Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

FOSTHIAZATE

(*RS*)-[*S*-(*RS*)-*sec*-butyl *O*-ethyl 2-oxo-1,3-thiazolidin-3-ylphosphonothioate]

2015

TABLE OF CONTENTS

FOSTHIAZATE

DISCLAIMER[1]

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

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

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

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

INTRODUCTION

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

From 2002, the development of WHO specifications follows the **New Procedure**, described in the 1st edition of "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (2002) and amended with the supplement of this manual (2006), which is available only on the internet through the FAO and WHO web sites. This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPS, rather than the JMPS.]

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

PART ONE: The Specification of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the above-mentioned Manual.

PART TWO: The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of Section 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.

FAO 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. FAO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version. Dates of publication of the earlier versions, if any, are identified in a footnote. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

* NOTE: PUBLICATIONS ARE AVAILABLE ON THE INTERNET AT (http://www.fao.org/pest-and-pesticide-management/expert-bodies-conventions/faowho-joint-meeting-on-pesticide-specifications-jmps/pesticide-specifications/en/) OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.

PART ONE

SPECIFICATIONS

FOSTHIAZATE

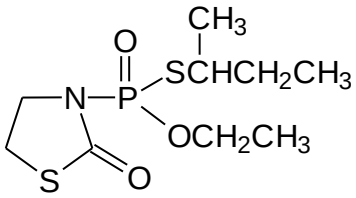
INFORMATION

ISO common name
fosthiazate (ISO 1750, published)

Synonyms
IKI-1145, TO-1145

Chemical names
IUPAC: (*RS*)-[*S*-(*RS*)-*sec*-butyl *O*-ethyl 2-oxo-1,3-thiazolidin-3ylphosphono-thioate]
CA: *O*-ethyl *S*-(1-methylpropyl) *P*-(2-oxo-3-thiazolidinyl)phosphonothioate

Structural formula



Molecular formula
$C_9H_{18}NO_3PS_2$

Relative molecular mass
283.4

CAS Registry number
98886-44-3

CIPAC number
585

Identity tests
HPLC retention time, UV spectrum, IR spectrum, MS spectrum

FOSTHIAZATE TECHNICAL MATERIAL

FAO Specification 585 / TC (December 2015[*])

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (585/2014). It should be applicable to TC produced by this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for TC produced by other manufacturers. The evaluation report (585/2014) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist of fosthiazate together with related manufacturing impurities, in the form of a clear light gold liquid having an odour characteristic of hydrogen sulfide, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (585/TC/M/2, CIPAC/4829) (Note 1)
The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Fosthiazate content** (585/TC/M/3, CIPAC/4829) (Note 1)
The fosthiazate content shall be declared (not less than 930 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

Note 1 The reverse phase HPLC method for determination of fosthiazate in TC and GR was adopted as full CIPAC method in 2013. Prior to its publication in a CIPAC Handbook, copies of the method can be obtained through the CIPAC prepublishment scheme, http://www.cipac.org/cipacpub.htm (ISBN 902951793).

[*] Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/pest-and-pesticide-management/expert-bodies-conventions/faowho-joint-meeting-on-pesticide-specifications-jmps/pesticide-specifications/pesticide-specifications-list/en/

FOSTHIAZATE GRANULES

FAO Specification 585 / GR (December 2015*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (585/2014). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated sources. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation report (585/2014) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist of granules containing technical fosthiazate, complying with the requirements of FAO specification 585/TC (December 2015), in the form of rust brown fine granules with a strong smell of garlic, together with suitable carriers and any other necessary formulants. It shall be dry, free from visible extraneous matter and hard lumps, free-flowing, essentially non-dusty and intended for application by machine.

2 Active ingredient

2.1 **Identity tests** (585/GR/M/2, CIPAC/4829) (Note 1)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Fosthiazate content** (585/GR/M/3, CIPAC/4829) (Note 1)

The fosthiazate content shall be declared (g/kg) and, when determined, the average content measured shall not differ from that declared by more than the appropriate tolerance, given in the following table:

Declared content, g/kg	Permitted tolerance
above 25 up to 100 Note: the upper limit is included in the range	± 10% or of the declared content

3 Physical properties

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

Pour density: 1.0 to 1.25 g/ml.
Tap density: 1.1 to 1.3 g/ml.

3.2 **Nominal size range** (MT 59.2, Handbook F, p.179, 1995)

250 to 850 µm; >92.5%
150 to 250 µm; <3.5%
< 150 µm; <4.5%

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/pest-and-pesticide-management/expert-bodies-conventions/faowho-joint-meeting-on-pesticide-specifications-jmps/pesticide-specifications/pesticide-specifications-list/en/

3.3 **Dustiness** (MT 171.1) (Note 2)
Nearly dust free (Note 3)

3.4 **Attrition resistance** (MT 178, Handbook H, p.302, 1998)
Minimum 99% attrition resistance.

4 Storage stability

4.1 **Stability at elevated temperature** (MT 46.3, Handbook J, p.128, 2000)
After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 4) and the formulation shall continue to comply with the clauses for:

- nominal size range (3.2),
- dustiness (3.3),
- attrition resistance (3.4)

Note 1 The reversed phase HPLC method for determination of fosthiazate in TC and granules was adopted as full CIPAC method in 2013. Prior to its publication in a CIPAC Handbook, copies of the method can be obtained through the CIPAC prepublishment scheme, http://www.cipac.org/cipacpub.htm (ISBN 902951793).

Note 2 MT 171.1 is a revised version of MT 171. Prior to publication of the method in a Handbook, copies of the method may be obtained through the the CIPAC prepublishment scheme, http://www.cipac.org/cipacpub.htm

Note 3 The optical method 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 4 Samples of the formulation taken before and after the storage stability test may be analyzed together after the test in order to reduce the analytical error.

PART TWO

EVALUATION REPORT

FOSTHIAZATE

Fosthiazate

FAO/WHO EVALUATION REPORT 585 / 2014

Recommendations

The meeting recommended that:

(i) The specifications for fosthiazate TC and GR proposed by ISK Biosciences Europe N.V and as amended, should be adopted by FAO.

Appraisal

Fosthiazate is an organophosphorous nematicide and is used for the control of nematodes in agricultural crops like potatoes, tomatoes and banana. Fosthiazate is still under patent protection.

A data package was provided by ISK Biosciences Europe N.V. (ISK) in 2010 in support of new FAO specifications for fosthiazate TC and GR. The compound has not been evaluated by JMPR and ICPS.

The structural formula of fosthiazate shows two asymmetrically substituted centers in the molecule - the phosporous and the carbon atom in the *sec*-butyl side chain. This leads to four enantiomers that can be grouped into 2 diastereomers.

However, the originally assigned IUPAC name referred only to one chiral center. The IUPAC name was updated correspondingly to adequately cover the stereoisomerism. The Meeting asked for clarification regarding the ratio of the diastereoisomers obtained during the manufacture. Data were provided to show that the ratio is 1:1:1:1. The proposer stated that fosthiazate is prepared and traded as the TC and as fine granules (formerly known as FG, formulation code no longer supported, now GR) and EC formulations. However, it is only the GR formulation that is being considered in this evaluation. The draft specification for the GR formulation included clauses for limiting water content to 4 g/kg and a pH range of 4 to 8.

The Meeting questioned whether these clauses were indeed required and asked the company to provide the necessary justifications. It was also questioned if the proposed upper limit of the pH range (pH 8) was appropriate to safeguard the stability of fosthiazate. Water was considered as non-relevant impurity for the GR formulation and removed from the specification. The clause for pH was proposed only because it is part of the specification guideline in the FAO Manual, as a consequence the Meeting concluded that it could be removed.

Fosthiazate is a liquid at room temperature and decomposes without boiling at 225°C. It has a vapour pressure of 5.6 $x10^{-4}$ at 25 °C. It has a moderate solubility in water ($\approx$ 9 g/l) that it is not pH dependent. Fothiazate is not fat soluble (log P_{ow} = 1.68) and is mostly miscible with a range of organic solvents. It is relatively stable to hydrolysis at pH 5 and 7 but rapidly hydrolysed at pH 9. It is not susceptible to photolysis.

Confidential information on the manufacturing process, on impurities at or above 1 g/kg in fosthiazate, was provided by the proposer. No relevant impurities were identified. Limits for the impurities were supported by 5 batch analyses. Mass balances were high (98-99%).

A letter of access was provided FAO to compare the confidential data with those submitted to CRD, UK, as EU Rapporteur Member State. Written confirmation was received was received from CRD on the similarity of the confidential data packages submitted in UK and to JMPS. The data supplied supports the minimum specification for the active ingredient.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 585/2014

Table 1. Physico-chemical properties of pure fosthiazate

<table>
<tr><th>Parameter</th><th>Value(s) and conditions</th><th>Purity %</th><th>Method reference (and technique if the reference gives more than one)</th><th>Study number</th></tr>
<tr><td>Vapour pressure</td><td>5.6 x 10^{-4} Pa at 25 °C</td><td>98.4%</td><td>EU Directive 92/69/EEC. Method equivalent to EEC method A4. Gas saturation method.</td><td>4039-89-0301-AS-002</td></tr>
<tr><td>Melting point</td><td>Not applicable; fosthiazate is a liquid.</td><td>Not applicable</td><td>Not applicable</td><td>Not applicable</td></tr>
<tr><td>Temperature of decomposition</td><td>225 °C at 99 kPa</td><td>99.0%</td><td>EU Directive 92/69/EEC. EEC Method A2.</td><td>4039-95-0202-AS-001</td></tr>
<tr><td>Solubility in water</td><td>9.88 g/l at 25 °C at pH 5
9.00 g/l at 25 °C at pH 7
9.46 g/l at 25 °C at pH 9</td><td>99.3%</td><td>EU Directive 92/69/EEC. Method equivalent to EEC method A6.
Shake flask method.</td><td>4039-92-0100-AS-001</td></tr>
<tr><td>Octanol/water partition coefficient</td><td>log P_{OW} = 1.68 at 25 °C
pH: not reported but not expected to be pH dependent</td><td>99.3%</td><td>EU Directive 92/69/EEC. Method equivalent to EEC A8. Shake flask method</td><td>4039-92-0099-AS-001</td></tr>
<tr><td>Hydrolysis characteristics</td><td>Calculated DT 50 for [^{14}C]-butyl and [^{14}C]-thiazolidinone labelled fosthiazate:
Half-life = 191 days and 163 days for B-label and T-label respectively at 25 °C at pH 5
Half-life = 102 days and 107 days for B-label and T-label respectively at 25 °C at pH 7
Half-life = 3.2 days and 3.3 days for B-label and T-label respectively at 25 °C at pH 9
<table>
<tr><th>pH</th><th>Period of observation days</th><th>% loss</th></tr>
<tr><td>5</td><td>30</td><td>11.15</td></tr>
<tr><td>7</td><td>30</td><td>20.5</td></tr>
<tr><td>9</td><td>30</td><td>6.2</td></tr>
</table></td><td>Radio-chemical purities >99%</td><td>In-house</td><td>1145-89-16101-1/I-221</td></tr>
<tr><td>Photolysis characteristics</td><td>Half-life xenon arc lamp= 190-212 days at pH5
Half-life dark= 190-212 days at pH 5</td><td>Radio-chemical purities >99%</td><td>In-house</td><td>5287-92-0153-EF-001</td></tr>
<tr><td>Dissociation characteristics</td><td>Does not dissociate in water</td><td>99.7</td><td>OECD 112, spectrophotometric method</td><td>4039-91-0392-AS-001</td></tr>
<tr><td>Solubility in organic solvents</td><td>13.5 g/l hexane at 25 °C
Soluble at any proportions at 25 °C with toluene, dichloromethane, methanol, acetone, ethyl acetate, n-octanol and acetonitrile</td><td>99.3</td><td>EU Directive 92/69/EEC. Method equivalent to EEC A6. Shake flask method.</td><td>4039-92-0100-AS-001</td></tr>
</table>

Table 2. Chemical composition and properties of fosthiazate 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 98.1 - 99.1% for the pilot plant production and 98.7 – 99.5 % for the full scale production. No unknowns were identified in both 5 batch analyses.
Declared minimum fosthiazate content	930 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities < 1 g/kg and maximum limits for them:	None
Stabilisers or other additives and maximum limits for them:	None

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC and/or TK	Not applicable as fosthiazate is a liquid.	Not applicable	Not applicable	Not applicable
Solubility in organic solvents (all at 20°C)	15.1 g/l n-hexane "solubilised" in xylene (freely soluble) "solubilised" N-methyl-2-pyrrolidone "solubilised" isopropyl alcohol	92.2	In-house	891005YI

USES

Fosthiazate is an organophosphorous nematicide and acts by inhibiting the acetylcholinesterase of soil borne pests. It is used for the control of nematodes in agricultural crops like potatoes, tomatoes and banana at typical use rates of 3 kg active ingredient/ha. Fosthiazate is still under patent protection.

FORMULATIONS AND CO-FORMULATED ACTIVE INGREDIENTS

The main formulation type available is GR (company designation 10FG), used as an agricultural nematicide.
Fosthiazate is not co-formulated with other pesticides.
The 10FG formulation is registered and sold in Algeria, Bosnia, Cameroon, China, Croatia, Egypt, and many other countries throughout the world including the European Union.
There is a EC formulation on the market but it is not the subject of this evaluation.

METHODS OF ANALYSIS AND TESTING

The analytical method for the active ingredient (including identity tests) determination in the technical material and 10FG was accepted as a full CIPAC method and will be published in the next Handbook. It is available under the pre-published methods on the CIPAC website. Fosthiazate is determined by gradient reverse phase HPLC (column: Hewlett-Packard

HYPERSIL ODS, 5 µm, 125 x 4 mm i.d.) with acetonitrile-water (1-2 v/v) and acetonitrile as mobile phases, ultra-violet detection at 220 nm and internal standard (dimethyl phthalate).

PHYSICAL PROPERTIES

Test methods for determination of physico-chemical properties were EC, CIPAC and in house as indicated. The physical properties and the methods for testing them, and the limits proposed for the TC and RG, comply with the requirements of the FAO Manual (March 2006 edition).

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE CONTENT OF ACTIVE INGREDIENT

The active ingredient is expressed as fosthiazate.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes:

(i) The proposer confirmed the toxicological data included in the summary below were derived from fosthiazate having impurity profiles similar to those referred to in the table above.

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

Table 1. Toxicology profile of the fosthiazate technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Purity % Note[2]	Guideline, duration, doses and conditions	Result	Study number
Rat (males)	oral	93.4%	Japanese MAFF test guidelines (1985) and U.S. Pesticide Assessment guidelines (1982); 14-day observation period; 41, 51, 64, 81 or 128 mg/kg bw; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	LD_{50} = 73 mg/kg bw	87/ISK093/626
Rat (females)	oral	93.4%	Japanese MAFF test guidelines (1985) and U.S. Pesticide Assessment guidelines (1982); 14-day observation period; 41, 51, 64, 81 or 128 mg/kg bw; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	LD_{50} = 57 mg/kg bw	87/ISK093/626
Rat (males)	dermal	93.4%	Japanese MAFF test guidelines (1985) and U.S. Pesticide Assessment guidelines (1982); 14-day observation period; 1965, 2472, 3115 and 3918 mg/kg bw; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	LD_{50} = 2372 mg/kg bw	87/ISK094/627
Rat (females)	dermal	93.4%	Japanese MAFF test guidelines (1985) and U.S. Pesticide Assessment guidelines (1982); 14-day observation period; 309, 494, 779, 1236, 1557, 1965 and 2472 mg/kg bw; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	LD_{50} = 853 mg/kg bw	87/ISK094/627
Rat (males)	inhalation	92%	Japanese MAFF test guidelines (NohSan No. 4200, 59) and U.S. EPA pesticide assessment guidelines, subdivision F, series 81-3 (Nov. 1984); 14-day observation period; 0.53, 0.8, 0.9 and 1.23 mg/l; U.S. EPA (Nov. 1983) and Japanese (59 NohSan No.3850) principles of Good Laboratory Practice.	LC_{50} = 0.83 mg/l	D-1695E

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

Species	Test	Purity % Note[2]	Guideline, duration, doses and conditions	Result	Study number
Rat (females)	inhalation	92%	Japanese MAFF test guidelines (NohSan No. 4200, 59) and U.S. EPA pesticide assessment guidelines subdivision F. Series 81-3 (Nov. 1984); 14-day observation period; 0.53, 0.8, 0.9 and 1.23 mg/l; U.S. EPA (Nov. 1983) and Japanese (59 NohSan No.3850) principles of Good Laboratory Practice.	LC_{50} = 0.56 mg/l	D-1695E
Rabbit	skin irritation	93.4%	OECD guidelines for testing of chemicals, section 4, sub-section 404 (1981), Japanese MAFF test guidelines (1985) and U.S pesticide assessment guidelines (1982); 72-hour observation period; 0.5 ml on a gauze patch (3 cm x 2 cm); OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	Non-irritant	87/ISK107/834
Rabbit (males and females)	eye irritation	93.4%	OECD guidelines for testing of chemicals, section 4, sub-section 405 (1987), Japanese MAFF test guidelines (1985) and U.S pesticide assessment guidelines (1982); 7-day observation period; 0.1 ml into the conjunctival sac of the right eye; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	Non-irritating (but fosthiazate was toxic to the rabbit by the ocular route after 72 hours)	87/ISK097a/906
Rabbit (females)	eye irritation	93.4%	OECD guidelines for testing of chemicals, section 4, sub-section 405 (1987), Japanese MAFF test guidelines (1985) and U.S pesticide assessment guidelines (1982); 7-day observation period; 0.1 ml into the conjunctival sac of the right eye; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	Non-irritating with washing of the eyes within 3 minutes of exposure. Eye Irritation – Category 2A Irritating to eyes	87/ISK097b/907
Guinea pigs (males and females)	skin sensitisation	93.6%	OECD guidelines for testing of chemicals (1981), Japanese MAFF test guidelines (1985) and U.S pesticide assessment guidelines (1982); 24-day observation period; Magnusson and Kligmann maximisation method; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	Sensitising	88/ISK108/145

Table 2. Toxicology profile of the technical material based on repeated administration (subacute to chronic)

Species	Test	Purity % Note[3]	Guideline, duration, doses and conditions	Result	Study number
Rats (males and females)	Short-term, feeding	92.6%	Preliminary toxicity study; 4 weeks; 0.05, 0.10, 0.48, 0.97, 9.69 and 40.87 mg/kg bw/day in males and 0.05, 0.10, 0.5, 1.0, 10.7 and 43.5 mg/kg bw/day in females; OECD, EPA and Japanese principles of Good Laboratory Practice.	NOAEL: 0.97 or 1.0 mg/kg bw/day	86/ISK071/0284
Rats (males and females)	Short-term, feeding	93.3%	13 weeks; 0.08, 0.77, 4.12 and 36.4 mg/kg bw/day in males; 0.09, 0.9, 4.7 and 41.0 mg/kg bw/day in females; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	NOAEL: 0.8 or 0.9 mg/kg bw/day	87/ISK091/0373
Mouse (males and females)	Short-term, feeding	92.6%	Preliminary toxicity study; 4 weeks; 0.9, 3.5, 17.6, and 69.0 mg/kg bw/day in males; 0.97, 4.1, 21.4 and 82.4 mg/kg bw/day in females; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	NOAEL: 17.6 or 21.4 mg/kg bw/day	86/ISK070/307
Dogs (males and females)	Short-term, oral	92.5 - 93.5%	Preliminary toxicity study ; 28 days; 0.021, 0.11, 0.54, 5.4 or 26.8 mg/kg bw/day; OECD, DHSS and Japanese principles of Good Laboratory Practice.	NOAEL: 0.54 mg/kg bw/day (both sexes)	86/ISK072/0537
Dogs (males and females)	Short-term, oral	93.3% purity	13 weeks; 0.054, 0.11, 0.54, or 5.4 mg/kg bw/day; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	NOAEL: 0.54 mg/kg bw/day (both sexes)	87/ISK090/0219

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

Species	Test	Purity % Note[3]	Guideline, duration, doses and conditions	Result	Study number
Dogs (males and females)	Short-term, oral	93.8%	OECD guidelines for testing of chemicals (1983), Japanese MAFF test guidelines (59 Noshan No. 4200, 1985) and U.S pesticide assessment guidelines (1984); 12 months; 0.05, 0.1 or 0.5 or 5 mg/kg bw/day; Japanese principles of Good Laboratory Practice.	NOAEL: 0.5 mg/kg bw/day (both sexes)	230
Rats (males and females)	Sub-acute, dermal	95.5%	3 weeks; 0.5, 2.5, 25 or 250 mg/kg bw/day; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	NOAEL: 2.5 mg/kg bw/day	89/ISK111/0200
Rats (males and females)	Long-term, carcinogenicity, feeding	93.3%	EPA guidelines 83-1 and 83-2; 2 years; 0.042, 0.41, 2.08 and 8.94 mg/kg bw/day in males and 0.055, 0.54, 2.63 and 12.53 mg/kg bw/day in females; OECD, UK DH, EPA and Japanese principles of Good Laboratory Practice.	NOAEL: 0.42 or 0.55 mg/kg bw/day No carcinogenic potential	89/ISK089/0557
Mouse (males and females)	Long-term, carcinogenicity, feeding	93.3%	EPA guideline No 83-5; 2 years; 1.02, 3.1, 10.3 and 30.5 mg/kg bw/day in males and 1.11, 3.2, 10.4 and 39.17 mg/kg bw/day in females; OECD, UK DH, EPA and Japanese principles of Good Laboratory Practice.	NOAEL: 3.1 or 3.2 mg/kg bw/day No carcinogenic potential.	89/ISK088/0624
Rats (males and females)	Multigeneration, feeding	93.3%	EPA FIFRA guideline, subdivision F, No. 83-4; 2 successive generations; OECD, DH, EPA and Japanese principles of Good Laboratory Practice.	NOAEL: 0.7 mg/kg bw/day	89/ISK109/0923

Species	Test	Purity % Note[3]	Guideline, duration, doses and conditions	Result	Study number
Rats (females)	Developmental, oral	93.3%	EPA FIFRA guideline, subdivision F, No. 83-4; 3, 5 or 10 mg/kg bw/day; OECD, DH, EPA and Japanese principles of Good Laboratory Practice.	NOAEL: 5 mg/kg bw/day No teratogenic potential	90/ISK123/0068
Rabbit (females)	Developmental, oral	93.3%	EPA guideline No 83-3; 0.5, 1.0, 1.5 or 2.0 mg/kg bw/day; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	NOAEL: 1.5 mg/kg bw/day No teratogenic potential	89/ISK118/0694
Hens	Delayed neurotoxicity, oral	93.7%	OECD guidelines (1981), U.S. EPA guidelines (1982) and Japanese MAFF guidelines (1985); 5, 10, 20, 30 or 40 mg/kg bw/day; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	No delayed neurotoxicity caused	88/ISK104/044

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

Species	Test	Purity % Note[4]	Guideline, duration, doses and conditions	Result	Study number
Bacteria *(Salmonella typhimurium and Escherichia coli)*	reverse gene mutation, *in vitro*	93.8 %	EPA guidelines 84-2; 313, 625, 1250, 2500 and 5000 µg/plate; OECD, EPA and Japanese principles of Good Laboratory Practice.	No genotoxic potential	IET 89-0054
Mammalian cells (Chinese hamster lung cells)	chromosome aberration, *in vitro*	93.8%	EPA guidelines 84-2; 12.5, 25, 50, 100 or 200 µg/mL without metabolic activation and 46.9, 93.8, 187.5, 375 or 750 µg/mL with metabolic activation; OECD, EPA and Japanese principles of Good Laboratory Practice.	No clastogenic potential	IET 89-0055
Mammalian cells (mouse lymphoma cells)	gene mutation, *in vitro*	93.6%	EPA guidelines 84-2; 40, 80, 160, 320, 640 and 1280 µg/mL without metabolic activation and 0, 5, 10, 20, 40, 80 and 160 µg/mL with metabolic activation; OECD, UK DH, EPA and Japanese principles of Good	No genotoxic potential	92/ISK192/0841

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

Species	Test	Purity % Note[4]	Guideline, duration, doses and conditions	Result	Study number
			Laboratory Practice.		
Bacteria (*B. subtilis*)	DNA repair assay, *in vitro*	93.8%	EPA guidelines 84-2; 500, 1000, 2000, 5000, 10000 or 20000 µg/disk; OECD, EPA and Japanese principles of Good Laboratory Practice.	No genotoxic potential	IET 89-0056
Mouse (males and females)	micronucleus, *in vivo*	93.8%	Oral dosing; 50 mg/kg bw in the time-response test (72 hours) and 12.5, 25 or 50 mg/kg bw in the dose-response test; OECD, EPA and Japanese principles of Good Laboratory Practice.	No genotoxic potential	IET 90-0007

Table 4. Ecotoxicology profile of fosthiazate technical material

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
Mallard duck (*Anas platyrhynchos)*	Acute oral	91.3%	U.S. EPA guideline 71-1; 14 days; 2, 4, 7, 12, 19, 32 or 53 mg a.s./kg bodyweight; EPA principles of Good Laboratory Practice.	LD50: 20 mg/kg bw	3917-91-0239-TX-004
Bobwhite quail (*Colinus virginianus*)	Acute oral	91.3%	U.S. EPA guideline 71-1; 14 days; 0.5, 1, 3, 8, 12, 16 or 32 mg as/kg bodyweight; EPA principles of Good Laboratory Practice.	LD50: 10 mg/kg bw	3917-91-0240-TX-003
Mallard duck (*Anas platyrhynchos*)	5-day dietary	93.8%	U.S. EPA guideline 71-2; 160, 320, 640, 1280, 2560 and 5120 ppm in the diet; OECD, DHSS, EPA and Japanese principles of Good Laboratory Practice.	LC50: 237 ppm	ISK 35/891275
Mallard duck (*Anas platyrhynchos*)	5-day dietary	92.3%	U.S. EPA guideline 71-1; 80, 125, 200, 320, 500, 800 and 1000 ppm (phase 1), and 1250 and 1600 ppm (phase 2) in the diet; EPA principles of Good Laboratory Practice.	LC50: >1600 ppm Significant reduction in food consumption considered to have resulted in an artificial LC50 value.	3917-91-0241-TX-003

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

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
Bobwhite quail (*Colinus virginianus*)	5-day dietary	92.3%	U.S. EPA guideline 71-1; 50, 80, 125, 200 and 320 ppm (phase 1), and 12.5 and 25 ppm (phase 2) in the diet; EPA principles of Good Laboratory Practice.	LC50: 139 ppm	3917-91-0242-TX-003
Mallard duck (*Anas platyrhynchos*)	Long-term, reproductive, feeding	92.1%	U.S. EPA guideline 71-4; 19 weeks; 10, 25 and 50 ppm in the diet; EPA principles of Good Laboratory Practice.	NOEC: 10 ppm	3922-91-0258-TX-003
Bobwhite quail (*Colinus virginianus*)	Long-term, reproductive, feeding	92.1%	U.S. EPA guideline 71-4; 19 weeks; 10, 25 and 50 ppm in the diet; EPA principles of Good Laboratory Practice.	NOEC: <10 ppm	3922-91-0259-TX-003
Rainbow trout (*Salmo gairdneri*)	Acute, static	93.5%	U.S. EPA guideline 72-1, OECD guideline No 203; 96 hours; 1.0, 1.8, 3.2, 5.6 and 10 mg/l; OECD, UK DH and EPA principles of Good Laboratory Practice.	LC_{50}: 7.1 mg/l	203/9

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
Rainbow trout	Acute, static	93.5%	U.S. EPA guideline 72-1; 96 hours; 25.9, 43.2, 72, 120 and 200 mg/l; OECD, UK DH, EPA and Japanese principles of Good Laboratory Practice.	LC_{50}: 114 mg/l	91/ISK177/0015
Bluegill Sunfish (*Lepomis macrochirus*)	Acute, static	93.5%	U.S. EPA guideline 72-1, OECD guideline No 203; 96 hours; 1.0, 1.8, 3.2, 5.6, 10 mg/l; OECD, UK DH and EPA principles of Good Laboratory Practice.	LC_{50}: 6.7 mg/l	203/10
Bluegill Sunfish (*Lepomis macrochirus*)	Acute, static	93.5%	U.S. EPA guideline 72-1; 96 hours; 45.1, 69.1, 115.2, 192 and 320 mg/l; OECD, UK DH, EPA and Japanese principles of Good Laboratory Practice.	LC_{50}: 171 mg/l	91/ISK178/0016
Waterflea (*Daphnia magna*)	Acute, static	93.5%	U.S. EPA guideline 72-2; 48 hours; 39, 65, 108, 180, 300 and 500 µg/l; OECD, UK DH, EPA and Japanese principles of Good Laboratory Practice.	LC_{50}: 0.282 mg/l	91/ISK179/0017

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
Green alga (Pseudokirchneriella subcapitanum)	Acute, static	93.6%	U.S. EPA guideline 122-2; 5 days; 5.10 mg/l; EPA principles of Good Laboratory Practice.	NOEC: >4.51 mg/l Single concentration tested.	16-01-1
Waterflea (*Daphnia magna*)	Chronic toxicity, semi-static	93.8%	OECD guideline No 202; 21 days; 5.5, 12, 27, 60 and 132 µg/l; OECD and EPA principles of Good Laboratory Practice.	NOEC: 0.060 mg/l	123468
Honey bee (*Apis mellifera*)	Acute contact	92.2%	U.S. FIFRA subdivision L, series 141-1; 48 hours; 0.0195, 0.039, 0.078, 0.156, 0.313 and 0.625 µg/bee; EPA principles of Good Laboratory Practice.	LD50: 0.256 µg/bee	272-101B
Honey bee (*Apis mellifera*)	Acute, oral and contact	94.3%	U.S. FIFRA subdivision L, series 141-1; 48 hours; 0.625, 0.125, 0.25, 0.50 and 1.0 µg/bee (oral route) and 0.25, 0.50, 1.0, 2.0, 4.0 and 8.0 µg/bee (contact route); EPA and Japanese principles of Good Laboratory Practice.	LD50: 0.61 µg/bee (oral) LD50: 0.75 µg/bee (contact)	6137-95-0179-TX-002

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
Carabid beetle (*Poecilus cupreus*)	Laboratory test	93.4%	BBA guideline part VI, No 23-2.1.8 (June 1991) and IOBC/WPRS (1992); 14 days; 4 kg/ha; OECD and German principles of Good Laboratory Practice.	3.4% adjusted mortality	1101007
Spiders (*Pardosa amentata* and *Pardosa palustris*)	Laboratory test	93.4%	BBA draft guideline (1994); 14 days; 4 kg/ha; OECD and German principles of Good Laboratory Practice.	5.3% adjusted mortality	1102065
Earthworm (*Eisenia foetida)*	Acute toxicity	93.4%	OECD guideline No 207, section 2; 14 days; 6.25, 12.5, 25, 50, 100, 125, 250, 500 and 1000 mg/kg dry soil; OECD and Swiss principles of Good Laboratory Practice.	LC50: 209 mg/kg dry soil NOEC: 100 mg/kg dry soil	323706
Soil micro-organisms	Nitrogen mineralization	93.4%	BBA Guideline VI 1-1 (1990); 60 days; 53 mg/kg dry soil; OECD and Swiss principles of Good Laboratory Practice.	< 25% effect	301184

Background information on toxicology/ecotoxicology

Fosthiazate has previously not been evaluated by the FAO/WHO JMPR and WHO/IPCS. It was evaluated by the European Commission in 2003. The EU classification is: harmful in contact with skin (R21), toxic if swallowed (R25), toxic by inhalation (R23) and may cause sensitisation by skin contact (R43) it has no genotoxic or carcinogenic potential. The environmental classification is: Dangerous for the environment (N), Very toxic to aquatic organisms (R50). May cause long-term adverse effects in the aquatic environment (R53).

The classification and labelling of fosthiazate in accordance with the Regulation (EC) No 1272/2008 as amended is presented below:

Symbol	Code GHS	Respective H-Statement
	06	H 301, H 331
	07	H 317, H 312
	09	H 410, (H 400 needs to applied only for classification)

The classification and labelling of Nemathorin 10G in accordance with the Regulation (EC) No 1272/2008 as amended is presented below:

Symbol	Code GHS	Respective H-Statement
	06	H 301
	09	H 411

ANNEX 2

REFERENCES

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
	FAO/WHO	2006	Manual on development and use of FAO and WHO specifications for pesticides. February 2006 Revision of First Edition. FAO Plant Production and Protection Paper.
4039-89-0301-AS-002		1990	IKI-1145 – Determination of Vapour Pressure
4039-95-0202-AS-001		1995	Fosthiazate -Freezing/Solidification Point, Boiling Point, Physical State, Colour, Odour, Autoflammability, Surface Tension
4039-92-0100-AS-001		1993	IKI-1145 - Solubility
4039-92-0099-AS-001		1993	IKI-1145 - Octanol/Water Partition Coefficient
1145-89-16101-1/I-221		1989	IKI-1145: Hydrolysis in Buffer Solutions at pH 5, 7 and 9
5287-92-0153-EF-001		1993	A Photolysis Study of Fosthiazate (IKI-1145) in Water at pH 5
4039-91-0392-AS-001		1992	IKI-1145 - Dissociation Constant
4039-92-0100-AS-001		1993	IKI-1145 - Solubility
891005YI		1989	IKI-1145 (TGAI) - Determination of Miscibility
87/ISK093/626		1989	IKI-1145 Technical: Acute Oral Toxicity Study in the Rat. GLP, unpublished.
87/ISK094/627		1989	IKI-1145 Technical: Acute Percutaneous Toxicity Study in the Rat. GLP, unpublished
D-1695E		1989	Acute Inhalation Toxicity Test of IKI-1145 Technical in Rats GLP, unpublished
87/ISK107/834		1989	IKI-1145 Technical: Primary Dermal Irritation Study in the Rabbit. GLP, unpublished
87/ISK097a/906		1989	IKI-1145 Technical: Primary Eye Irritation Study in the Rabbit. GLP, unpublished.
87/ISK097b/907		1989	IKI-1145 Technical: Primary Eye Irritation Study in the Rabbit (Eye Washing Study). GLP, unpublished.
88/ISK108/145		1991	IKI-1145 Technical: Dermal Sensitization Study in Guinea Pigs. GLP, unpublished.
86/ISK071/0284		1989	IKI-1145 Technical (Fosthiazate): Preliminary Toxicity Study in Dietary Administration to CD Rats for Four Weeks. GLP, unpublished.

87/ISK091/0373	1989	IKI-1145 Technical: Toxicity Study by Dietary Administration to CD Rats for 13 Weeks Followed by a 10 Week Reversibility Period. GLP, unpublished
86/ISK070/307	1989	IKI-1145 Technical: Preliminary Toxicity Study by Dietary Administration to CD-1 Mice for Four Weeks. GLP, unpublished.
86/ISK072/0537	1989	IKI-1145: Preliminary Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for Four Weeks. GLP, unpublished.
87/ISK090/0219	1989	IKI-1145 Technical: Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for 13 Weeks. GLP, unpublished.
230	1991	Chronic Oral Toxicity Study on the Dog Treated with IKI-1145 Technical for 12 Months. GLP, unpublished.
89/ISK111/0200	1989	IKI-1145 Technical: Twenty-one Day Dermal Toxicity Study in Rats. GLP, unpublished.
89/ISK089/0557	1990	IKI-1145: Combined Chronic Toxicity and Carcinogenicity Study by Dietary Administration to CD Rats for 104 Weeks (Final Report). GLP, unpublished.
89/ISK088/0624	1990	IKI-1145: Carcinogenicity Study by Dietary Administration to CD-1 Mice for up to 104 Weeks. GLP, unpublished.
89/ISK109/0923	1990	IKI-1145: Reproductive Performance Study in Rats Treated Continuously Through Two Successive Generations - Final Report. GLP, unpublished.
90/ISK123/0068	1990	IKI-1145: Teratology Study in the Rat. GLP, unpublished.
89/ISK118/0694	1989	IKI-1145: Teratology Study in the Rabbit. GLP, unpublished. GLP, unpublished.
88/ISK104/044	1989	IKI-1145 Technical: Acute Delayed Neurotoxicity Study in the Hen. GLP, unpublished.
IET 89-0054	1989	IKI-1145 Technical: Reverse Mutation Test. GLP, unpublished.
IET 89-0055	1989	IKI-1145 Technical: *In Vitro* Cytogenetics Test. GLP, unpublished.
92/ISK192/0841	1993	IKI-1145 Technical: Investigation of Mutagenic Activity in the TK +/- Mouse Lymphoma Cell Mutation System.
IET 89-0056	1989	IKI-1145 Technical: DNA Repair Test (Rec-Assay) GLP, unpublished.
IET 90-0007	1990	IKI-1145 Technical: Micronucleus Test in Mice. GLP, unpublished.
3917-91-0239-TX-004	1992	Acute Oral Toxicity (LD_{50}) Study in Mallard Ducks with IKI-1145.
3917-91-0240-TX-003	1992	Acute Oral Toxicity (LD_{50}) Study in Bobwhite Quail with IKI-1145.
ISK 35/891275	1989	The Dietary Toxicity (LC_{50}) of IKI-1145 Technical to the Mallard Duck.
3917-91-0241-TX-003	1992	Dietary (LC_{50}) Study in Mallard Ducks with IKI-1145.

3917-91-0241-TX-003	1992	Dietary (LC_{50}) Study in Bobwhite Quail with IKI-1145.
3922-91-0258-TX-003	1995	A Reproduction Study in Mallard Ducks with IKI-1145
3922-91-0259-TX003	1995	A Reproduction Study in Bobwhite Quail with IKI-1145
203/9	1989	IKI-1145 TGAI: An Acute Toxicity to Rainbow Trout (*Salmo gairdneri*).
91/ISK177/0015	1991	IKI-1145 Technical: Acute Toxicity to Rainbow Trout.
203/10	1989	IKI-1145 TGAI: Acute Toxicity to Bluegill Sunfish (*Lepomis macrochirus*).
91/ISK178/0016	1991	IKI-1145 Technical: Acute Toxicity to Bluegill Sunfish.
91/ISK179/0017	1991	IKI-1145 Technical: Acute Toxicity to *Daphnia magna*.
16-01-1	1995	The Toxicity of IKI-1145 to *Selenastrum capricornutum*
123468	1994	*Daphnia magna*, Reproduction Test with IKI-1145 Technical
272-101B	1989	IKI-1145 Technical: An Acute Contact Toxicity Study with the Honey Bee.
6137-95-0179-TX-002	1995	Technical Fosthiazate: Acute Toxicity to Honey Bees (*Apis mellifera*).
1101007	1995	Effects of IKI-1145 Technical on the Carabid Beetle *Poecilus cupreus L.* (Coleoptera, Carabidae) in the Laboratory.
1102065	1995	Effects of IKI-1145 Technical on Spiders *Pardosa* spec. (Araneae, Lycosidae) in Laboratory.
323706	1992	Acute Toxicity (LC_{50}) Study of IKI-1145 Technical to Earthworms.
301184	1992	The Effects of IKI-1145 Technical on Soil Respiration and Nitrification.