Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

THIAMETHOXAM

(EZ)-3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine

2021

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THIAMETHOXAM

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 that 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 1999 onward, the development of FAO specifications follows the **New Procedure**, described first in the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products" and later in the 1st edition of “Manual for Development and Use of FAO and WHO Specifications for Pesticides” (2002) - currently available as 3rd revision of the 1st edition (2016) - , 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 JMPM, rather than the JMPS.]

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently from the year 1999 onwards the publication of FAO specifications under the **New Procedure** has changed. Every specification consists now of two parts namely the specifications and the evaluation report(s):

Part One: **The Specification** of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the “Manual on development and use of FAO and WHO specifications for pesticides”.

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

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

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

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PART ONE

SPECIFICATIONS

THIAMETHOXAM

INFORMATION

ISO common name

Thiamethoxam (ISO 1750 approved)

Synonyms

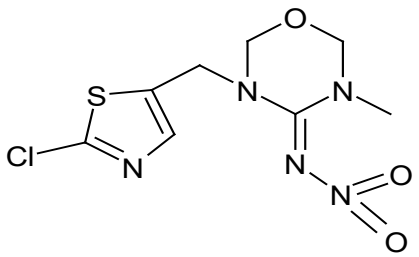
None

Chemical names

IUPAC (*EZ*)-3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine

CA 3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-*N*-nitro-4*H*-1,3,5-oxadiazin-4-imine

Structural formula



Molecular formula

$C_8H_{10}ClN_5O_3S$

Relative molecular mass

291.7 g/mol

CAS Registry number

153719-23-4

CIPAC number

637

Identity tests

IR spectroscopy for TC, retention time in reverse phase HPLC (TC, formulations).

THIAMETHOXAM TECHNICAL MATERIAL

FAO Specification 637 / TC (March 2021)

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 (637/2012 & 637/2020). 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 (637/2012 & 637/2020), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of thiamethoxam together with related manufacturing impurities, in the form of white to beige granular powder, and shall be free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (CIPAC 637/TC/M/2, CIPAC Handbook O, p. 148, 2017)

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

2.2 **Thiamethoxam content** (CIPAC 637/TC/M/3, CIPAC Handbook O, p. 149, 2017)

The thiamethoxam content shall be declared (not less than 980 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

THIAMETHOXAM WATER DISPERSIBLE GRANULES

FAO Specification 637 / WG (March 2021)

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 (637/2012 & 637/2020). It should be applicable to WG produced by this manufacturer 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 WG produced by other manufacturers. The evaluation report (637/2012 & 637/2020), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of a homogeneous mixture of technical thiamethoxam, complying with the requirements of the FAO specification 637/TC (March 2021), together with carriers and any other necessary formulants. It shall be in the form of granules for application after disintegration and dispersion in water. The formulation shall be dry, free-flowing, essentially non-dusty, and free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 **Identity tests** (CIPAC 637/TC/M/2, CIPAC Handbook O, p. 148, 2017)

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

2.2 **Thiamethoxam content** (CIPAC 637/TC/M/2, CIPAC Handbook O, p. 152, 2017)

The thiamethoxam 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 table of tolerances.

Declared content in g/kg	Tolerance
Above 100 up to 250	± 6% of declared content
Note In each range the upper limit is included	

3 Physical properties

3.1 **Wettability** (MT 53.3, CIPAC Handbook F, p. 164, 1995)

The formulation shall be completely wetted in 40 seconds in CIPAC water D.

3.2 **Wet sieve test** (MT 185, CIPAC Handbook K, p. 149, 2003)

Maximum: 0.5% retained on a 75 µm test sieve.

3.3 **Degree of dispersion** (MT 174, CIPAC Handbook F, p. 435, 1995)

Dispersibility: minimum 60% after 1 minute of stirring.

3.4 **Suspensibility** (MT 184.1, CIPAC Handbook P, p. 245, 2021) (Notes 1 & 2)

A minimum of 80% shall be in suspension after 30 min in CIPAC Standard Water D at 25 ± 5°C.

3.5 **Persistent foam** (MT 47.3, Handbook O, p. 177, 2017) (Note 3)

Maximum: 60 ml after 1 minute in Standard CIPAC water D.

3.6 **Dustiness** (MT 171.1, CIPAC Handbook P, p. 235, 2021) (Note 4)

Essentially non-dusty.

3.7 **Flowability** (MT 172.2, CIPAC Handbook P, p. 241, 2021)

At least 99% of the formulation shall pass through a 5 mm test sieve after 20 drops of the sieve

3.8 **Attrition resistance** (MT 178.2, CIPAC Handbook K, p. 140, 2003)

Minimum: 90% attrition resistance.

4 **Storage stability**

4.1 **Stability at elevated temperature** (MT 46.4, CIPAC Handbook P, p. 232, 2021)

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower that 95% relative to the determined average content found before storage (Note 7) and the formulation shall continue to comply with the clauses for:

- wet sieve test (3.2)
- degree of dispersion (3.3)
- suspensibility (3.4)
- dustiness (3.6)
- attrition resistance (3.8)

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Note 1 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in method MT 184.

Note 2 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However the simpler gravimetric method may be used on a routine basis provided that it has been shown to give equal results to those of the chemical assay. Occasionally discrepancies can occur with gravimetric methods therefore, in case of dispute, chemical assay shall be the "referee method".

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

Note 4 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 submethod of MT 171.2, usually shows good correlation with the gravimetric submethod, 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 5 Analysis of the formulation, before and after the storage stability test, may be carried out concurrently (i.e. after storage) to reduce analytical error.

THIAMETHOXAM SUSPENSION CONCENTRATE

FAO Specification 637 / SC (March 2021)

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 (637/2012). It should be applicable to SC produced by this manufacturer 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 SC produced by other manufacturers. The evaluation report (637/2012), as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of a suspension of fine particles of technical thiamethoxam, complying with the requirements of FAO specification 637/TC (March 2021), in the form of a beige to brown liquid, consisting of an aqueous phase together with suitable formulants. After gentle agitation the material shall be homogeneous (Note 1) and suitable for further dilution in water.

2 Active ingredient

2.1 **Identity tests** (637/SC/M/2, CIPAC Handbook O, p. 148, 2017)

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

2.2 **Thiamethoxam content** (637/SC/M/2, CIPAC Handbook O, p. 148, 2017)

The thiamethoxam content shall be declared (g/kg or g/l at 20 ± 2ºC, Note 2) and, when determined, the average content measured shall not differ from that declared by more than the appropriate tolerance, given in the table of tolerances.

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

3 Physical properties

3.1 **pH range** (MT 75.3, CIPAC Handbook J, p. 131, 2000),

pH range: 4 to 8

3.2 **Pourability** (MT 148.1, CIPAC Handbook J, p. 133, 2000)

Maximum "residue": 5%.

3.3 **Spontaneity of dispersion** (MT 160, CIPAC Handbook F, p. 391, 1995) (Notes 3 & 4)

A minimum of 70% shall be in suspension after 5 min in CIPAC Standard Water D at 30 ± 2°C.

3.4 **Suspensibility** (MT 184.1, CIPAC Handbook P, p. 245, 2021) (Note 4)

A minimum of 80% of the thiamethoxam content found in section 2.2 shall be in suspension after 30 min in CIPAC Standard Water D at 25 ± 2°C.

3.5 **Wet sieve test** (MT 185, CIPAC Handbook K, p. 149, 2001) (Note 5)

Maximum: 0.5% of the formulation shall be retained on a 75 µm test sieve.

3.6 **Persistent foam** (MT 47.3, Handbook O, p. 177, 2017) (Note 6)

Maximum: 30 ml after 1 min.

4 Storage stability

4.1 **Stability at 0°C** (MT 39.3, CIPAC Handbook J, p. 128, 2000)

After storage at 0 ± 2°C for 7 days, the formulation shall continue to comply with clauses for:
- suspensibility (3.4),
- wet sieve test (3.5)

4.2 **Stability at elevated temperature** (MT 46.4, CIPAC Handbook P, p. 232, 2021)

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 7) and the formulation shall continue to comply with the clauses for:
- pH range (3.1),
- pourability (3.2),
- spontaneity of dispersion (3.3),
- suspensibility (3.4),
- wet sieve test (3.5)

Note 1 Before sampling to verify the formulation quality, inspect the commercial container carefully. On standing, suspension concentrates usually develop a concentration gradient from the top to the bottom of the container. This may even result in the appearance of a clear liquid on the top and/or of sediment on the bottom. Therefore, before sampling, homogenize the formulation according to the instructions given by the manufacturer or, in the absence of such instructions, by gentle shaking of the commercial container (for example by inverting the closed container several times). Large containers must be opened and stirred adequately. After this procedure, the container should not contain a sticky layer of non-dispersed matter at the bottom. A suitable and simple method of checking for a non-dispersed sticky layer "cake" is by probing with a glass rod or similar device adapted to the size and shape of the container. All the physical and chemical tests must be carried out on a laboratory sample taken after the recommended homogenization procedure.

Note 2 Unless homogenization is carried out carefully, it is possible for the sample to become aerated. This can lead to errors in the determination of the mass per millilitre and in calculation of the active ingredient content (in g/l) if methods other than MT 3.3 are used. If the buyer requires both g/kg and g/l at 20°C, then in case of dispute the analytical results shall be calculated as g/kg.

Note 3 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However the simpler gravimetric method may be used on a routine basis provided that it has been shown to give equal results to those of the chemical assay method. Occasionally discrepancies can occur with gravimetric methods therefore, in case of dispute, chemical assay shall be the "referee method".

Note 4 The test is done gravimetrically.

Note 5 This test detects coarse particles (e.g. caused by crystal growth) or agglomerates (crust formation) or extraneous materials which could cause blockage of spray nozzles or filters in the spray tank.

Note 6 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 7 Samples of the formulation taken before and after the storage stability test may be analyzed concurrently after the test in order to reduce the analytical error.

THIAMETHOXAM SUSPENSION CONCENTRATE FOR SEED TREATMENT

FAO Specification 637 / FS (March 2021)

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 (637/2012 & 637/2020). It should be applicable to FS produced by this manufacturer 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 FS produced by other manufacturers. The evaluation report (637/2012 & 637/2020), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of a suspension of fine particles of technical thiamethoxam, complying with the requirements of FAO specification 637/TC (March 2021), in the form of a liquid in an aqueous phase together with suitable formulants, including colouring matter (Note 1). After gentle stirring or shaking, the material shall be homogeneous and suitable for further dilution with water if necessary (Note 2).

2 Active ingredient

2.1 Identity tests (637/SC/M/2, CIPAC Handbook O, p. 148, 2017)

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

2.2 Thiamethoxam content (637/SC/M/2, CIPAC Handbook O, p. 148, 2017)

The thiamethoxam content shall be declared (g/kg or g/l at 20 ± 2ºC, Note 3) and, when determined, the average content measured shall not differ from that declared by more than the appropriate tolerance, given in the table of tolerances.

Declared content in g/kg or g/l at 20 ± 2ºC	Tolerance
Above 250 up to 500	± 5% of declared content
Above 500	± 25g/kg or g/L
Note In each range the upper limit is included	

3 Physical properties

3.1 pH range (MT 75.3, CIPAC Handbook J, p. 131, 2000)

pH range: 4 to 8

3.2 Pourability (MT 148.1, CIPAC Handbook J, p. 133, 2000)

Maximum "residue": 5%

3.3 **Wet sieve test** (MT 185, CIPAC Handbook K, p. 149, 2003) (Note 4)

Maximum: 0.5% retained on a 75µm test sieve.

3.4 **Adhesion to seeds** (MT 194, CIPAC Handbook N, p. 145, 2011)

Minimum percentage of thiamethoxam remaining on *wheat* seeds after the test: 95%
Minimum percentage of thiamethoxam remaining on *maize* seeds after the test: 95%

4 Storage stability

4.1 **Stability at 0°C** (MT 39.3, CIPAC Handbook J, p. 128, 2000)

After storage at 0 ± 2°C for 7 days, the formulation shall continue to comply with the clause for:
- wet sieve test (3.3).

4.2 **Stability at elevated temperature** (MT 46.4, CIPAC Handbook P, p. 232, 2021)

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 5) and the formulation shall continue to comply with the clauses for:
- pH range (3.1),
- pourability (3.2),
- wet sieve test (3.3),
- adhesion to seeds (3.4)

Note 1 The influence of treatment on germination is of major importance but it is not the subject of a specification clause because no test method is applicable to all types of seeds. To avoid adverse effects, users should apply the formulation strictly according to the recommendations of the manufacturer and should not treat seeds for which effect on germination is not known. Treated seeds should be stored in a suitable container and should be protected from excessive temperature and moisture. The formulation shall contain a dye or pigment that permanently colours the seed after treatment (red is recommended). In some countries, there may be a legal requirement that a specific colour shall be used. The same colour must not be used for denaturing seeds intended for use as livestock feeding stuffs.

Note 2 Before sampling to verify the formulation quality, inspect the commercial container carefully. On standing, suspension concentrates usually develop a concentration gradient from the top to the bottom of the container. This may even result in the appearance of a clear liquid on the top and/or sediment on the bottom. Therefore, before sampling, homogenize the formulation according to the instructions given by the manufacturer or, in the absence of such instructions, gently shake the commercial container (for example by inverting the closed container several times, large containers must be opened and stirred adequately). After this procedure, the container should not contain a sticky layer of non-dispersed matter at the bottom. A suitable and simple method of checking for a non-dispersed sticky layer ("cake") is by probing with a glass rod or similar device adapted to the size and shape of the container. All the physical and chemical tests must be carried out on a laboratory sample taken after the recommended homogenization procedure.

Note 3 Unless homogenization is carried out carefully, it is possible for the sample to become aerated. This can lead to errors in the determination of the mass per millilitre, and in calculation of the active ingredient content (in g/l) if methods other than MT 3.3 are used. If the buyer requires both g/kg and g/l at 20°C, then in case of dispute the analytical results shall be calculated as g/kg.

Note 4 This test should detect coarse particles (e.g. caused by crystal growth) or extraneous materials which could cause blockage of spray nozzles or filters of the application equipment.

Note 5 Samples of the formulation taken before and after the storage stability test may be analyzed concurrently after the test in order to reduce the analytical error.

PART TWO

EVALUATION REPORTS

THIAMETHOXAM

FAO/WHO EVALUATION REPORT 637/2020

Recommendations

The Meeting recommended the following:

i) The thiamethoxam TC, WG and FS produced by Rotam Agrochemical Co., Ltd. and Jiangsu Rotam Chemistry Co., Ltd. should be accepted as equivalent to the thiamethoxam reference profile
ii) The FAO specifications for thiamethoxam TC should be extended to the material produced by Rotam Agrochemical Co., Ltd.
iii) The FAO specifications for thiamethoxam WG and FS should be extended to the materials produced by Jiangsu Rotam Chemistry Co., Ltd.

Appraisal

The Meeting considered data and supporting information submitted in October 2017 by Rotam Agrochemical Co., Ltd. (Rotam) for the determination of the equivalence for thiamethoxam TC (FAO specification 637/TC), and by Jiangsu Rotam Chemistry Co., Ltd for extension of the existing FAO specifications for WG and FS (FAO specifications 637/TC, -WG and FS (all 2014)). The data submitted were broadly in accordance with the requirements of the Manual on Development and Use of FAO and WHO specifications for Pesticides (March 2016 - 3rd revision of the 1st Edition) and supported the draft specifications.

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on all impurities present at or above 1 g/kg, as well as any relevant impurities below 1 g/kg, and their manufacturing limits in the TC. Mass balances ranged from 99.09 to 99.72 % in the 5-batch data. The maximum limits for the impurities were supported by the 5-batch data and statistically justified. The proposer declared the minimum purity of the thiamethoxam TC as 980 g/kg which is statistically justified (mean value - 3 times the standard deviation = 980/kg) and complies with the existing TC specifications (not less than 980g/kg).

The manufacturing process, impurity profile and five batch analyses were compared with the data submitted in the reference profile. Rotam utilizes a similar synthetic route as that of the reference product. However, the impurity profile was found to differ from the reference source with four impurities not present in the reference profile. The Meeting concluded that the assessment of equivalence could not be decided on Tier-1 and the potential effects of the presence of the new impurities had to be taken into account (Tier-2).

An *in-vivo* mutagenicity study (Ames test) for thiamethoxam TC has been conducted as Tier-1 data. Thiamethoxam TC produced by Rotam does not show mutagenicity in this *in vitro* bacterial assay (OECD 471).

When the structure of one of the new impurities was screened in (Q)SAR models, a a potential for skin sensitization was indicated. Thus the Meeting requested Rotam to carry out a study on skin sensitization. However, when evaluated the study protocol had some deviations from the OECD test guideline 406. The main deviation observed was the chosen concentration for injection “3” which is not the correct concentration that imply the exposure is not maximized. The Meeting concluded that the study cannot be considered as valid and as a new skin sensitization has to be submitted.

A new skin sensitization test was provided by Rotam. The new test shows that thiametoxam TC had no skin sensitization potential in Albino Dunkin Hartley guinea pigs. The Meeting concluded that the data were acceptable.

An acute oral toxicity in rats was provided for Tier-2 assessment. The results of the study allowed the conclusion that neither clinical signs nor deaths occurred at a dose, which is both higher than the LD_{50} determined in the acute oral toxicity study carried out with the reference TC produced by Syngenta and the dose in the acute neurotoxicity study at which deaths and clinical signs occurred (studies evaluated by JMPR). The meeting requested to Rotam to justify these results.

Rotam responded that the design of the OECD test guideline 423 is to estimate the approximate LD_{50} of a test item but not to provide precise LD_{50} value. Moreover, the LD_{50} value may vary depend upon many factors which impact the LD_{50}. The Meeting agreed that the proposer’s justification was sufficient.

An i*n vivo* mouse micronucleus test according to OECD test guideline 474 (1997) was also submitted. The doses applied to the mice in the micronucleus assay exceeded the LD_{50} reported by JMPR in mice without producing any deaths. Since exposure of the target tissue, the bone marrow, was not proven, the negative outcome is not validated. However, as the in vivo micronucleus test is not a data requirement for Tier-2 equivalence determination, the Meeting decided not to investigate the point further

In conclusion the Tier-2 assessment does not show an increase in hazard for thiamethoxam produced by Rotam.

The Meeting also noted that an in-house-method using HPLC-UV (254 nm) with external standardization for the determination of the active ingredient content in thiamethoxam TC (Ref. 0851) had been used but not the CIPAC method. The method was properly validated according to EU SANCO/3030/99 rev.4 guideline. The Meeting requested Rotam to provide a bridging study for comparison of the results of the in-house method with the results produced by the published CIPAC method. The results showed, that the results of both method agreed well and the data were therefore considered acceptable. The determination of impurities was achieved using an HPLC-UV (250 nm) method. This method was properly validated. The content of residual water was determined using the CIPAC method MT 30.1 (Karl Fischer titration).

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, CIPAC, EEC and OPPTS where appropriate.

The confirmation of the structural identity of thiamethoxam and the impurities was achieved using LC-MS, FT-IR and NMR (^{13}C-NMR and ^{1}H-NMR spectrometer).

The Meeting was provided with data on melting point, vapour pressure, solubility in water and octanol/water partition coefficient. The melting range is in good agreement with the reference material. (139.1 °C (Syngenta) vs. 139.2-140 °C (Rotam)).

The Meeting concluded that Rotam's thiamethoxam TC was equivalent to the thiamethoxam reference TC based on a Tier-2 evaluation. Therefore, the Meeting recommended the extension the existing FAO specification for thiamethoxam TC to the material produced by Rotam.

Rotam was requested to provide further data concerning the FS formulation and its adhesion to seeds (maize and wheat) after accelerated storage (14 days at 54°C). The data was provided and showed, that Rotam's FS complied with the "adhesion to seeds" clause and limits in the reference specification. In addition, Rotam confirmed that the methods used in the adhesion to seeds tests and to determine the thiamethoxam content in the WG and FS formulations before and after the accelerated storage test were CIPAC methods.

A suitable data package on the physical-chemical and storage stability properties of Rotam's WG and FS formulations had been submitted and demonstrated, that these formulations compy with all clauses of the published thiamethoxam specifications for these formulations. The Meeting therefore concluded that the FAO specifications for thiamethoxam WG and FS can be extended to the corresponding fomulations produced by Rotam.

In addition, the Meeting recommended to editorially update the published specifications for TC, WG, SC and FS by referring to the analytical methods now published in Handbook M and revised MT methods that are deemed to lead to equivalent results. These methods include i.a. the method for dustiness (MT 171.1) for the WG, the suspensibility method (MT 184.1) and the harmonized method for accelerated storage, MT 46.4, all now published in Handbook P. The FS specification was revised to reflect the updated specification guidelines published in the Manual (March 2016 - 3rd revision of the 1st Edition). Some of the MT methods - in particular the persistent foam method, MT 47.3 and suspensibilty, MT 184.1 - have concentration limits of approx. 10 % w/v and are not applicable for formulations that are applied undiluted or little diluted. The FS is diluted before use, but as the dilution rates of the FS range between 15 and 75 % w/v (see evaluation report 636/2012) and hence exceed the upper concentration limits of MT 47.3 and MT 184.1, the clauses for persistent foam and suspensibility were removed.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 637/2020

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

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 99.09 – 99.7 %
Declared minimum [a.i.] content	980 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 of the TC	139.2-140ºC	98.8%	OECD 102	Study No: 0823

FORMULATIONS AND CO-FORMULATED ACTIVE INGREDIENTS

The main formulation types available are WG, FS and SC. These formulations are registered and sold in many countries throughout the world. Thiamethoxam may be co-formulated with other insecticides and fungicides especially when manufacturing FS formulations.

METHODS OF ANALYSIS AND TESTING

Rotam used an in-house method that can be considered identical to the CIPAC method 637/TC/M (HPLC-UV method with external standardization) for the determination of the active ingredient content in thiamethoxam TC. The validation data (specificity, linearity of response, linearity range, precision and accuracy in one laboratory) were provided. The method is validated according to the EU SANCO/3030/99 rev.4 guideline

The determination of impurities was achieved using the HPLC-UV method. The method is validated with respect to specificity, linearity of response, precision, accuracy and limit of quantification for impurities according to the EU SANCO/3030/99 rev.4 guideline.

Test methods for determination of physico-chemical properties of the technical active in-gredient were OECD, CIPAC, EU and OPPTS.

PHYSICAL PROPERTIES

The physical properties, the methods for testing them, and the limits proposed for the WG and FS formulation comply with the requirement described in the existing FAO specifications for thiamethoxam WG and FS (637/WG and 637/FS, 2014)

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The active ingredient is expressed as thiamethoxam.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

(i) The proposer confirmed that the toxicological data included in the summary below were derived from thiamethoxam 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 2. Toxicology profile of thiamethoxam technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Purity % Note[2]	Guideline, duration, doses and conditions	Result	Study number
Rat (f)	Acute Oral	98.9	Guideline: OECD No.423 (2001); OPPTS 870.1100 (2002); EC 96/54 No L248, B1, Tris, 1996, 14d observation period; dose levels: 300, 2000 mg/kg bw.	LD_{50} > Cut-off Value 5000 mg/kg bw	2944
Rat (m,f)	Acute Dermal	98.9	Guideline: OECD No.402 (1987), OPPTS 870.1200, EEC directive 92/69 No L383, B3, Tris ; 14d observation period; limit dose: 2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	2945
Rat (m,f)	Acute Inhalation	98.9	Guideline: OECD No.403 (2009); OPPTS 870.1300; EEC directive 93/21 No L110, B2 tris(1993); 4h exposure (nose only), 14d observation period; nominal concentration: 5.62 mg/L, actual concentration: 2.49 mg/L	LC_{50} 4h > 2.49 mg/L	2949
Rabbit (f)	Skin irritation	98.9	Guideline: EC directive 92/69 No L383, B4 tris (1992). OECD 404 (2002). OPPTS 870.2500 (1998); Observations: 1-72 h; dose: 0.5 g/animal	Non-irritating	2946
Rabbit (f)	Eye irritation	98.9	Guideline: EC directive 92/69 No L383, B5, tris1992; OECD No. 405 (2002); OPPTS 870.2400; Observations: 1,24,48 and 72 h; dose: 0.1 g/animal	Non-irritating	2947
Guinea pig (m)	Skin sensitization	98.5	OECD Guideline 406; EC directive 96/54 No L248, B.6 tris (1996). OPPTS Skin Sensitization 870.2600 (March 2003); After the challenge with 75% Thiamethoxam TC, neither in the test nor in the control animals were any skin reactions observed.	Not a skin sensitizer	9488

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

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

Species	Test	Purity % Note[3]	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
Salmonella typhimurium	*In vitro g*enotoxicity testing - bacterial assay for gene mutation (Ames test)	98.9	Guideline: OECD-471, OPPTS-870.5100 (1998) EC directive No. 440/2008 B13/14 (2008); concentration 0.313, 0.625, 1.25, 2.5 and 5 mg/plate, in the absence and presence of S-9 with five strains of *Salmonella typhimurium.*	Negative	2950
Mice	I*n vivo* genotoxicity testing (somatic cells) - Metaphase analysis in rodent bone marrow, or micronucleus test in rodents	98.9	Guideline: OECD-474, OPPTS . 870.5395 (1998) EC directive 2000/32 NoL136, B.12 tris, 2000; Dose: 375, 750 and 1500 mg/kg b.w.	Negative (Non mutagenic.) It did not exert any cytotoxic effect.). However, the exposure of target is not proven and the micronuvleus test is not mandatory for Tier-2. Test is not taken into account.	2951

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

ANNEX 2
REFERENCES

(sorted by study number)

Study number	Author	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
RRL 0824		2011	Vapour Pressure and Henry's Law Constant of Thiamethoxam Technical RRL 0824
RRL 0823		2011	Study on The Physico-Chemical Properties of Thiamethoxam Technical RRL 0823
RRL 2073		2017	Study on The Method Validation of Thiamethoxam Technical RRL 2073
RRL 2074	u	2017	Study on The Determination of Active Ingredient Content of Thiamethoxam Technical RRL 2074
RCC 2944		2012	Acute Oral Toxicity Study in Rats with Thiamethoxam Technical RCC 2944
RCC 2945		2012	Acute Dermal Toxicity Study in Rats with Thiamethoxam Technical RCC 2945
RCC 2949		2012	Acute Dermal Toxicity Study in Rats with Thiamethoxam Technical RCC 2949
RCC 2946		2012	Acute Dermal Irritation/Corrosion Study in Rabbits with Thiamethoxam Technical RCC 2946
RCC 2947		2012	Acute Eye Irritation/Corrosion Study in Rabbits with Thiamethoxam Technical RCC 2947
RCC 9488		2019	Contact Hypersensitivity (skin-sensitisation) in Albino Guinea Pigs, Maximization Test (Magnusson and Kligman Method) with Thiamethoxam Technical
RCC 2950		2012	*In Vitro* Genotoxicity Testing - Bacterial Assay for Gene Mutation RCC 2950
RCC 2951		2012	Micronucleus Test in Bone Marrow Cells of Mouse with Thiamethoxam Technical RCC 2951
		2012	Preliminary analysis of five representative production batches of thiamethoxam technical grade active ingredient (TGAI) to determine % thiamethoxam and to quantify its associated impurities

THIAMETHOXAM

FAO/WHO EVALUATION REPORT 637/2012

Recommendations

The Meeting recommended that the specifications for thiamethoxam TC, WG, SC and FS, proposed by Syngenta Crop Protection and as amended, should be adopted by FAO.

Appraisal

The data for thiamethoxam were evaluated in support of new FAO specifications for TC, WG, SC and FS.

Thiamethoxam is currently under patent in many countries. Thiamethoxam has not been evaluated by the WHO IPCS. It was evaluated by FAO/WHO JMPR in 2010, evaluated by the European Commission with Spain as the rapporteur member state in the year 2007 and by the US EPA in 2000.

The draft specifications and the supporting data were provided by Syngenta Crop Protection AG (Syngenta) in 2011 for consideration by the JMPS.

Thiamethoxam is a white to beige coloured granular powder. It has a low volatility and has a melting point of 139.1°C. It is moderately soluble in water; 4.1 g/L at 25°C. It is not fat soluble and is not likely to bioaccumulate with a log P_{ow} of ca. 0.13. It is considered to be stable to hydrolysis at all environmentally relevant pH values. It undergoes photolysis with a half-life of 2-3 days at pH 7 and 25°C. Thiamethoxam does not have a dissociation constant within the range pH 2 to 12.

Thiamethoxam is the ISO common name for (*EZ*)-3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine The ISO common name refers to both the *E* and *Z*-isomers.

The meeting were provided with commercially confidential information on the manufacturing process and specification for purity and impurities, supported by 5 batch analysis data for two manufacturing plants. Mass balances were >990g/kg and no unidentified impurities greater than 1 g/kg were reported. The meeting noted that residual solvents were not declared in the final TC product. The proposer explained that this is because any solvents used are removed at the end of the manufacturing process by vacuum distillation to a level below which they would need to be declared in the specification.

Thiamethoxam TC is produced in two plants: one in Germany, the other in Mexico. A statement has been provided confirming that the confidential data on the manufacturing process and declaration of composition submitted to the FAO were the same as those submitted to the UK National Regulatory Authority for the material produced in Germany. Later on, Syngenta provided a data package and the Meeting concluded that the TC produced in Mexico was chemically equivalent to that produced in Mexico and the two plants produce to the same manufacturing specification.

The data provided supported a minimum thiamethoxam content of 980 g/kg. There are no relevant impurities proposed by Syngenta or identified by the Meeting.

The proposed specifications for TC, WG, SC and FS were essentially in accordance with the requirements of the manual (FAO/WHO 2010, 2nd revision of 1st edition).

For the TC the melting point provided was for purified material and not the TC. The proposer stated that this information was not available for the TC and the meeting considered this acceptable. On the other hand, the solubilities in organic solvents are available for the technical material only.

The draft specifications for WG, SC and FS formulations contained a clause for control of pH range. As thiamethoxam is not sensitive to hydrolysis in the pH range 5 to 9, the necessity of the clause was questioned. In addition the meeting noted that different pH ranges were proposed for the SC, FS and WG specifications, when it would be expected that a similar pH range would be proposed to ensure the stability of the products. The proposer explained that they would prefer to have the pH clause remain for the SC and FS formulations for product stability reasons. Although thiamethoxam is not sensitive to hydrolysis, a small amount of hydrolysis could result in the formation of nitrous oxide, which, even in small concentrations, could cause over pressurization of the product containers. The proposer therefore requested that the pH clause for the aqueous products only (i.e. the SC and FS) was retained and that the range for both was harmonised to 4 to 8. The clause for pH for the WG was removed as it is not required.

The draft specification for the WG initially contained reference to a water soluble bag, however the company clarified that this had been left in by mistake and that the products are not available in a water soluble bag. The specification was revised to reflect this.

The meeting considered that for the WG specification a more detailed description would be preferred; however the proposer explained that there are two different formulation processes used to manufacture their WG products, resulting in different forms of the granules (either spherical granules or rod-like granules). Hence a more precise description is not possible. The meeting accepted this explanation. The meeting also confirmed with the proposer that on the basis of supporting data the limits proposed for the clauses for persistent foam and attrition were applicable.

The FS specification includes clauses for persistent foam, suspensibility and wet sieve. The company confirmed that their FS products are diluted before use, with dilutions ranging from 15% w/v to 75% w/v, therefore these clauses are relevant. The proposer has tested the technical properties and proposed limits in the specification on the basis of a 75% w/v dilution. A footnote had been added to the specification to clarify the concentration to be tested.

For the description the meeting questioned if all FS products were a red colour. The proposer agreed to remove reference to the colour from the description and include this information in a footnote to the specification.

For both the FS and SC specifications the clause for suspensibility was given on the basis of gravimetric results. On request the company provided the results for chemical assay. It was noted that on the basis of the chemical assay results higher limits for the clauses could be supported. The proposer revised the specifications and provided limits for the clauses on the basis of the chemical assay data. The clause for spontaneity of dispersion for the SC specification was also given on the basis of gravimetric results. The proposer explained that only data based on the gravimetric tests were available therefore the limit should be based on the gravimetric result.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 637/2012

USES

Thiamethoxam is a systemic broad spectrum insecticide and belongs to the neonicotinoid class (IRAC Group 4A, subclass: thianicotinyl). Thiamethoxam displays root-, leaf- and stem-systemic activity. In target insects it shows quick stomach and contact action. Thiamethoxam acts by interfering with the nicotinic acetylcholine receptor of the nervous system.

It has registered uses in many countries on many crops (e.g. agriculture, horticulture, viticulture).

IDENTITY OF THE ACTIVE INGREDIENT

ISO common name

Thiamethoxam (ISO 1750 approved)

Synonyms

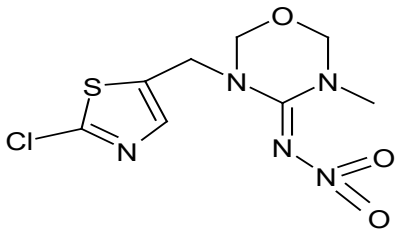
None

Chemical names

IUPAC (*EZ*)-3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine

CA 3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-*N*-nitro-4*H*-1,3,5-oxadiazin-4-imine

Structural formula



Molecular formula

$C_8H_{10}ClN_5O_3S$

Relative molecular mass

291.7 g/mol

CAS Registry number

153719-23-4

CIPAC number

637

Identity tests

IR spectroscopy for TC, retention time in reverse phase HPLC (TC, formulations).

Table 1. Physico-chemical properties of pure thiamethoxam

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Reference
Vapour pressure	$6.6 \cdot 10^{-9}$ Pa (extrapolated) at 25°C	99.7	OECD 104, EEC A.4	1
Melting point,	Melting point: 139.1 °C	99.7	OECD 102, EEC A.1	2
Boiling point and/or temperature of decomposition	Decomposition temperature: thermal decomposition starts at about 147°C before boiling point is reached	99.3	OECD 103, OPPTS 830.7220, EEC A.2	3
Solubility in water	4.1 g/l at 25 °C at pH 7.3	99.7	OECD 105, OPPTS 796.1840, EEC A.6	4
Octanol/water partition coefficient	log P_{OW} = -0.13 at 25 °C at pH 6.9	99.7	OECD 107, EEC A.8	5
Hydrolysis characteristics	pH 5 at 25°C no degradation after 30 days pH 7 at 25°C 643 days pH 9 at 25°C 8.4 days pH 5 at 25°C no degradation after 30 days pH 7 at 25°C 572 days pH 9 at 25°C 4.2 days	Guanidine-labelled 98.8 (radiochemical purity) Thiazolyl labelled 97.8 (radiochemical purity)	EPA 161-1, OECD 111 EPA 161-1, OECD 111	6 7

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Reference
Photolysis characteristics	The photolytic half-lives of thiamethoxam were determined at 25 °C in phosphate buffered aqueous solutions (pH 5) using xenon arc light irradiation. Samples were exposed to light for 12 hours at an average intensity of 410 W/m^2 per day followed by 12 hours dark intervals with a total incubation time for 30 days. DT_{50}: Guanidin-labelled: 2.3 d Thiazolyl-labelled : 3.1 d	radio-chemical purity: 97.3 98.5	EPA 161-2	8 and 9
Dissociation characteristics	Thiamethoxam does not have a dissociation constant within the range pH 2 to 12	99.7	OECD 112	10
Solubility in organic solvents *	Not available			

* Solubility in organic solvents is only available for thiamethoxam technical material

Table 2. Chemical composition and properties of thiamethoxam technical materials (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data		Confidential information supplied and held on file by FAO. Mass balances were 99.1 – 99.4 %		
Declared minimum thiamethoxam content		980 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	Reference
Melting temperature range of the TC**				
Solubility in organic solvents	48 g/l Acetone 110 g/l Dichloromethane 7 g/l Ethyl acetate < 1 mg/l Hexane 13 g/l Methanol 620 mg/l Octanol 680 mg/l Toluene (all at 25°C)	98.2	Based upon CIPAC MT157.3	11

**Melting temperature is only available for the pure active ingredient

HAZARD SUMMARY

Thiamethoxam is moderately hazardous (WHO class III). Thiamethoxam is not classified as hazardous in contact with skin or by inhalation, and is nor irritating to skin or eyes neither a skin sensitizer.

Thiamethoxam was tested for different endpoints including gene mutation, chromosome aberration and DNA-damage in bacteria in vitro and in mammalian cells *in vitro* and *in vivo*. No mutagenic effects were noted in any test *in vitro* and *in vivo*.

The results of extensive tests demonstrate low acute, short-term and long-term toxicity of thiamethoxam to birds.

Based on acute toxicity tests in the laboratory, thiamethoxam is classified as non-toxic to fish, daphnia and algae. Toxicity to the midge *Chironomus riparius* was high after application to water and sediment.

Thiamethoxam has high acute toxicity to bees via the oral and the contact route of exposure. Thiamethoxam has low acute toxicity to earthworms and to aerobic sewage sludge bacteria.

GHS classification is: Harmful if swallowed. Very toxic to aquatic life with long lasting effects.

FORMULATIONS

The main formulation types available are WG, SC and FS.

The WG, SC and FS formulations are registered and sold in many countries throughout the world. Thiamethoxam may be co-formulated with other insecticides and fungicides especially when manufacturing FS formulations.

METHODS OF ANALYSIS AND TESTING

The analytical method for the active ingredient (including identity tests) is CIPAC Method 367 and includes sub-methods for TC, WG, SC and FS respectively. The thiamethoxam content is determined by reverse phase HPLC with UV detection at 254 nm using external standardisation.

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

PHYSICAL PROPERTIES

The physical properties, the methods for testing them and the limits proposed for the WG, SC and FS formulations, comply with the requirements of the FAO/WHO Manual.

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The active ingredient is expressed as thiamethoxam.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from thiamethoxam 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 3. Toxicology profile of the thiamethoxam technical material, based on acute toxicity, irritation and sensitization

Species	Test	Purity % Note[4]	Guideline, duration, doses and conditions	Result thiamethoxam technical	Reference
Rat (m,f)	Acute Oral LD_{50}, (OECD 401)	98.6	14d observation period; dose levels: 0, 900, 1500, 2300, 3800, 6000 mg/kg bw.	LD_{50} = 1563 mg/kg bw	12
Rat (m,f)	Acute Dermal LD_{50}, (OECD 402)	98.6	14d observation period; limit dose: 2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	13
Rat (m,f)	Acute Inhalation (4h) LC_{50}, (OECD 403)	98.6	4h exposure (nose only), 14d observation period; nominal concentration: 10.9 and 56.6 mg/L analytical concentration: 1.02 and 3.72 mg/L	LC_{50} > 3.72 mg/L	14
Rabbit (f)	Skin irritation, (OECD 404)	98.6	Observations: 1-72 h; dose: 0.5 g/animal	Non-irritating	15
Rabbit (f)	eye irritation, (OECD 405)	98.6	Observations: 1-72 h; dose: 0.1 g/eye	Non-irritating	16
Guinea pig (m,f)	skin sensitization (maximization test), (OECD 406)	98.6	Intradermal: 1% TMX topically (48 h): 30% TMX topically (24h): 10% TMX observations: 24-48 h	Non-sensitising	17

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

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

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result thiamethoxam technical	Reference
Rat (m,f)	Short term toxicity	98.4	3m dietary (OECD 408) Tif:RAIf rat dose levels: 0, 25, 250, 1250, 2500, 5000 ppm	NOAEL = 250 ppm/17.6 mg/kg bw/day (m) NOEL = 1250 ppm/92.5 mg/kg bw/day (f)	18
Dog (m,f)	Short term toxicity	98.6	3m dietary (OECD 409) Beagle dog dose levels: 0, 50, 250, 1000, 2500/2000 ppm	NOEL = 250 ppm 8.23 mg/kg bw/day (m) 9.27 mg/kg bw/day (f)	19
Dog (m,f)	Short term toxicity	98.6	1 year dietary (OECD 452) Beagle dog dose levels: 0, 25, 150, 750, 1500 ppm	NOEL = 150 ppm 4.05 mg/kg bw/day (m) 4.49 mg/kg bw/day (f)	20
Rat (m,f)	Short term toxicity	98.6	28-day dermal (OECD 410) Tif:RAIf, SPF rat dose levels: 0, 20, 60, 250, 1000 mg/kg bw/day	NOAEL = 250 mg/kg bw/day (m) NOEL = 60 mg/kg bw/day (f)	21
Mouse (m,f)	Carcinogenicity	98.6	18m dietary (OECD 453) Tif:MAGf SPF mice dose levels: 0, 5, 20, 500, 1250, 2500 ppm	No carcinogenic effects NOAEL = 1250 ppm (162/215 mg/kg bw/d m/f)	22

[5] 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 thiamethoxam technical	Reference
Rat (m,f)	Chronic toxicity/ Carcinogenicity	98.6	2 year dietary (OECD 453) Tif:RAIf rat dose levels: 0, 10, 30, 500, 1500 ppm (males); 0, 10, 30, 1000, 3000 ppm (females)	Not carcinogenic NOAEL = 1500 ppm/63 mg/kg bw/day (m) 1000 ppm/50.3 mg/kg bw/day (f)	23
Rat (m,f)	Reproductive toxicity	98.6	2 generation, dietary (OECD 416) Tif:RAI SPF rat dose levels: 0, 10, 30, 1000, 2500 ppm	No effects on reproductive parameters NOAEL parental: 1000 ppm (45.6-144 mg/kg bw/day NOEL offspring: 30 ppm (1.8-6.4 mg/kg bw/day) NOEL reproduction: 2500 ppm (148-541 mg/kg bw/day)	24
Rat (m,f)	Reproductive toxicity	98.6	2 generation, dietary (OECD 416) Tif:RAI SPF rat dose levels: 0, 20, 50, 1000, 2500 ppm	No effects on reproductive parameters NOEL parental: 50 ppm (3-3.7 mg/kg bw/day NOEL offspring: 1000 ppm (75-110 mg/kg bw/day) NOEL reproduction: 2500 ppm (156-209 mg/kg bw/day)	25
Rat (f)	Developmental toxicity Ref.	98.6	Gavage feeding (OECD 414) Tif:RAIf rat dose levels: 0, 5, 30, 200, 750 mg/kg bw/day	Not teratogenic NOEL maternal: 30 mg/kg bw/day NOEL development: 200 mg/kg bw/day	26

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result thiamethoxam technical	Reference
Rabbit (f)	Developmental toxicity	98.6	Gavage feeding (OECD 414) Russian Chbb:HM rabbit dose levels: 0, 5, 15, 50, 150 mg/kg bw/day	Not teratogenic NOEL maternal = 15 mg/kg bw/day NOEL developmental = 50 mg/kg bw/day	27

Table 5. Mutagenicity profile of technical thiamethoxam based on in vitro and in vivo tests

Species	Test	Purity % Note[6]	Guideline, duration, doses and conditions	Result thiamethoxam technical	Reference
Bacterial gene mutation (Salmonella/E.coli)	Ames test (OECD 471)	98.6	312.5 to 5000 µg/plate, +/- activation	Not mutagenic	28 29
Chinese hamster cells	Cytogenetic test in Chinese hamster cells in vitro (OECD 473)	98.6	283.8 to 2270 µg/ml, - activation (21h) 851.3 to 1702.5 µg/ml, - activation (45h) 1135 to 4540 µg/ml, + activation (3h)	Not clastogenic	30
Chinese hamster (V79)	Gene mutation in V79 cells in vitro (OECD 476)	98.6	61.7 to 2220 µg/ml, - activation (21h) 123.3 to 3330 µg/ml, + activation (5h)	Not mutagenic	31
Rat hepatocytes	DNA repair test on rat hepatocytes in vitro (OECD 482)	98.6	13 to 1665 µg/ml (16-18h)	Not genotoxic	32
Mouse hepatocytes	DNA repair test on mouse hepatocytes in vitro (OECD 482)	98.6	7.3 to 235 µg/ml (16-18h)	Not genotoxic	33
Mouse somatic cells	Micronucleus test mouse bone marrow in vivo (OECD 474)	98.6	0, 312.5, 625, 1000 and 1250 (females only) mg/kg bw	Not clastogenic or aneugenic	34

[6] Purity is the content of pure active ingredient in the technical material, expressed as a percentage

Table 6. Ecotoxicology profile of technical thiamethoxam

Species	Test	Purity % Note[7]	Guideline, duration, doses and conditions	Result thiamethoxam	Reference
Anas platyrhynchos (Mallard duck)	Acute oral	98.6	Observation: 14 days; EPA Pesticide Assessment Guidelines, E, 71-1, 1982 and draft revised guideline, 1988; Treatment levels: 76, 137, 247, 444 and 800 mg a.s./kg bw	LD_{50} = 576 mg/kg bw Vomiting at all dose levels.	35
Colinus virginianus (Bobwhite quail)	Acute oral	98.6	Observation: 14 days; EPA Pesticide Assessment Guidelines, E, 71-1, 1982 and draft revised guideline, 1988; Treatment levels: 125, 250, 500, 1000 and 2000 mg a.s./kg bw	LD_{50} = 1552 mg/kg bw	36
Anas platyrhynchos (Mallard duck)	Short term	98.6	Treatment 5 days plus 3 days observation; EPA Pesticide Assessment Guidelines, E, 71-2, 1982 and draft revised guideline, 1988; Treatment levels: 163, 325, 650, 1300, 2600 and 5200 mg/kg diet	LC_{50} > 5200 mg/kg feed	37
Colinus virginianus (Bobwhite quail)	Short term	98.6	Treatment 5 days plus 3 days observation; EPA Pesticide Assessment Guidelines, E, 71-2, 1982 and draft revised guideline, 1988; Treatment levels: 163, 325, 650, 1300, 2600 and 5200 mg/kg diet	LC_{50} > 5200 mg/kg feed	38
Anas platyrhynchos (Mallard duck)	Reproduction	98.3	Treatment over 21 weeks. EPA Pesticide Assessment Guidelines, E, 71-4, 1982; Treatment levels: 100, 300 and 900 mg/kg diet	NOEC= 300 mg/kg diet	39
Colinus virginianus (Bobwhite quail)	Reproduction	99.7	Treatment over 23 weeks. EPA Pesticide Assessment Guidelines, E, 71-4, 1982; Treatment levels: 100, 300 and 900 mg mg/kg diet	NOEC = 900 mg/kg diet	40
Oncorhynchus mykiss (Rainbow trout)	Acute	98.6	96 hours exposure under flow-through conditions/ freshwater; OECD 203; Test concentration: 125 mg/l (mean measured)	LC_{50} >125 mg a.s./l	41

[7] Purity is the content of pure active ingredient in the technical material, expressed as a percentage

Species	Test	Purity % Note[7]	Guideline, duration, doses and conditions	Result thiamethoxam	Reference
Oncorhynchus mykiss (Rainbow trout)	Acute	98.6	96 hours exposure under flow-through conditions/ freshwater; OECD 203; Test concentration: 100 mg/l (nominal)	LC_{50} >100 mg a.s./l	42
Lepomis macrochirus (Bluegill sunfish)	Acute	99.2	96 hours exposure under flow-through conditions/ freshwater; OECD 203; Test concentrations: 14, 24, 40, 64 and 114 mg/l (mean measured)	LC_{50} >114 mg a.s./l	43
Cyprinus carpio (Common carp)	Acute	98.6	96 hours static exposure/ freshwater; OECD 203; Test concentration: 120 mg/l (nominal)	LC_{50} >120 mg a.s./l	44
Oncorhynchus mykiss (Rainbow trout)	Early-life-stage	99.2	88 days exposure under flow-through conditions/ freshwater; US-EPA FIFRA 72-4; Test concentrations: 1.3, 2.5, 5.1, 10 and 20 mg/l (mean measured)	NOEC = 20 mg a.s./l	45
Daphnia magna (Water flea)	Acute	98.6	48 hours static exposure/ freshwater; OECD 202; Test concentrations: 10, 18, 32, 58 and 100 mg/l (nominal)	EC_{50} >100 mg a.s./l	46
Daphnia magna (Water flea)	Chronic	98.6	21 days exposure under semi-static conditions/ freshwater; OECD 202, 1984, Revised draft of OECD 202 Part II, 1996; Test concentrations: 6.0, 12.5, 25.0, 50.0 and 100 mg/l (nominal)	NOEC = 100 mg a.s./l	47
Pseudokirchneriella subcapitata (former name: *Selenastrum capricornutum*) (Freshwater Green Algae)	Growth inhibition	98.6	72 hours exposure; OECD 201; Test concentrations: nominal: 0.8, 1.6, 3.2, 6.4, 12.8, 25.6, 50 and 100 mg/l, measured at the end of the study: 0.66, 0.93, 1.9, 4.5, 9.9, 20.6, 45.2, 81.8 mg/l	E_rC_{50} >81.8 mg a.s./l E_bC_{50} >81.8 mg a.s./l	48

Species	Test	Purity % Note[7]	Guideline, duration, doses and conditions	Result thiamethoxam	Reference
Chironomus riparius	Spiked water and sediment exposure, emergence rate & development of midge	98.6	30 days exposure; OECD draft proposal, 1997; BBA Guideline Proposal, 1995; spiked water: 1.25, 2.5, 5, 10, 20 and 50 µg/l; spiked sediment: 12.5, 25, 50, 100, 200 and 400 µg/kg sediment dry weight (dw)	Water exposure: NOEC = 0.010 mg a.s./l Sediment exposure: NOEC = 0.10 mg a.s./kg sediment dw	49
Apis mellifera (Honeybee)	Acute toxicity, Oral and contact; Mortality / behaviour	98.6	48 hours exposure; EPPO 170 (1992); Oral doses: 0.002, 0.004, 0.008, 0.012, 0.016, 0.02 µg/bee; Contact doses: 0.005, 0.01, 0.02, 0.03 0.04, 0.05 µg/bee	Oral LD_{50} = 0.005 µg a.s./bee Contact LD_{50} = 0.024 µg a.s./bee	50
Eisenia foetida (Earthworm)	Acute toxicity, Mortality / behaviour	98.6	14 days exposure; OECD 207; soil concentration: 1000 mg/kg dry soil	LC_{50} >1000 mg a.s./kg dry soil	51
Aerobic bacteria (Sewage treatment plant sludge)	Oxygen consumption	98.6	3 hours exposure; OECD 209; test concentrations: 1.0, 3.2, 10, 32, 100 mg/l	EC_{50} > 100 mg a.s./l	52

ANNEX 2

REFERENCES

Ref.	Year	Study title. Study identification number. All studies under GLP and owned by Syngenta Crop Protection AG
1	1995	Report on vapour pressure curve. CGA293343/0029.
2	1995	Report on melting point / melting range. CGA293343/0012.
3	1997	Report on boiling point / boiling range. CGA293343/0295
4	1995	Report on water solubility. CGA293343/0025
5	1995	Report on octanol / water partition coefficient. CGA293343/0021
6	1997	Hydrolysis of ^{14}C-guanidine CGA 293343 under laboratory conditions. CGA293343/0373
7	1998	Hydrolysis of 2-^{14}C-thiazolyl-CGA-293343 under laboratory conditions CGA293343/0753
8	1997	Photodegradation of ^{14}C-[Guanidine]-CGA-293343 in pH 5 buffered solution under artificial light. CGA293343/0375
9	1998	Photodegradation of ^{14}C-[Thiazolyl]-CGA-293343 in pH 5 buffered solution under artificial light. CGA293343/0798
10	1995	Report on dissociation constant in water. CGA293343/0026
11		CGA293343/0479
12	1996	An acute oral toxicity study of CGA 293343 tech. in rats CGA293343/0054
13	1996	An acute dermal toxicity study of CGA 293343 tech. in rats CGA293343/0053
14	1996	CGA 293343 tech.: Acute inhalation toxicity study in rats CGA293343/0084
15	1996	A primary skin irritation study of CGA 293343 tech. in rabbits CGA293343/0056
16	1996	A primary eye irritation study of CGA-293343 tech. in rabbits CGA293343/0057
17	1995	CGA 293343 tech. - skin sensitisation test in the guinea pig - maximization test CGA293343/0027
18	1996	CGA 293343 tech. - 3-month oral toxicity study in rats (administration in food) CGA293343/0033
19	1996	CGA 293343 technical - 3-Month subchronic dietary toxicity study in Beagle dogs CGA293343/0115
20	1998	CGA 293343 tech. - 12-month chronic dietary toxicity study in Beagle dogs CGA293343/0628
21	1996	CGA 293343 tech. - 28-day repeated dose dermal toxicity study in the rat CGA293343/0112
22	1998	CGA 293'343 tech.: 18-month oncogenicity study in mice CGA293343/0538
23	1998	CGA 293343 tech. - 24-month carcinogenicity and chronic toxicity study in rats CGA293343/0294
24	1993	CGA 293343 tech.: Rat dietary two-generation reproduction study CGA293343/0626 (CGA293343/1096, CGA293343/1110)

25 2004 CGA 293343 tech.: THIAMETHOXAM - Two Generation Reproduction Study in Rats; (CGA293343/1925)
26 1996 CGA 293343 tech. - Rat oral teratogenicity study
CGA293343/0082
CGA293343/1188
27 1996 CGA 293343 tech. - Rabbit oral teratogenicity
CGA293343/0083
28 1995 CGA 293343 technical - Salmonella and Escherichia / mammalian-microsome mutagenicity test CGA293343/0024
29 1999 CGA 293343 technical - Salmonella / mammalian-microsome mutagenicity test
CGA293343/1127
30 1996 CGA 293343 tech. - Cytogenetic test on Chinese hamster cells in vitro
CGA293343/0062
31 1996 CGA 293343 tech. - Gene mutation test with Chinese hamster cells V79
CGA293343/0032
32 1996 CGA 293343 tech. - Autoradiographic DNA repair test on rat hepatocytes (OECD conform) *in vitro*
CGA293343/0038
33 2000 CGA 293343 tech. - Autoradiographic DNA repair test on mouse hepatocytes (OECD conform) *in vitro* CGA293343/1195
34 1995 CGA 293343 tech. - Micronucleus test, mouse, (OECD conform)
CGA293343/0028
35 1996 CGA 293343 - Acute oral toxicity (LD_{50}) to the mallard duck.
CGA293343/0044
36 1996 CGA 293343 - Acute oral toxicity (LD_{50}) to the bobwhite quail.
CGA293343/0046
37 1996 CGA 293343 - Subacute dietary toxicity (LC_{50}) to the mallard duck.
CGA293343/0045
38 1996 CGA 293343 - Subacute dietary toxicity (LC_{50}) to the bobwhite quail.
CGA293343/0047
39 1998 The reproductive toxicity test of CGA 293343 technical with the mallard duck (*Anas platyrhynchos*).
CGA293343/0889
40 1998 The reproductive toxicity test of CGA 293343 technical with the northern bobwhite (*Colinus virginianus*).
CGA293343/0653
41 1996 Acute Toxicity Test of CGA 293343 tech. to rainbow trout (*Oncorhynchus mykiss*) in the flow-through system. CGA293343/0036
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CGA293343/0388
43 1996 A 96-hour flow-through acute toxicity test with the Bluegill sunfish (*Lepomis macrochirus*).
CGA293343/0145
44 2003 Thiamethoxam (CGA 293343 technical): Acute toxicity to mirror carp (*Cyprinus carpio*).
CGA293343/1835
45 1997 CGA 293343: an early life-stage toxicity test with the rainbow Trout (*Oncorhynchus mykiss*).
CGA293343/0205
46 1996 Acute toxicity of CGA 293343 to the cladoceran *Daphnia magna* Straus, under static conditions.
CGA293343/0043
47 1997 *Daphnia magna* reproduction test: effects of CGA 293343 on the reproduction of the cladoceran *Daphnia magna* strauss.
CGA293343/0323

48 1996 Growth inhibition test of CGA 293343 tech. to green algae (*Selenastrum capricornutum*) in a static system.
CGA293343/0035
49 1998 Toxicity test of CGA 293343 tech. on sediment-dwelling *Chironomus riparius* (syn. *Chironomus thummi*) under static conditions.
CGA293343/0720
50 1995 Testing toxicity to Honeybee - *Apis mellifera* L.
CGA293343/0018
51 1995 CGA 293343 tech: 14-day acute toxicity test with the earthworm (*Eisenia foetida*).
CGA293343/0023
52 1996 Report on the test for activated sludge respiration inhibition of CGA293343 tech.
CGA293343/0034