosphorothioyl)oxy]phenyl}thio)phenyl dimethyl phosphate or CL 52828

The "temephos-oxon" content shall not exceed 0.3% of the temephos content found under 2.2.

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\* 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/>.

<sup>1</sup> "Temephos-oxon" is a name of convenience for the compound having the following structure:



3.2 “**iso-Temephos**”<sup>1</sup>, O-{4-[(4-{[methoxy(methylthio)phosphoryl]oxy}phenyl)thio]phenyl} O,O-dimethyl thiophosphate or CL 78791

The “*iso-temephos*” content shall not exceed 1.4% of the temephos content found under 2.2.

#### 4 Physical properties

4.1 **Pour and tap density** (MT 186, CIPAC Handbook K, p.151, 2003)

Pour density: 1.30 to 1.60 g/ml.

Tap density: 1.30 to 1.60 g/ml.

4.2 **Nominal size range** (MT 58.2, CIPAC Handbook F, p.173, 1995)

The nominal size range of the formulation shall be declared (250-1250 µm).  
Not less than 96% of the formulation shall be within the nominal size range.

4.3 **Dustiness** (MT 171, CIPAC Handbook F, p.425, 1995, Note 1)

Essentially non-dusty.

#### 5 Storage stability

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

After storage at  $45 \pm 2^\circ\text{C}$  for 6 weeks, the determined average active ingredient content must not be lower than 95% relative to the determined mean content found before storage (Note 2) and the formulation shall continue to comply with the clauses for:

- nominal size range (4.2);
- dustiness (4.3).

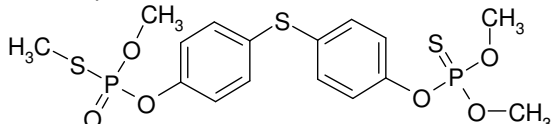
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Note 1 Measurement of dustiness must be carried out on the sample “as received” and, where practicable, the sample should be taken from a newly opened container, because changes in the water content of samples may influence dustiness significantly. The optical method, MT 171, usually shows good correlation with the gravimetric method and can, therefore, be used as an alternative where the equipment is available. Where the correlation is in doubt, it must be checked with the formulation to be tested. In case of dispute the gravimetric method shall be used.

Note 2 Samples of the formulation taken before and after the storage stability test should be analyzed concurrently after the test in order to reduce the analytical error.

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<sup>1</sup> “*iso-Temephos*” is a name of convenience for the compound having the following structure:



# WHO SPECIFICATIONS FOR PUBLIC HEALTH PESTICIDES

## TEMEPHOS EMULSIFIABLE CONCENTRATE

WHO specification 340/EC (September 2008\*)

*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 (340/2005, 340/2010). It should be applicable to relevant products of these manufacturers, and those of any other formulators who use only TC from the evaluated sources. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation reports (340/2005, 340/2010), as PART TWO, forms an integral part of this publication.*

### 1 Description

The material shall consist of technical temephos, complying with the requirements of WHO specification 340/TC (September 2008), dissolved in suitable solvents, together with any other necessary formulants. It shall be in the form of a stable homogeneous liquid, free from visible suspended matter and sediment, to be applied as an emulsion after dilution in water.

### 2 Active ingredient

#### 2.1 Identity tests (340/EC/M/2, CIPAC Handbook 1C, p.2233, 1985)

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 Temephos content (340/EC/M/3, CIPAC Handbook 1C, p.2233, 1985)

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

Declared content, g/kg or g/l at $20 \pm 2^\circ\text{C}$	Tolerance
above 250 up to 500`	$\pm 5\%$ of the declared content
Note: the upper limit is included in the range	

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\* 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 **“Temephos oxon”**<sup>1</sup>, 4-({4-[(dimethoxyphosphorothioyl)oxy]phenyl}thio)phenyl dimethyl phosphate or CL 52828

The “temephos-oxon” content shall not exceed 0.3% of the temephos content found under 2.2.

- 3.2 **“iso-Temephos”**<sup>2</sup>, O-{4-[(4-{[methoxy(methylthio)phosphoryl]oxy}phenyl)thio]phenyl} O,O-dimethyl thiophosphate or CL 78791

The “iso-temephos” content shall not exceed 1.4% of the temephos content found under 2.2.

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

Maximum: 2 g/kg.

### 4 Physical properties

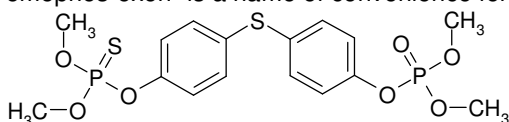
- 4.1 **Emulsion stability and re-emulsification** (MT 36.3, CIPAC Handbook K, p.137, 2003) (Note 2)

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

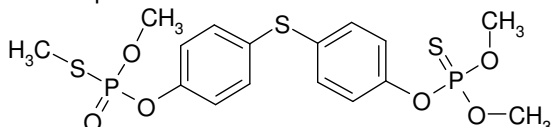
Time after dilution	Limits of stability
0 h	Initial emulsification complete
0.5 h	“Cream”/sediment, maximum: 1 ml
2.0 h	“Cream”/sediment, maximum: 2 ml “Free oil”: none
24 h	Re-emulsification complete
24.5 h	“Cream”/sediment, maximum: 2 ml “Free oil”: none.

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

<sup>1</sup> “Temephos-oxon” is a name of convenience for the compound having the following structure:



<sup>2</sup> “iso-Temephos” is a name of convenience for the compound having the following structure:



4.2 **Persistent foam** (MT 47.2, CIPAC Handbook F, p.152, 1995) (Note 3)

Maximum: 60 ml after 1 min.

5 **Storage stability**

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

After storage at  $0 \pm 2^\circ\text{C}$  for 7 days, no solid and/or liquid shall separate.

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 95% relative to the determined average content found before storage (Note 4) and the formulation shall continue to comply with the clause for:

- 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 results shall be calculated as g/kg.

Note 2 This test will normally only be carried out after the heat stability test 5.2. Emulsion stability should be tested with the formulation at 0.1% concentration.

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

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

## PART TWO

### EVALUATION REPORTS

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#### TEMEPHOS

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<b>2008</b> <b>FAO/WHO evaluation report</b> based on submission of data from BASF SE.	<b>24</b>
<b>2005</b> <b>FAO/WHO evaluation report</b> based on submission of data from BASF Aktiengesellschaft <sup>1</sup> .	<b>26</b>
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<sup>1</sup> 2008 footnote. The company name was changed to BASF SE in 2008.

# WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

## TEMEPHOS

### FAO/WHO EVALUATION REPORT 340/2010

#### Recommendations

The Meeting recommended that the existing WHO specifications for temephos TC, GR and EC should be extended to encompass the corresponding products of Gharda Chemicals Limited.

#### Appraisal

The Meeting considered data provided by Gharda Chemical Limited (GCL), India, to support extension of the existing (September 2008) WHO specifications for temephos TC, GR and EC.

The Meeting was provided with confidential information on the manufacturing process, together with 5 batch analysis data and manufacturing specifications for temephos and all detectable impurities. The method of manufacture was compared with that of BASF SE and is almost identical.

GCL provided 5 batch analysis data with analysis methods, validation data and limits for the impurities. The 5 batch analysis confirmed that the minimum purity complies with the existing WHO specification. Mass balances were high with a range of 994-1002 g/kg. The confidential data were confirmed as similar to those supporting registration of GCL in Australia to conclude that the national evaluations should be applicable to the profile submitted to WHO.

GCL stated that *iso*-temephos and temephos oxon could occur in their TC. There was no toxicity data available for impurities but WHO/PCS estimated their toxicity, relative to temephos, and defined acceptable limits based on the BASF TC minimum purity. The impurity profile was similar to the BASF SE reference profile and can be considered equivalent.

The Meeting was provided with data on the physio-chemical properties which are similar to BASF SE. The Gharda hydrolysis study stated temephos is hydrolytically unstable but it should not hydrolyse in normal use. The decomposition temperature is high but temephos is used at much lower temperatures.

The analytical method for determination of the active ingredient is normal phase HPLC using a silica column with UV detection at 254 nm and is a full CIPAC method. The Gharda method for the determination of the active ingredient is reverse phase HPLC using a C18 column with UV detection at 240 nm. The Gharda method and validation data demonstrated that this method is comparable with the CIPAC method for the determination of temephos content. The Gharda methods used for the determination of impurities are based on HPLC/UV and GC/FID and are equivalent to the BASF SE methods. Gharda stated that the CIPAC and BASF methods are applicable to their product and confirmed this by providing a 2 batch analysis based on these methods.

The methods used to determine the physico-chemical properties and chemical composition are all referenced CIPAC, AOAC, OECD and EPA or validated in-house methods. Methods were referenced or provided in the supporting documents.

The GCL temephos EC and GR complied with the existing WHO specification.

**SUPPORTING INFORMATION  
FOR  
EVALUATION REPORT 340/2010**

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## Physico-chemical properties of temephos

**Table 1. Physico-chemical properties of pure temephos**

Parameter	Value(s) and conditions	Purity %	Method reference and study number
Vapour pressure	2.757 x 10 <sup>-7</sup> Pa at 25°C	94%	OECD 104 / C.TMO.005
Melting point, boiling point and/or temperature of decomposition	Melting point: 30°C-30.5°C	94%	
	Boiling point: temephos began to decompose at 202–206°C and the boiling point could not be determined. Decomposition temperature: around 206°C	95%	OECD 102 / C.TMO.006
Solubility in water	0.04 mg/L at 20 °C	94%	OECD 105 / C.TMO.010
Octanol/water partition coefficient	Log Pow = 4.41 at 25°C ± 1 °C, pH not stated	94%	OECD 107 / C.TMO.014
Hydrolysis characteristics	Hydrolytically unstable at pH 4, 7 and 9. Half Life is 79.3 days at pH 4, 28.7 days at pH 7 and 49.1 days at pH 9, all at 25°C (calculated)	96%	OECD 111 / C.TMO.016
Photolysis characteristics	Does not undergo photolysis No absorption above the baseline in the range of 290 nm-700 nm	98%	EPA Guideline “Photolysis of aqueous solution in sunlight” (CG-6000) / C.TMO.015
Dissociation characteristics	Non dissociative (Considering the structure of the compound, it is unlikely that the gain or loss of a proton would occur in aqueous temephos solutions)	94%	OECD 112 / C.TMO.009

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

Manufacturing process, maximum limits for impurities $\geq 1$ g/kg, 5 batch analysis data	Confidential information supplied and held on file by WHO. Mass balances were 99.4-100.2%, with no unknowns.
Declared minimum temephos content	920 g/kg
Relevant impurities $\geq 1$ g/kg and maximum limits for them	<i>O</i> -{4-[(4-{[methoxy(methylthio)phosphoryl]oxy}phenyl)thio]phenyl} <i>O,O</i> -dimethyl thiophosphate (“ <i>iso</i> -temephos”): 13 g/kg. 4-({4-[(dimethoxyphosphorothioyl)oxy]phenyl)thio)phenyldimethyl phosphate (“temephos oxon”): 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	Melting Point: 30.0-30.5 °C Boiling point: temephos began to decompose at around 202–206°C and the boiling point could not be determined.

### Methods of analysis and testing

The analytical methods for temephos and the two relevant impurities are GCL methods. A comparison with the CIPAC method for temephos (CIPAC Handbook 1C, p.2233, 1985) and the BASF SE method for the relevant impurities (BASF method M 1640.AC) confirmed that the methods are equivalent. GCL stated that the CIPAC and BASF methods are applicable to their product and confirmed this by providing a 2 batch analysis based on these methods.

Test methods for determination of physico-chemical properties of the technical active ingredient of GCL were OECD / OPPTS / EEC methods while those for the formulations were GCL in-house methods, as indicated in the specifications. A comparison of the methods confirmed that they are equivalent to CIPAC methods.

## **ANNEX 1**

### **HAZARD SUMMARY PROVIDED BY THE PROPOSER**

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

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

Species	Test	Guideline, duration, doses and conditions	Purity %	Result	Study number
Wistar Rat	Acute oral	OECD 423	93.0%	LD <sub>50</sub> : > 2000 mg/kg	T.TMO.014
Wistar Rat	Acute dermal	OECD 402	93.0%	LD <sub>50</sub> : > 2000 mg/kg bw	T.TMO.015
Wistar Rat	Acute Inhalation	OECD 403	93.0%	LC <sub>50</sub> = > 3.02 mg/L	T.TMO.019
White Rabbit	Skin irritation	OECD 404	93.0%	Mild irritant	T.TMO.016
White Rabbit	Eye irritation	OECD 405	93.0%	Non irritant	T.TMO.017
Guinea pig(Albino)	Skin sensitisation	OECD 406	93.0%	Non sensitizer	T.TMO.018

## ANNEX 2

### REFERENCES

Author and year	Study title. Study identification number. Report identification number. Company conducting the study.
GCL 09/2007	FAO/WHO Specifications for Pesticides – Proposers (Gharda) completed template with (i) Manufacturing Process and 5 batch analysis (Confidential) & (ii) specifications including physico-chemical properties, toxicological summaries, comments & references.(with updates)
GCI 09/2007	Proposers (Gharda) specifications including Temephos TC, EC and GR
GCL 04/2009	Analysis and certification limits for Temephos Technical Gharda Chemical Limited. Revised 5 batch analysis, validation data, methods of analysis for AI and Impurities and Identity Test). Report No C.TMO.017
GCL 12/2009	Proposers (GCL) updated specifications for Temephos TC, GR and EC
WHO 1999	Full specification for Temephos WHO/SIT/19.R4. Revised 10 December 1999 incorporating WHO/SIF/34.R3 and WHO/SIF/40.R1 (Superseded)
GCL 04/2009	Method of Analysis for Temephos – Method 1 TMP, incorporated as part of Report No C.TMO.017
GCL 04/2009	Methods of Analysis for Impurities of Temephos – Method 2, 3 and 4 TMP, incorporated as part of Report No C.TMO.017
GCL 2011	Method of Analysis for Temephos and Relevant Impurities – CIPAC Method 340 TC/M and BASF Method for Relevant Impurities, both incorporated as part of Report No C.TMO.018
GCL 11/2007	Vapour pressure of Temephos - Gharda Chemical Limited Report No. C.TMO.005
GCL 11/2007	Determination of boiling (decomposition) point of Temephos - Gharda Chemical Limited Report No. C.TMO.006
GCL 11/2007	Determination of dissociation characteristics of Temephos - Gharda Chemical Limited Report No. C.TMO.009
GCL 11/2007	Solubility of Temephos in water - Gharda Chemical Limited Report No. C.TMO.010
GCL 11/2007	Partition coefficient (n-octanol; water) of Temephos - Gharda Chemical Limited Report No. C.TMO.014
GCL 3/2008	Hydrolysis of Temephos in water as a function of pH at 25 °C – Interim Report. Gharda Chemical Limited Report No. C.TMO.016
GCL 9/2007	Photodegradation of Temephos in water - Gharda Chemical Limited Report No. C.TMO.015
GCL 9/2007	1988 Acute oral toxicity in rat, T.TMO.001
GCL 9/2007	1988 Acute dermal toxicity study in rabbit, T.TMO.003
GCL 9/2007	1988 Acute inhalation toxicity in rat, T.TMO.004
GCL 9/2007	1988 Acute dermal irritation study in rabbit, T.TMO.005
GCL 9/2007	1988 Acute eye irritation study in rabbit, T.TMO.006
GCL 9/2007	Temephos –Crop Protection Publication. The Pesticide Manual 13 <sup>th</sup> Ed
GCL 9/2007	2008 Skin sensitisation study in Guinea Pig, T.TMO.013
APVMA March 2008	Comparison of Manufacturing Process, QC, specifications and batch analyses for Temephos active submitted to APVMA (Australian Pesticides and Veterinary Medicines Authority) with that submitted to WHO

Author and year	Study title. Study identification number. Report identification number. Company conducting the study.
Gharda Chemical Limited 26/3/2008	Email re: Differences between DoC of APVMA (Australian Pesticides and Veterinary Medicines Authority) for comparison of manufacturing process, specifications and batch analyses of Temephos active to that submitted to WHO
Gharda Chemical Limited 26/3/2009	Hydrolysis of Temephos in water as a function of pH at 25 °C – Final Report. Gharda Chemical Limited Report No. C.TMO.016
APVMA (Australia) March 2011	Report from APVMA Australia. Comparison of Manufacturing Process, DoC and 5 batch analyses of Temephos submitted to WHO and APVMA (Australian National Authority)
GCL 2/2010	2010 Acute oral toxicity in Wistar rat, T.TMO.014 IIBAT
GCL 2/2010	2010 Acute dermal toxicity study in rat, T.TMO.015 IIBAT
GCL 2/2010	2010 Acute inhalation toxicity in rat, T.TMO.019 IIBAT
GCL 2/2010	2010 Acute dermal irritation study in rabbit, T.TMO.016 IIBAT
GCL 2/2010	2010 Acute eye irritation study in rabbit, T.TMO.017 IIBAT
GCL 2/2010	2010 Skin sensitisation study in Guinea Pig, T.TMO.018 IIBAT

# WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

## TEMEPHOS

### FAO/WHO EVALUATION REPORT 340/2008

#### Recommendation

The Meeting recommended that the HPLC-UV method should be accepted by WHO as validated for use in support of the specifications for temephos TC, EC and GR.

#### Appraisal

The 2005 JMPS recommended adoption of specifications for temephos TC, EC and GR, subject to acceptable validation of the analytical method for determination of the relevant impurities, “temephos-oxon”<sup>1</sup> and “*iso*-temephos”<sup>1</sup>.

WHO/PCS proposed maximum acceptable limits of 10 and 20 g/kg for “temephos-oxon” and “*iso*-temephos”, respectively, in temephos TC. The manufacturing limits were below these calculated limits and therefore within the acceptable ranges. The 2005 Meeting agreed that the two impurities should be designated as relevant, with specified limits of 3 and 13 g/kg for “temephos-oxon” and “*iso*-temephos”, respectively. Taking into account the TC minimum purity of 925 g/kg, the 2005 Meeting noted that these limits correspond to rounded values of 0.3% and 1.4 % of the temephos content for “temephos-oxon” and “*iso*-temephos”, respectively, in the formulation.

In 2008, the results of a peer validation of an analytical method for simultaneous determination of “temephos-oxon” and “*iso*-temephos” in temephos TC, EC and GR, conducted by BASF SE, were reported to WHO. Three batches each of temephos TC, batches of EC, GR and a fortified blank GR formulation were analyzed in two independent laboratories, using the HPLC-UV-DAD method described in Appendix 1.

Data for linearity, precision and recovery were similar from both laboratories. The recovery was determined from a temephos GR formulation blank fortified at 0.95 and 9.49 g/kg, relative to the nominal content of temephos, with “temephos-oxon” and “*iso*-temephos”, respectively. The fortified samples were subsequently analyzed and the recoveries were found to be 97.67 and 95.16%, with 2.92 and 1.88% RSD for “temephos-oxon” and “*iso*-temephos”, respectively, indicating good recovery, precision and accuracy. The linearity of detector response over concentration ranges of 0.3-1.2 g/kg and 4-16 g/kg, for “temephos-oxon” and “*iso*-temephos”, respectively was good, with  $r^2$  values  $>0.999$ . No interfering compounds were observed. Results from concurrent analysis of the TC, EC and GR samples are given in Table 1 for “temephos-oxon” and in Table 2 for “*iso*-temephos”.

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<sup>1</sup> “Temephos-oxon” and “*iso*-temephos” are names of convenience, as the compounds do not have ISO common names. Detailed information on identity is given in temephos specifications.

Table 1. Determination of “temephos-oxon” in temephos TC and the EC and GR formulations (n=5 for TC, n=6 for EC and GR)

Lab	TC 1		TC 2		TC 3		EC		GR	
	mean, g/kg*	RSD, %	mean, g/kg*	RSD, %	mean, g/kg*	RSD, %	mean, g/kg*	RSD, %	mean, g/kg*	RSD, %
1	0.60	1.90	0.59	0.69	0.82	1.39	0.46	1.50	0.32	3.57
2	0.59	1.08	0.59	0.57	0.78	1.03	0.44	1.87	0.29	2.86

Table 2. Determination of “*iso*-temephos” in temephos TC and the EC and GR formulations (n=5 for TC, n=6 for EC and GR)

Lab	TC 1		TC 2		TC 3		EC		GR	
	mean, g/kg*	RSD, %	mean, g/kg*	RSD, %	mean, g/kg*	RSD, %	mean, g/kg*	RSD, %	mean, g/kg*	RSD, %
1	7.53	0.27	8.88	0.58	6.8	3.8	8.23	1.06	59.0	1.48
2	7.67	0.55	9.0	0.37	6.77	0.78	8.47	0.28	61.2	1.40

\* In tables 1 and 2, g/kg values refer to either g impurity per kg TC (samples TC 1-3) or g impurity per kg active ingredient in the formulation (EC and GR samples).

# WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

## TEMEPHOS

### FAO/WHO EVALUATION REPORT 340/2005

#### Recommendations

The Meeting recommended that:

- (i) the existing (1999) WHO specifications for temephos TC, GR and EC should be withdrawn;
- (ii) the specifications for temephos TC, GR and EC, proposed by BASF Aktiengesellschaft<sup>1</sup> and as amended, should be adopted by WHO, subject to satisfactory validation of the analytical method(s) for the determination of the relevant impurities.

#### Appraisal

The Meeting considered data and proposed specifications for temephos, submitted by BASF Aktiengesellschaft<sup>1</sup>, in support of a revision of existing WHO specifications for TC, GR and EC (WHO/SIT/19/R4, WHO/SIF/31.R4 and WHO/SIF/34.R3 which had been revised in 1999).

Temephos is not under patent. It is registered and sold in Australia and many countries in Central and South-America, Asia, Europe and Africa. It was first registered by US EPA in 1965 (by American Cyanamid Co, now BASF<sup>1</sup>) and reviewed there for re-registration in 1991 (EPA 1991).

Temephos is a non-systemic organophosphorus pesticide, used only in public health applications.

Pure temephos has a low melting point (about 30°C) and the technical material is a viscous yellow to brown liquid at room temperature. It is a relatively high molecular weight organophosphorus compound, of low volatility and decomposing at about 100°C at atmospheric pressure. Temephos is of very low solubility in water (30 µg/l at 25°C) but is soluble in many organic solvents. It has no acidic or basic characteristics, it is stable to hydrolysis (half-life >30 days at pH 4-9 at 25°C) and photolysis occurs only slowly (half-life 15 days, continuous irradiation with artificial sunlight).

The Meeting was provided with commercially confidential information on the manufacturing process and 5-batch analysis data on all impurities ≥1 g/kg. Mass balances were acceptably high (98.1–99.2%), with no unknowns exceeding 1 g/kg. The data were confirmed as broadly similar to those submitted for registration in Brazil, except that the minimum content of active ingredient (925 g/kg) was slightly higher than in the profile submitted to Brazil. The Meeting noted that certain data in the 5-batch analysis did not conform to the manufacturing specification. The manufacturer stated that the manufacturing specification was identical to that

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<sup>1</sup> 2008 footnote. The company name was changed to BASF SE in 2008.

presented for registration of temephos and had been accepted by all authorities involved. The manufacturing specification was based on long experience of temephos: the TC was normally within the specified ranges and was expected to remain so in future (BASF 2006a).

The manufacturer proposed that none of the impurities should be considered as relevant. However, WHO/PCS advised (PCS 2006) that two impurities, “*iso*-temephos”<sup>1</sup> and “temephos oxon”<sup>1</sup> qualified for designation as relevant impurities. No data were available on the toxicity of these impurities but, by inference from the data of Gallo & Lawryk (1991), they were considered likely to be appreciably more acutely toxic than temephos itself. WHO/PCS estimated the toxicity (relative to temephos) of each impurity as the geometric mean of relative toxicities of pairs of analogous organophosphorus compounds. Using these estimates and the standard approach to calculation (Appendix J, FAO/WHO 2006), WHO/PCS proposed maximum acceptable limits of 10 and 20 g/kg for “temephos oxon” and “*iso*-temephos”, respectively, in temephos TC. The manufacturing limits were below these calculated limits and therefore within the acceptable ranges. The Meeting agreed that the two impurities should be designated as relevant, with specified limits of 3 and 13 g/kg for “temephos-oxon” and “*iso*-temephos”, respectively. Taking into account the TC minimum purity of 925 g/kg, the Meeting noted that these limits correspond to rounded values of 0.3% and 1.2%<sup>2</sup> of the temephos content for “temephos-oxon” and “*iso*-temephos”, respectively, in the formulations.

The Meeting noted that the purity of material used in some of the hazard tests, including acute toxicity, was higher than that represented by the manufacturing specification. The manufacturer provided data on the impurity levels present in the materials tested for acute toxicity. The high doses of TC administered corresponded to relatively high doses of the impurities and, consequently, it was considered that the potential for additional hazards, associated with those impurities, had been adequately assessed in the tests (BASF 2006b). WHO/PCS reviewed the additional data and concluded that the slight differences in the impurity levels involved were unlikely to have had any effect on the results (PCS 2006).

The Meeting questioned the apparently high toxicity of temephos EC to aquatic arthropods, notably *Daphnia*. The company confirmed the data but noted that corresponding data for the TC were not available (BASF 2006c). WHO/PCS considered that there were insufficient data to identify the underlying reasons for the exceptional toxicity of the EC but observed that all formulations of temephos are very toxic to aquatic arthropods (PCS 2006).

The manufacturer had provided an appropriate database for the assessment of the mutagenicity of temephos, with all studies being negative. WHO/PCS informed the Meeting that a single study, conducted with an unidentified temephos preparation, had reported borderline positive results for genotoxicity (Aiub *et al.* 2002). WHO/PCS advised that this study was difficult to interpret and did not change the overall conclusion that temephos from the source under evaluation is not genotoxic (PCS 2006). The manufacturer also provided a published study on human

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<sup>1</sup> “Temephos-oxon” and “*iso*-temephos” are names of convenience, as the compounds do not have ISO common names. Detailed information on identity is given in temephos specifications.

<sup>2</sup> 2008 footnote. The value of 1.2% was an editorial error in the 2005 evaluation, the correct value for “*iso*-temephos” in the formulations is 1.4%.

volunteers (Laws *et al.* 1967) but the Meeting noted that FAO and WHO wished to discourage such studies and agreed that it should not be considered as part of the hazard profile for the purposes of developing FAO/WHO specifications.

The analytical method for determination of temephos in TC, GR and EC is a full CIPAC method, based on normal-phase HPLC with UV detection at 254 nm and internal standardization with either dimethyl 4-nitrophthalate or 4-nitrophenyl 4-nitrobenzenoate.

Analytical methods for the determination of impurities were based on reversed-phase HPLC with gradient elution and external standardization.

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

The meeting considered other points arising from the proposed specifications.

GR. The proposed specification did not include a clause for attrition resistance. The manufacturer stated that, because the sand grain carrier is not be abraded in the MT 178 test and the active ingredient is present as a viscous surface film, the test would simply measure the dust content of the sand used to prepare the formulation. The Meeting therefore agreed that attrition during handling is unlikely to occur and that the clause for dustiness was sufficient by itself.

The proposed clause for storage stability specified testing at 45°C for 6 weeks, instead of the more usual 54°C test for 2 weeks. The manufacturer stated that, depending on the surface activity of the sand, thermal breakdown of the liquid film of temephos can occur at 54°C, whereas at 45°C the formulations are stable. The Meeting accepted the proposed clause.

The product may be dispensed by volume for application and therefore bulk density is important. However, because the carrier is of rounded sand grains, pour and tap densities are similar.

EC. The clause and test method for emulsion stability and re-emulsification, initially proposed by the manufacturer, were consistent with the existing specification but inconsistent with the requirements of the FAO/WHO manual. They were subsequently amended by the manufacturer, to comply with current requirements.

**SUPPORTING INFORMATION  
FOR  
EVALUATION REPORT 340/2005**

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## Uses

Temephos is a non-systemic organophosphorus insecticide, mainly used as a larvicide to control mosquito, midge, black fly and other insects in public health, and to control fleas on dogs and cats. It is also used for mosquito control in potable water.

## Identity

### ISO common names

Temephos (BSI, draft E-ISO)

*Synonyms* AC 52 160 (Cyanamid)

BAS 317 I (BASF)

OMS 786; ENT 27 165

### Chemical names

*IUPAC:* *O,O,O',O'*-tetramethyl *O,O'*-thiodi-*p*-phenylene bis(phosphorothioate)

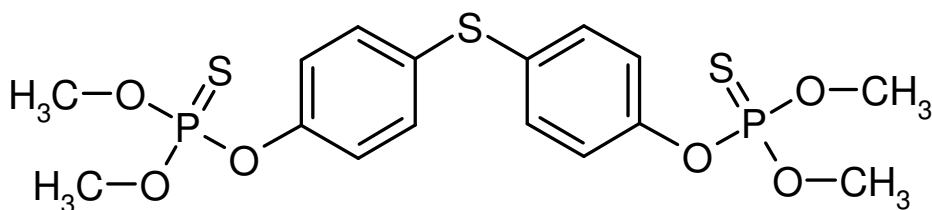
*O,O,O',O'*-tetramethyl *O,O'*-thiodi-*p*-phenylene diphosphorothioate

*O*-[4-({4-[(dimethoxyphosphorothioyl)oxy]phenyl}thio)phenyl] *O,O*-dimethyl thiophosphate.

*CA:* phosphoric acid, *O,O'*-(thiodi-1,4-phenylene) *O,O,O',O'*-tetramethyl ester

*O,O'*-(thiodi-4,1-phenylene) bis(*O,O*-dimethyl phosphorothioate)

### Structural formula



### Empirical formula

C<sub>16</sub>H<sub>20</sub>O<sub>6</sub>P<sub>2</sub>S<sub>3</sub>

### Relative molecular mass

466.5

### CAS Registry number

[3383-96-8]

### CIPAC number

340

### Identity tests

HPLC retention time, IR spectrum, TLC.

## Physico-chemical properties of temephos

**Table 1. Physico-chemical properties of pure temephos**

Parameter	Value(s) and conditions	Purity %	Method	Reference
Vapour pressure	$8 \times 10^{-6}$ Pa at 25 °C (extrapolated)	>98	OECD 104	TM-301-006
Melting point	30-30.5 °C	>98	OECD 102	TM-301-006
Boiling point	Decomposes before boiling	>98	OECD 102	TM-301-006
Temperature of decomposition	120-125 °C	>98	OECD 102	TM-301-006
Solubility in water	0.03 mg/l at 25 °C distilled water	>97.5 radiochemical purity	OECD 105	TM-311-001
Octanol/water partition coefficient	$\log P_{K_{OW}} = 4.91$ at 25 °C, pH not stated	>97.5 radiochemical purity	OECD 107	TM-315-001
Hydrolysis characteristics, at 25 °C	Half-life >30 days at 25 °C at pH 5, 7 and 9	>96 radiochemical purity	US-EPA Assessment Guidelines, Subdiv. N, § 161-1 (1982)	TM-360-001
Photolysis characteristics	Half-life = 15 days in water at pH 7 at 25 °C. Experiment conducted with 24 hours direct continuous irradiation with a Xenon arc lamp, at a concentration of 30 µg/l in water.	>96 radiochemical purity	US-EPA Assessment Guidelines, Subdiv. N, § 161-2 (1982)	TM-324-001
Dissociation characteristics	Does not dissociate	-	-	-

**Table 2. Chemical composition and properties of technical temephos (TC)**

Manufacturing process, maximum limits for impurities $\geq 1$ g/kg, 5 batch analysis data	Confidential information supplied and held on file by WHO. Mass balances were 98.1-99.2%, unknowns were each <0.1%.
Declared minimum temephos content	925 g/kg
Relevant impurities $\geq 1$ g/kg and maximum limits for them	<i>O</i> -{4-[(4-{[methoxy(methylthio)phosphoryl]oxy}phenyl)thio]phenyl} <i>O,O</i> -dimethyl thiophosphate (CL78791, "iso-temephos"): 13 g/kg. 4-({4-[(dimethoxyphosphorothioyl)oxy]phenyl} thio)phenyl dimethyl phosphate (CL52828, "temephos oxon"): 3 g/kg.
Relevant impurities < 1 g/kg and maximum limits for them	None
Stabilisers or other additives and maximum limits for them	None
Melting and boiling temperature of the TC	Viscous liquid at room temperature, decomposes below the boiling point at atmospheric pressure.

### Hazard summary

Temephos has not been evaluated by the FAO/WHO JMPR. US EPA concluded that there was no evidence of carcinogenicity with temephos and that temephos formulations should be classified as slightly toxic end use products (EPA toxicity class III) (EPA 2001).

The WHO hazard classification of temephos is: U, unlikely to present acute hazard in normal use (WHO 2002).

### **Formulations**

The main formulation types available are GR and EC - common names are Abate and Abathion. These formulations are registered and sold in Australia and many countries in Central and South America, Asia, Europe and Africa.

Temephos is not usually co-formulated with other pesticides.

### **Methods of analysis and testing**

The analytical method for determination of the active ingredient (including identity tests) is a full CIPAC method (CIPAC 1C). Temephos is determined by HPLC, using a silica-based column, ethyl acetate/hexane as eluent, UV detection at 254 nm and internal standardization with either dimethyl 4-nitrophthalate or 4-nitrophenyl 4-nitrobenzoate.

The methods for determination of impurities were also based on HPLC with UV detection and external standardization.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, EU or US-EPA, while those for the formulations were CIPAC, as indicated in the specifications.

### **Physical properties**

The physical properties, the methods for testing them and the limits proposed for the GR and EC formulations, comply with the requirements of the manual (FAO/WHO 2002).

### **Containers and packaging**

No special requirements for containers and packaging have been identified.

### **Expression of the active ingredient**

The active ingredient is expressed as temephos, in g/kg or g/l.

## **ANNEX 1**

### **HAZARD SUMMARY PROVIDED BY THE PROPOSER**

Note: BASF provided written confirmation that the toxicological and ecotoxicological data included in the following summary were derived from temephos having impurity profiles similar to those referred to in Table 2, above.

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

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Rat (CHRCO Charles River) (m,f)	oral	94.7	EPA Guideline 81-1	LD <sub>50</sub> (m) = 4204 mg/kg bw LD <sub>50</sub> (f) >10,000 mg/kg bw	TM-410-002
Rabbit (NZ white) (m,f)	dermal	94.7	EPA Guideline 81-2	LD <sub>50</sub> (m) = 2000 mg/kg bw LD <sub>50</sub> (f) = 2378 mg/kg bw	TM-410-002
Rat (outbred Sprague-Dawley) (m,f)	inhalation	94.7	EPA Guideline 81-3	LC <sub>50</sub> >4.79 mg/l	TM-413-002
Rabbit (NZ white) (m,f)	skin irritation	94.7	EPA Guideline 81-5	Non-irritating	TM-410-002
Rabbit (NZ white) (m)	eye irritation	94.7	EPA Guideline 81-4	Non-irritating	TM-410-002
Guinea pig (Hartley) (m)	skin sensitization	94.7	modified Buehler (9-induction)	Non-sensitizer	TM-416-002

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

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Rat (Nelson strain) (m,f)	90 d oral	96.4	Administered via diet at 0, 2, 6 and 18 ppm (equivalent to 0.1, 0.3, and 0.9 mg/kg bw/d). Also at 350 ppm (17.5 mg/kg bw/d), to determine maximum tolerated dose and induce histopathological effects.	Systemic NOEL = 18 ppm (0.9 mg/kg bw/day) Systemic LOEL = 350 ppm (17.5 mg/kg bw/day) ChE NOEL = 6 ppm (0.3 mg/kg bw/day/day) ChE LOEL = 18 ppm (0.9 mg/kg bw/day)	TM-425-001
Rat (Nelson strain) (m,f)	90 d oral	87.1	Administered via diet at 0, 6, 18 and 54 ppm (equivalent to, 0.3, 0.9 and 27.0 mg/kg bw/d) to determine if ChE activity inhibitions in the above 90-d rat study were definite and reproducible.	ChE NOEL = 6 ppm (0.3 mg/kg bw/day/day) ChE LOEL = 18 ppm (0.9 mg/kg bw/day)	TM-425-003

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

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Dog (beagle) (m,f)	90 d oral	96.4	Administered via diet at 0, 2, 6 and 18 ppm (equivalent to 0.05, 0.15 and 0.45 mg/kg bw/d). Also at 700 ppm which was reduced to 500 ppm after first week.	ChE NOEL = 18 ppm (0.45 mg/kg bw/day) ChE LOEL = 700/500 ppm (12.5 mg/kg bw/day)	TM-425-002
Rabbit (NZ white) (m,f)	21-day dermal	93.1	Treated 5 d/week for 3 weeks at 0, 25, and 50 mg/kg bw/d for 3 weeks and 100 mg/kg bw/d for 5 d/week for 2 weeks followed by 75 mg/kg bw/d 5 d/week for 3 <sup>rd</sup> week.	All dose levels caused decreased in plasma cholinesterase levels following treatment for 21 d. Brain cholinesterase levels of mid-dose males also depressed. Plasma & brain cholinesterase levels returned to normal 10 and 17 d after treatment, respectively. No treatment-related pathological changes observed in any of the treatment groups.	TM-420-005
Rat (CD Sprague-Dawley) (m,f)	Chronic toxicity, carcinogenicity	93.5	Administered via diet at 0, 10, 100 and 300 ppm (equivalent to 0, 0.5, 5.0 and 15 mg/kg bw/d).	NOEL = 300 ppm (15 mg/kg bw/d), highest dose tested. No evidence of carcinogenicity.	TM-427-001 TM-428-002
Rat (Sherman strain) (m,f)	1-generation reproduction	90	Administered via diet at 0 and 500 ppm (approximately 25 mg/kg bw/d).	NOEL (reproductive) >500 ppm (25 mg/kg bw/d), highest dose tested. NOEL (systemic ChE) <500 ppm (25 mg/kg bw/d), highest dose tested.	Gaines <i>et al.</i> 1967
Rat (CFE strain) (m,f)	3-generation reproduction	87.1	Administered via diet at 0, 25 and 125 ppm (equivalent to 0, 1.25 and 6.25 mg/kg bw/d)	NOAEL (parental) >125 ppm (6.25 mg/kg bw/d), highest dose tested. NOAEL (offspring) >125 ppm (6.25 mg/kg bw/d), highest dose tested.	TM-430-001
Rabbit (NZ white) (f)	Teratogenicity, developmental toxicity	Not stated	Administered by oral gavage at 0, 3, 10 and 30 mg/kg bw/d to pregnant rabbits on days 6-18 of gestation.	NOAEL >30 mg/kg bw/d	TM-432-003

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

Species	Test	Purity %	Duration and conditions or guideline adopted	Result	Reference
Hen, adult (strain not specified)	Acute neurotoxicity	99.9	Single oral dose in arachis oil (20% v/v) via syringe at 227-1705 mg/kg bw.	No neurotoxicity observed. LD <sub>50</sub> = 579 mg/kg bw	TM-451-001
Hen, mature (White Leghorn)	42-day neurotoxicity	Not stated	Single oral dose 550 mg/kg bw in corn oil administered to 60 hens via disposable syringe. 21 d after initial dose, all surviving test birds were again treated at 550 mg/kg bw in conjunction with atropine.	No delayed neurotoxicity observed.	TM-451-002

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

Species	Test	Purity %	Conditions and doses	Result	Reference
<i>S. typhimurium</i> (TA 98, TA 100, TA 1535, TA 1537, TA 1538) and <i>E. coli</i> (WP-2 <i>uvrA</i> )	Microbial mutagenesis, <i>in vitro</i>	94.7	with and without metabolic activation, up to 5000 µg/plate and 1000 µg/disk	negative	TM-435-003
CHO cells, HGPRT locus, tested twice	Mammalian cell mutagenesis, <i>in vitro</i>	94.7	with and without metabolic activation, up to 5000 µg/ml	negative	2005/7004343
CHO cells	Chromosomal aberration, <i>in vitro</i>	94.7	10- and 20-h harvest times, with and without metabolic activation; highest dose 7.5 µg/ml	negative	TM-435-005
Primary rat hepatocytes	DNA repair (UDS) assay, <i>in vitro</i>	94.7	Up to 5000 µg/ml	negative	TM-435-004

**Table D. Ecotoxicology profile of temephos technical material**

Species	Test	Purity %	Duration and conditions	Results	Reference
Water flea <i>Daphnia magna</i>	Acute toxicity	43% EC	Static; 48 h	LC <sub>50</sub> = 0.000011 ppm NOEC = 0.000032 ppm	TM-560-005
Water flea <i>Daphnia magna</i>	Acute toxicity	5% GR	Static; 48 h	LC <sub>50</sub> = 0.00054 ppm	Mayer & Ellersieck 1986
Scud <i>Gammarus lacustris</i>	Acute toxicity	86.2	Static; 48 h	LC <sub>50</sub> = 0.082 ppm	Mayer & Ellersieck 1986

**Table D. Ecotoxicology profile of temephos technical material**

Species	Test	Purity %	Duration and conditions	Results	Reference
Stone fly <i>Pteronarcis</i> spp.	Acute toxicity	86.2	Static; 48 h	LC <sub>50</sub> = 0.01 ppm	Mayer & Ellersieck 1986
Bluegill sunfish <i>Lepomis macrochirus</i>	Acute toxicity	86.2	Static; 96 h	LC <sub>50</sub> = 21.8 ppm	Mayer & Ellersieck 1986
Bluegill sunfish <i>Lepomis macrochirus</i>	Acute toxicity	43% EC	Static; 96 h	LC <sub>50</sub> = 1.14 ppm	Mayer & Ellersieck 1986
Rainbow trout <i>Oncorhynchus mykiss</i>	Acute toxicity	90	Static; 96 h	LC <sub>50</sub> = 9.58 ppm	TM-511-001
Bluegill sunfish <i>Lepomis macrochirus</i>	Bioconcentration	Specific activity = 30 $\mu$ Ci/mg; 570 ppm, radio-purity = 96%	Flow-through, 42-d	Accumulated in fish exposed continuously to 0.65 ppb of <sup>14</sup> C-temephos. Declined rapidly in depuration. <sup>1</sup>	TM-519-002
Eastern oyster <i>Crassostrea virginica</i>	Acute toxicity	86.2	96 h	EC <sub>50</sub> = 0.22 ppm	Goodyear <i>et al.</i> 1999
Eastern oyster <i>Crassostrea virginica</i>	Acute toxicity	43% EC	Flow-through; 96 h	EC <sub>50</sub> = 19 ppb	Mayer & Ellersieck 1986
Eastern oyster <i>Crassostrea virginica</i>	Acute toxicity	5% GR	Flow-through; 96 h	EC <sub>50</sub> = 15 ppb	TM-560-006
Pink shrimp <i>Penaeus duorarum</i>	Acute toxicity	43% EC	48 h	EC <sub>50</sub> = 0.0053 ppm	Goodyear <i>et al.</i> 1999
Pink shrimp <i>Penaeus duorarum</i>	Acute toxicity	5% GR	Flow-through; 96 h	EC <sub>50</sub> = 14 ppb	TM-560-007
Sheepshead minnow <i>Cyprinodon variegatus</i>	Acute toxicity	43% EC	Flow-through testing conditions; 96 h	EC <sub>50</sub> = 4.7 ppm	TM-560-008
Sheepshead minnow <i>Cyprinodon variegatus</i>	Acute toxicity	5% GR	Flow-through testing conditions; 96 h	EC <sub>50</sub> > 5.4 ppm	TM-560-009
Bobwhite quail <i>Colinus virginianus</i>	Acute oral toxicity	94.7	Oral administration in corn by gavage with a disposable syringe.	LD <sub>50</sub> = 25.2 mg/kg bw	TM-505-005

<sup>1</sup> Fish metabolism profile was very similar to that of rat or bean leaves: unaltered parent compound was main constituent of residues and its sulfoxide was the only significant metabolic product.

**Table D. Ecotoxicology profile of temephos technical material**

Species	Test	Purity %	Duration and conditions	Results	Reference
Bobwhite quail <i>Colinus virginianus</i>	Sub-acute dietary toxicity	86.9	Administered in diet, 5 d.	LC <sub>50</sub> = 92 ppm	MRID 00022923
Mallard duck <i>Anas platyrhynchos</i>	Acute oral toxicity	94.7	Oral administration in corn oil via gavage.	LD <sub>50</sub> = 2150 mg/kg bw	TM-505-004
Mallard duck <i>Anas platyrhynchos</i>	Sub-acute dietary toxicity	86.9	Administered in diet, 5 d	LC <sub>50</sub> = 894 ppm	MRID 00022923
Ring-necked pheasant <i>Phasianus colchicus</i>	Acute oral toxicity	92	Oral administration, gelatin capsule into crop or proventriculus.	LD <sub>50</sub> = 31.5 mg/kg bw	Tucker <i>et al.</i> 1971
Chukar partridge <i>Alectoris graeca</i>	Acute oral toxicity	92	Oral administration, gelatin capsule into crop or proventriculus.	LD <sub>50</sub> = 270 mg/kg bw	Tucker <i>et al.</i> 1971
Quail <i>Coturnix coturnix japonica</i>	Acute oral toxicity	92	Oral administration, gelatin capsule into crop or proventriculus.	LD <sub>50</sub> = 84.1 mg/kg bw	Tucker <i>et al.</i> 1971
Common pigeon <i>Columba livia</i>	Acute oral toxicity	92	Oral administration, gelatin capsule into crop or proventriculus.	LD <sub>50</sub> = 50.1 mg/kg bw	Tucker <i>et al.</i> 1971
House sparrow <i>Passer domesticus</i>	Acute oral toxicity	92	Oral administration, gelatin capsule into crop or proventriculus.	LD <sub>50</sub> = 35.4 mg/kg bw	Tucker <i>et al.</i> 1971

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## Appendix 1

### Method for the determination of the relevant impurities, “temephos-oxon” and “*iso*-temephos”, in temephos TC, EC and GR

(adapted from BASF method M1640.AC)

#### Outline

Temephos TC or EC is dissolved in acetonitrile/water (4:1 v/v) and the “temephos-oxon”<sup>1</sup> and “*iso*-temephos”<sup>1</sup> content is determined directly by reversed-phase HPLC with gradient-elution, UV detection at 254 nm and external standardization. The relevant impurities in temephos GR are extracted into acetonitrile, using sonication and shaking/mixing, and the extract is filtered for HPLC. Samples are analyzed in duplicate.

#### Materials

“*Temephos-oxon*”, analytical standard grade

“*iso-Temephos*”, analytical standard grade

Acetonitrile, HPLC grade

Water, HPLC grade

Diluent mixture: acetonitrile/water, 4:1 v/v

Mobile phase A: acetonitrile/water, 1:1 v/v

Mobile phase B: acetonitrile/water, 9:1 v/v

#### Equipment

Volumetric flasks, grade A, 50 ml

Ultrasonic bath

Glass vials, 20 ml, with leak-tight caps compatible with acetonitrile

Disposable syringe filters, compatible with acetonitrile and capable of producing about 2 ml filtrate suitable for HPLC.

Shaker, rotating, to shake glass vials; alternatively, a reciprocating or orbital shaker may be used if the vials can be secured laying on their sides.

#### HPLC system and operating conditions (typical)

HPLC system equipped with auto-sampler, gradient programming, column oven, UV absorbance or photodiode array detector for operation at 254 nm, together with an appropriate data system. The solvent delivery system must be capable of delivering mobile phase at 2 ml/min.

HPLC column: 250 mm x 4.6 mm Vydac Apex C<sub>8</sub>, 5 µm particle size, or equivalent. Flush the column with mobile phase B at 2 ml/min for approximately 30 min. Equilibrate the column with mobile phase A until a steady baseline is achieved. The following linear gradient is used for analyses.

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<sup>1</sup> “Temephos-oxon” and “*iso*-temephos” are names of convenience, as the compounds do not have ISO common names. Detailed information on identity is given in temephos specifications.

time (min)	% A	% B
0	100	0
3	100	0
20	0	100
25	0	100
25.1	100	0
40	100	0

Flow rate: 2 ml/min  
Column temperature: 40 ± 1 °C  
Detector wavelength: 254 nm  
Injection volume: 10 µl  
Typical retention times: “temephos-oxon” 7.9 min  
“*iso*-temephos” 9.2 min  
temephos 13.2 min

### HPLC system suitability checks

Ensure that baseline separation is achieved between the peaks for temephos, “temephos-oxon” and “*iso*-temephos. If not, an improved separation system is required.”

Ensure that chromatograms obtained from injections of blank diluent mixture and the calibration solutions show no significant interference with the relevant impurity peaks. If the chromatograms of samples show evidence of significant interference, an improved separation system is required.

Ensure that the detector response is linear over the concentration ranges of the working standards. If necessary, adjust the concentrations of working standards and/or sample solutions/extracts, to ensure that all measured peaks are within the linear response range of the detector.

Ensure that the RSD of peak areas from duplicate injections of the same standard or sample extract/solution is <10%<sup>1</sup>. If not, either continue to make duplicate injections until the column is adequately conditioned, and the criterion is met, or use a better HPLC system.

### Standards preparation

Solutions are stable for at least two weeks at room temperature (≈22°C) but, preferably, should be stored in a refrigerator or freezer.

#### *Stock standard solutions*

Weigh accurately, to the nearest 0.01 mg, approximately 25 mg of “temephos-oxon” analytical standard into a 50 ml volumetric flask. Dissolve and make to volume in acetonitrile (SS<sub>oxon</sub>, ≈0.5 mg/ml).

Weigh accurately, to the nearest 0.01 mg, approximately 25 mg of “*iso*-temephos” analytical standard into 50 ml volumetric flasks. Dissolve and make to volume in acetonitrile (SS<sub>iso</sub>, ≈0.5 mg/ml).

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<sup>1</sup> This criterion effectively defines the limit of quantification (LOQ) of the method. The specification limits represent levels well above the expected LOQ so, in practice for the determination of compliance with the specifications, the RSD from duplicate injections normally should be much lower than 10%.

### *Working standards for HPLC*

The two relevant impurities may be combined in working standards, to minimize overall analysis times, and this is assumed in the instructions given below. If required they may be kept separate, to allow the relative concentrations to be varied, and the instructions given below should be amended accordingly.

From the stock standard solutions, prepare a working standard of “iso-temephos” and “temephos-oxon” in diluent mixture, to contain 0.07 mg/ml and 0.015 mg/ml, respectively (*WS<sub>oxon+iso</sub>*), corresponding to the specification limits<sup>1</sup> for temephos TC and formulations.

To check the linearity of detector response, prepare three working standards of “temephos-oxon” and “*iso*-temephos” in diluent mixture, having concentrations corresponding to 0.5, 1.0 and 2.0 times the specification limits<sup>1</sup>. Linearity should be checked intermittently through the service life of the detector’s light source, ideally with each batch of sample analyses.

### **Sample preparation**

Each material is to be analyzed in duplicate.

TC. Accurately weigh (to the nearest 0.1 mg) approximately 250 mg TC into a 50 ml volumetric flask, add 30 ml diluent and swirl to dissolve. Make to volume with diluent and mix well (A1, A2, B1, B2, etc.), prior to HPLC analysis.

EC. Accurately weigh (to the nearest 0.1 mg) into a 50 ml volumetric flask sufficient formulation to contain approximately 250 mg temephos, add 30 ml of diluent and swirl to dissolve. Make to volume with diluent and mix well (A1, A2, B1, B2, etc.), prior to HPLC analysis.

GR. Accurately weigh approximately 5000 mg formulation into a 20 ml glass vial. Add 10 ml acetonitrile, cap the vial securely and sonicate it for approximately 2 min in the ultrasonic bath. Secure the vial in the shaker and mix the contents well for approximately 30 min, then filter an aliquot of the supernatant, using disposable syringe filters (A1, A2, B1, B2, etc.), prior to HPLC analysis.

For reliable quantification, impurity concentrations must be within the calibrated linear range. Consequently, where the recommended sample preparation produces sample extracts/solutions with impurity concentrations outside that range, either the extract/solution concentration must be adjusted accordingly or linearity must be demonstrated for an appropriate range of working standard concentrations.

### **HPLC analysis**

Inject 10 µl aliquots of each solution in the following sequence: *WS<sub>oxon+iso</sub>*, A1, A2, *WS<sub>oxon+iso</sub>*, B1, B2, *WS<sub>oxon+iso</sub>*, etc. Measure peak areas.

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<sup>1</sup> Each sample solution/extract for HPLC, prepared according to the instructions given in the sample preparation section, should contain temephos at ≈5 mg/ml, so that the relevant impurity concentrations corresponding to the specification limits will be ≈0.015 and ≈0.07 mg/ml for temephos-oxon and *iso*-temephos, respectively.

## Calculations

Calculate the average peak areas produced by “*iso*-temephos” and “temephos-oxon” in the duplicate sample and (bracketing) standard chromatograms and use the averages to calculate the specific response (SR) values, as follows.

$$SR_1 (\text{Sample}) = \frac{[\text{peak area of analyte}]}{[\text{sample concentration (mg/ml)}]}$$

$$SR_2 (\text{Standard}) = \frac{[\text{peak area of analyte}]}{[\text{standard concentration (mg/ml)}]}$$

Use  $SR_1$  and  $SR_2$  to calculate the concentration of “*iso*-temephos” and “temephos-oxon” in the sample using the following equation:

$$w \% (\text{Analyte}) = \frac{[SR_1]}{[SR_2]} \times P$$

where:

“sample concentration” refers to the concentration of sample in the extract/solution injected (A1, A2, B1, B2, etc.);

“standard concentration” refers to the concentration of the impurity in the standard solution injected (WS<sub>oxon+iso</sub>);

SR1 = average specific response ratio for injections of sample;

SR2 = average specific response ratio for injections of standard;

P = purity of standard in % (for example, if the purity is 98.5%, P = 98.5).

For checking compliance with specification limits, w% must be multiplied by 10 in the case of temephos TC or by 1000/(temephos content, g/kg) in the case of EC or GR.