FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

THIFENSULFURON-METHYL

methyl 3-[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)carbamoyl]sulfamoyl]-2-thiophenecarboxylate

FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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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.

FAO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may arise as a result of, or in connection with, the manufacture, sale, transportation, storage, handling, preparation and/or use of pesticides which are found, or are claimed, to have been manufactured to comply with these specifications.

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

FAO is not responsible, and does not accept any liability, for the testing of pesticides for compliance with the specifications, nor for any methods recommended and/or used for testing compliance. As a result, FAO does not in any way warrant or represent that any pesticide claimed to comply with a FAO specification actually does so.

[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 "Manual on development and use of FAO and WHO specifications for pesticides".

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

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

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

* NOTE: PUBLICATIONS ARE AVAILABLE ON THE INTERNET AT (http://www.fao.org/agriculture/crops/core-themes/theme/pests/pm/jmps/ps/en/) OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.

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THIFENSULFURON-METHYL

INFORMATION

Common name (ISO 1750 published)

thifensulfuron-methyl

Synonyms

thifensulfuron (BSI, ANSI[2], draft E-ISO); thiameturon (WSSA[3] former name)

Chemical names

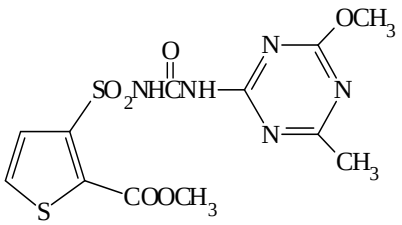
IUPAC: methyl 3-[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)carbamoyl]sulfamoyl]-2-thiophenecarboxylate

CAS: methyl 3-[[[[(4-methoxy-6-methyl-1,3,5- triazin-2-yl)amino] carbonyl] amino]sulfonyl]-2-thiophenecarboxylate

CAS Registry number
792 77-27-3

CIPAC number
452. 201

Structural formula



Molecular formula

$C_{12}H_{13}N_5O_6S_2$

Relative molecular mass

387. 4

Identity tests: reversed phase HPLC retention time, IR spectrum

[2] American National Standards Institute

[3] Weed Science Society of America

THIFENSULFURON-METHYL TECHNICAL MATERIAL

FAO specification 452.201/TC (December 2010*)

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 (452.201/2000 and 452.201/2010). It should be applicable to relevant products of 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 the products of other manufacturers. The evaluation reports (452.201/2000 and 452.201/2010) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of thifensulfuron-methyl together with related manufacturing impurities, in the form of a white to light grey fine crystalline solid, and shall be free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (CIPAC 452/TC/M-, CIPAC Handbook K, p. 115, 2003)

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 **Thifensulfuron-methyl content** (CIPAC 452/TC/M-, CIPAC Handbook K, p. 115, 2003)

The thifensulfuron-methyl content shall be declared (not less than 960 g/kg) and, when determined, the mean measured content shall not be lower than the declared minimum content.

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

THIFENSULFURON-METHYL WATER DISPERSIBLE GRANULES

FAO specification 452.201/WG (December 2010*)

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 report (452.201/2000 and 452.201/2010). It should be applicable to relevant products of 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 the products of other manufacturers. The evaluation reports (452.201/2000 and 452.201/2010) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of a homogenous mixture of technical thifensulfuron-methyl, complying with the requirements of FAO specification 452.201/TC, in the form of a white to light grey fine crystalline solid, 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.

Where the material is packaged in sealed water-soluble bags, it shall consist of a defined quantity of thifensulfuron-methyl water dispersible granules complying with the requirements of FAO specification 452.201/TC, in the form of a white to light grey fine crystalline solid, contained in a sealed water-soluble bag.

2 Active ingredient

2.1 **Identity tests** (CIPAC 452/WG/M-, CIPAC Handbook K. p. 117, 2003)

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 **Thifensulfuron-methyl content** (CIPAC 452/WG/M-, CIPAC Handbook K. p. 117, 2003)

The thifensulfuron-methyl content shall be declared (g/kg) and, when determined, the content measured shall not differ from that declared by more than the following tolerance:

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

Declared content, g/kg	Permitted tolerance
above 500	± 25 g/kg

3 Physical properties

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

pH range: 4.0 to 7.0

3.2 **Wettability** (MT 53.3, Handbook F, p. 164, 1994)

The formulation shall be completely wetted in 10 seconds, without swirling.

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

Maximum: 2% retained on a 75 µm test sieve.

3.4 **Degree of dispersion** (MT 174, Handbook F, p. 435, 1994)

Dispersibility: minimum 75% after 1 minute of stirring.

3.5 **Suspensibility** (MT 184, Handbook K, p. 142, 2003) (Notes 1 and 2)

A minimum of 60% of the thifensulfuron-methyl content found under 2.2 shall be in suspension after 30 minutes in CIPAC standard water D at 30±2°C.

In the case of water-soluble bag packaging, the requirements of clause 5.3 shall be applied.

3.6 **Persistent foam** (MT 47.2, Handbook F, p. 152, 1994) (Note 3)

Maximum 60 ml after 1 minute.

3.7 **Dustiness** (MT 171, Handbook F, p. 425, 1994) (Note 4)

Essentially non-dusty.

3.8 **Flowability** (MT 172, Handbook F, p. 430, 1994)

At least 99.9 % of the product shall pass through a 5 mm test sieve after 20 drops of the sieve.

4 Storage stability

4.1 **Stability at elevated temperature** (MT 46.3)

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 and the formulation shall continue to comply with the clauses for:

- pH range (3.1),
- wet sieve test (3.3),
- degree of dispersion (3.4),
- suspensibility (3.5)
- dustiness (3.7)

In the case of water soluble bag packaging, the package should be enclosed in a watertight sachet, box or any other container at 54±2ºC

for 14 days. The determined average active ingredient content must not be lower than 95% relative to the determined average content before storage, and the formulation shall continue to comply with the clauses for:

- pH range (3.1),
- degree of dispersion (3.4),
- dissolution of bag (5.1),
- suspensibility (5.2)
- persistent foam (5.3)

None of the bags tested should show signs of leakage or rupture during normal handling before or after storage.

5 Material packaged in a sealed water soluble bag

5.1 **Dissolution of the bag** (MT 176, Handbook F, p. 440, 1994)

The dissolution of the bag shall be tested on a sample of the emptied and cleaned bag taken according to the procedure described in Note 5, together with an appropriate proportion of the WG.

Flow time of the suspension: maximum 60 sec.

5.2 **Suspensibility** (MT 184, Handbook K, p. 142, 2003) (Notes 2, 3 and 6)

The suspensibility shall be tested on a suspension containing the WG and the bag material in the actual ratio of application, prepared according to the procedure described in Note 5.

A minimum of 60% of the thifensulfuron-methyl content found under 2.2 shall be in suspension (Note 2) after 30 minutes in CIPAC standard water D at 30±2ºC.

5.3 **Persistent foam** ((MT 47.2, Handbook F, p. 152, 1994)) (Note 3)

The persistent foam shall be tested on a suspension containing the WG and the bag in the actual ratio of application, prepared according to the procedure described in note 6.

Maximum: 60 ml after 1 minute.

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, MT 184, may be used on a routine basis provided that it has been shown to give equal results to those of chemical assay. 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.

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 method, MT 171, usually shows good correlation with the gravimetric method and can, therefore, be used as an alternative where the equipment is available. Where the correlation is in doubt, it

must be checked with the formulation to be tested. In case of dispute the gravimetric method shall be used.

Note 5 The sampling of the bag for the dissolution test should be as follows:
"Lay the empty cleaned bag in its original configuration (double layer). Delineate and then cut up a test sample including part of the upper seal (5 cm) and symmetrically including the vertical seal (10 cm)."
If the size of the bag is less than this dimension, use the whole bag.
Carry out the dissolution test immediately to avoid any modification of the sample.

Note 6 The procedure for adding the bag material to the solution for the persistent foam test should be as follows:
"Prepare a stock solution of the bag material (1 mg/ml) by weighing approximately a 100 mg sample (n mg) of the bag (excluding sealed parts) to the nearest mg. Dissolve this sample by stirring in the standard water used for the tests to give a final volume of n ml. Store the stock solution in a stoppered bottle before use.
Calculate the volume (V ml) of the stock solution of the bag to be added to the test suspension of the water dispersible granule according to the following equation:

$$V(ml) = X \times \frac{1000B}{W}$$

where: B (g) = weight of the emptied and cleaned bag
W (g) = nominal weight of the WG contained in the bag
X (g) = weight of the WG sample used in the test."

PART TWO

EVALUATION REPORTS

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THIFENSULFURON-METHYL
FAO/WHO EVALUATION REPORT 452.201/2010

Recommendation

The Meeting recommended that

(i) the existing FAO specifications for thifensulfuron-methyl TC and WG should be extended to encompass the products of Cheminova

Appraisal

Data provided by Cheminova A/S for thifensulfuron-methyl TC and WG were evaluated in support of the determination of equivalence with the existing FAO specifications for thifensulfuron-methyl.

Thifensulfuron-methyl is not under patent. Thifensulfuron-methyl has not been evaluated by the FAO/WHO JMPR and WHO/IPCS. It was evaluated by the European Commission and was included into Annex I of Directive 91/414, on July 1, 2002. Thifensulfuron-methyl is currently registered in the United States of America, Canada, Australia and other countries.

Written confirmation by U S EPA was received confirming that the confidential data provided on the manufacturing process and batch analyses of thifensulfuron-methyl were identical to those submitted for registration in the US.

The manufacturing process was declared to be similar to the one previously submitted and evaluated for the FAO specifications for TC and WG.

The declared minimum active ingredient content in the TC is 960 g/kg and complies with the existing FAO specification for the TC. The manufacturing limits for impurities identified in the technical material did not exceed the limits in the reference profile. No relevant impurities were identified. According to 5 batch analysis data submitted an impurity not present in the reference profile was identified at a level < 0.75 g/kg and no manufacturing QC limit was set. As the proposer has declared that no relevant impurities are formed in the technical active substance and as this impurity is found at a content < 1 g/kg, no more data is required. It cannot be excluded that, based on the two rather similar manufacturing routes for the material under consideration and that of the reference profile, this impurity to be present in the reference source as well but not being specified as the content is inferior to the general limit of 1 g/kg specified. The two purity/impurities profiles can therefore be considered as being similar and chemically equivalent.

Data on physical-chemical properties like melting point and solubility in organic solvents for technical material (97.4 %) were provided. For the determination of these

properties of the technical active ingredient OECD, CIPAC and EEC test methods were used.

The same batch with a purity of 97.4% was used for studies on acute toxicity, skin irritation, eye irritation, skin sensitisation and bacterial mutagenicity assay (Ames test). Considering results, they can be declared similar to those provided for the reference profile. It was noted, that the reference specification dated from the year 2000 and was one of the first specifications according to the new procedure, but the data requirements as defined in the FAO/WHO Specification Manual from 1999 were less detailed that with the 2006 Edition. As an example, the hazard data summary with dose levels, Guideline used, purity of the material and references was introduced only later.

The thifensulfuron-methyl content in TC and WG is determined by reversed phase HPLC using a C_{18} substituted silica column and UV detection. The method is a full CIPAC Method and published in Handbook K. The quantification is with external standard. There is a slight inconsistency in the CIPAC numbering system, with the CIPAC number 452 referring to the free acid, and the methyl ester carrying the number 452.201. However, due to some changes introduced in the handling of these numbers, the analytical method still carries the number 452, e.g. 452/TC/M for thifensulfuron-methyl technical. In order to avoid possible problems in retrieving and using the CIPAC method, the reference as indicated in the CIPAC Handbooks (452) is used in the specifications, but the correct numbering is used for designation of the specifications and evaluation reports (452.201).

The methods for determination of impurities are based on HPLC using a reverse phase column (C18), UV detection and external standard.

The proposer confirmed in writing, that their material complies with all clauses of the existing specification for TC and WG. After request the data for WG formulation were submitted which demonstrate that Cheminova's WG formulation complies with the requirements described in the existing FAO specification. Cheminova produces a WG which is available in conventional packaging only and not in Water soluble bags. The clauses in the WG specification which apply for this kind of packaging are therefore applicable to the DuPont material only.

The Meeting agreed that the purity/impurity, acute dermal, skin irritation, eye irritation and mutagenicity indicated equivalence with the reference profile supporting the existing FAO specifications (FAO/WHO evaluation report 452.201/2000).

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 452.201/2010

Physico-chemical properties of thifensulfuron-methyl

Table 1. Physical and chemical properties of technical grade thifensulfuron-methyl

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC and/or TK	173 °C. Decomposition occurs (endothermic reaction).	97.4	OECD 102	CHA Doc. No.: 129 TIM
Solubility in organic solvents	10-14 g/l acetone at 20 °C 10-14 g/l acetonitrile at 20 °C 29-33 g/l 1,2-dichloroethan at 20 °C 4.228 g/l ethyl acetate at 20 °C Very low solubility in n-hexane at 20 °C 2.845 g/l methanol at 20 °C 0.170 g/l xylene at 20 °C	97.4	CIPAC Method 181 (for solubilities >10 g/L) EEC Method A.6 (for solubilities <10 g/L)	CHA Doc. No.: 130 TIM

Table 2. Chemical composition and properties of thifensulfuron-methyl 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 98.4 – 99.1 % and percentages of unknowns were 0.9 – 1.6 %.
Declared minimum [a.i.] content	960 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

Formulations

The formulation type available for Cheminova thifensulfuron-methyl is the WG. Thifensulfuron-methyl may be co-formulated with other herbicides like metsulfuron-methyl.
Cheminova formulations are currently registered and sold in several countries e.g. in the US.

Physical properties of thifensulfuron-methyl formulations

The physical properties, the methods for testing them and the limits proposed for the WG formulation, comply with the requirements of the FAO/WHO Specifications manual (FAO/WHO, 2006).

Methods of analysis and testing

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

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as thifensulfuron-methyl.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: Cheminova provided written confirmation that the toxicological data included in the following summary were derived from thifensulfuron-methyl having impurity profiles similar to those referred to in Table 2, above

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

Species T	est	Purity % Note[4]	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
Wistar rats, female	oral	97.4	OECD 423, Method B1 (EC), OPPTS 870.1100 Animals received a single oral administration of technical thifensulfuron-methyl at a dose of 2000 or 5000 mg/kg bw. Dosing were performed sequentially, starting with 2000 mg/kg bw. The animals were then observed for 14 days.	LD_{50} > 5000 mg/kg bw No mortality or other signs of systemic toxicity were observed in the treatment group. No classification required according to EU labelling classification Commision Directive 2001/59/EC	CHA Doc. No.: 128 TIM
Wistar rats, male and female	dermal	97.4	OECD 402, Method B3 (EC), OPPTS 870.1200 Animals were administered a single 24-hour semi-occluded dermal application of technical thifensulfuron-methyl at a dose level of 2000 mg/kg bw. Animals were then observed for 14 days.	LD_{50} > 2000 mg/kg bw No mortality was seen in the study and there were no signs of systemic toxicity or dermal irritation. No classification required according to EU labelling classification Commision Directive 2001/59/EC	CHA Doc. No.: 125 TIM
HsdRccHan™ : WIST rats, male and female	inhalation	97.4	OECD 403, Method B2 (EC), OPPTS 870.1300 Animals were exposed to technical thifensulfuron-methyl at 5.03 mg/L using a nose only exposure system for a 4-hour period. Animals were then observed daily for 14	LC_{50} > 5.03 mg/L No mortality was observed in the treatment group. Increased respiratory rate was noted during exposure and one hour post exposure. One day post exposure, the animals exhibited hunched posture only and on day 2	CHA Doc. No.: 124 TIM

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

Species T	est	Purity % Note[4]	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
			days.	they all appeared normal.	
Albino Rabbits (New Zealand)	skin irritation	97.4	OECD 404, Method B4 (EC), OPPTS 870.2500 Animals received a single 0.5 g dose of technical thifensulfuron-methyl applied to an area of clipped skin for 4 hours. Animals were examined for signs of primary irritation at 1, 24, 48 and 72 hours following removal of the chemical.	Technical thifensulfuron-methyl produced a primary irritation index of 0.0 and was classified as non-irritant to rabbit skin according to the Draize classification scheme.	CHA Doc. No.: 122 TIM
New Zealand White rabbits	eye irritation	97.4	OECD 405, Method B5 (EC), OPPTS 870.2400, A single dose of technical thifensulfuron-methyl (0.1 ml) was applied to the conjunctival sac of the right eye of the animals. Animals were then observed for 72 hrs.	Technical thifensulfuron-methyl was classified as a minimal irritant to the rabbit eye according to a modified Kay and Calandra Classification system (Class 3 on a 1 to 8 scale). No corneal or iridal effects were observed. Moderate conjunctival irritation was noted in both eyes after one hour, however, the effects were reversible as both eyes appeared normal after 48 hrs. No classification required according to EU labelling classification Commission Directive 2001/59/EC	CHA Doc. No.: 126 TIM
CBA/Ca (CBA/CaOlaHsd) mice, female	skin sensitisation	97.4	OECD 429, Method B42 (EC), OPPTS 870.2600 Local lymph node assay in the mouse: Three groups of mice were treated with technical thifensulfuron-methyl in DMSO at concentrations of 50%, 25% or 10%. The test solution (25 µl) was applied daily for three consecutive days to the dorsal surface of each ear. On day 6 all mice were	Technical thifensulfuron-methyl was considered to be a non-sensitizer A stimulation index of less than 3 was recorded for each treatment group. No death or signs of systemic toxicity was noted. No classification required according to EU labelling classification Commission	CHA Doc. No.: 127 TIM

Species T	est	Purity % Note[4]	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
			injected via the tail vein with 250 µl of phosphate buffered saline containing ^{3}H-methyl thymidine. Animals were observed daily and killed 5 hours following the administration of ^{3}H-methyl thymidine. A single cell suspension of the lymph node cells were prepared for each animal and after 18 hours incubation with trichloroacetic acid, the incorporation of ^{3}H-methyl thymidine was determined and compared to vehicle.	Directive 2001/59/EC	

Table 4. Mutagenicity profile of the technical material based on in vitro and in vivo tests

Species Te	st	Purity % Note[5]	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
Salmonella typhimurium Escherichia coli	*In vitro* test. Reverse mutation in four strains of *Salmonella typhimurium* and one strain of *Escherichia coli.*	97.4	OECD 471, Method B13/14 (EC), OPPTS 870.5100 Technical thifensulfuron-methyl was tested in concentrations ranging from 1.5 to 5000 µg/plate in the absence and presence of S-9 in the four strains of *Salmonella typhimurium* and the one strain of *Escherichia coli*. The plates were incubated at 37 °C for 48 hrs.	The sensitivity of the assay was validated. Technical thifensulfuron-methyl did not increase the frequency of revertant colonies in the four strains of *Salmonella typhimurium* and the one strain of *Escherichia coli* when tested in concentrations up to the lower limit of toxicity. Therefore, technical thifensulfuron-methyl was considered to be non-mutagenic under the conditions of this test.	CHA Doc. No.: 123 TIM

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

ANNEX 2

REFERENCES

Study number	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
122 TIM	2009a	Thifensulfuron-Methyl technical : Acute Dermal Irritation in the Rabbit. CHA Doc. No.: 122 TIM. 0545/0724. GLP.
123 TIM	2009	Reverse Mutation Assay "Ames Test" using Salmonella typhimurium and Escherichia coli. CHA Doc. No.: 123 TIM. '0545/0727. GLP
124 TIM	2009	Thifensulfuron-Methyl technical : Acute Inhalation Toxicity (Nose only) Study in the Rat. CHA Doc. No.: 124 TIM. 0545/0722. GLP
125 TIM	2009b	Thifensulfuron-Methyl technical : Acute Dermal Toxicity (Limit Test) in the Rat. CHA Doc. No.: 125 TIM. 0545/0723. GLP
126 TIM	2009c	Thifensulfuron-Methyl technical : Acute Eye Irritation in the Rabbit. CHA Doc. No.: 126 TIM. 0545/0725. GLP
127 TIM	2009d	Thifensulfuron-Methyl technical: Local Lymph node Asay in the Mouse. CHA Doc. No.: 127 TIM. 0545/0726. GLP
128 TIM	2009e	Thifensulfuron-Methyl technical: Acute Oral Toxicity in the Rat – Acute Toxic Class Method. CHA Doc. No.: 128 TIM. 0545/0721. GLP
129 TIM	2009	Thifensulfuron-methyl Technical: Determination of Melting Point/Melting Range. CHA Doc. No.: 129 TIM. 0545/0733. GLP.
130 TIM	2009	Determination of the Solubility of Thifensulfuron-Methyl in different organic Solvents. CHA Doc. No.: 130 TIM. CHE0209-PC-053. GLP

THIFENSULFURON-METHYL
FAO/WHO EVALUATION REPORT 452.201/2000

Recommendation

The Meeting recommended that

(i) the proposed specifications for thifensulfuron-methyl TC and WG proposed by DuPont, as amended, should be adopted by FAO.

Appraisal

Thifensulfuron-methyl is a selective sulfonylurea herbicide. Data and draft specifications for TC and WG were provided in 2000.

Thifensulfuron-methyl is moderately soluble in water at pH 5 (0.223 g/l) and quite soluble at pH 7 (2.24 g/l) and pH 9 (8.83 g/l) at 25°C. It has very low vapour pressure at 25°C. Thifensulfuron-methyl is acidic (pK_a 4.0) and a proposal that the TC specification should include a clause for acidity was rejected by the meeting because the test result would be simply a measure of the active ingredient itself.

Thifensulfuron-methyl hydrolyses readily at high and low pH, with half-lives of 28.8 and 6.0 hours at pH 4 and pH 10, respectively, in sterile buffers at 28°C. It is much more stable at neutral pH; the half-life at pH 7 at 45°C is 250 hours. Photolytic degradation of thifensulfuron-methyl is slow.

The meeting was provided with information on the manufacturing process and the nature of the impurities exceeding 1 g/kg and their maximum limits (2-20 g/kg) in the TC. The list of impurities and their maximum limits were identical to the thifensulfuron-methyl impurity profile provided to the French national authorities for review under the European Union approval procedure. The review has been completed and the pesticide has been approved in France.

Analyses for impurities were provided to the meeting for 5 batches of TC produced in Puerto Rico and another 5 batches of TC material produced in France. Material balances were high (990.3 - 997.3 g/kg). Analytical data were also included for an additional 8 related impurities which occurred at levels below 1 g/kg and which were not detected in some batches.

None of the impurities was considered to be a relevant impurity. The proposer had included in the draft TC specification a maximum limit for water of 5 g/kg and stated that a level below this was routinely achieved in the manufacturing process.

However, no information was available on levels of water that could be detrimental to the storage stability of the TC and, in the absence of such information, the meeting decided not to include a maximum limit for water.

The proposer certified that the technical grade active ingredients used to produce the toxicological and ecotoxicological profiles of thifensulfuron-methyl are representative of the thifensulfuron-methyl found in commercial products manufactured by DuPont. Thifensulfuron-methyl TC has low acute toxicity to rats and rabbits, was not irritant in rabbit skin and eye tests and was not sensitizing in a guinea-pig skin sensitization test. Thifensulfuron-methyl TC also showed low sub-chronic (90 days) toxicity in the mouse and dog, while the rat had the lowest NOEL, at 100 ppm, in sub-chronic feeding studies.

In chronic feeding studies, thifensulfuron-methyl TC showed low toxicity to the mouse and dog. The lowest NOEL was for the female rat at 25 ppm. Thifensulfuron-methyl TC was of low toxicity in rat reproduction studies and was negative in genotoxicity testing.

Thifensulfuron-methyl TC and WG were used in the ecotoxicological testing and were of low toxicity, or showed no effects, towards birds, bees, earthworms and beneficial insects and mites. The no-effect concentration for soil microbial respiration was >0.53 mg ai/ kg soil.

The proposed specifications were reworded according to the requirements of the 5th edition of the FAO Manual.

REFERENCES

Cambon, J-P. and Bastide, J. 1996. Hydrolysis kinetics of thifensulfuron-methyl in aqueous buffer solutions. *J. Agric. Food Chem.*, 44, 333-337.

Tomlin, C.D.S (ed). 1997. The Pesticide Manual, 11th edition. British Crop Protection Council, pp 1188-1190.

Woods, T.S. 2000. FAO Specifications for Thifensulfuron-methyl. Letter of 22 March 2000 from Thomas S Woods, Formulations Technology Manager, DuPont Agricultural Products, Wilmington, DE, USA

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 521.201/2000

Uses

Thifensulfuron-methyl is a selective systemic herbicide, absorbed by the leaves and roots of plants and interferes with the synthesis of branched amino acids by the acetolactate synthase (ALS) in sensitive plants. It is used for the post-emergence control of broad-leaved weeds in autumn- and spring-sown cereals, with typical application rates of 9-60 g /ha. Formulation types in clude water- dispersible granules (WG). Thifensulfuron-methyl is normally used in combination with metsulfuron-methyl.

Table 1: Physical and chemical properties of pure thifensulfuron-methyl

Parameter	Value and conditions	Purity	Method ref
Vapour pressure	1.7×10^{-8} Pa 1.3×10^{-10} mm Hg at 25°C	99.6%	Knudsen gas effusion, 6316/PC-23-C
Melting point	171.1±1.2ºC	99.7%	Mettler Thermosystem Mel-Temp Apparatus, OECD 102
Temperature of decomposition	not applicable		
Solubility in water	0.223 g/l (pH 5, 25°C) 2.24 g/l (pH 7, 25°C) 8.83 g/l (pH 9, 25°C)	98.3%	AMR 1662-60 Shake Flask, CIPAC MT 157
Octanol/water partition coefficient	1.06 g/l (pH 5, 25°C) 0.0222 g/l (pH 7, 25°C) 0.00060 g/l (pH 9, 25°C)	99.7%	DuPont 1502 Shake Flask OECD 107
Hydrolysis half-life	8.3 h (pH 4, 45°C) 39 h (pH 5, 45°C) 250 h (pH 7, 45°C) 10 h (pH 9, 45°C)	>98%[1]	AMR 224-84, US EPA "Hydrolysis as a function of pH"
Photolysis	DT50 = 117 h (pH 5) DT50 = 128 h (pH 7) DT50 = 129 h (pH 9)	not	stated
Dissociation constant	pKa = 4.0 (25°C)		not stated

[1] radiochemical purity of [^{14}C]thifensulfuron-methyl >98%

Cambon and Bastide (1996) studied the hydrolysis kinetics of thifensulfuron-methyl in aqueous buffer solutions. The hydrolysis rate is pH dependent and follows pseudo-first-order kinetics (table below). The products of acid hydrolysis are shown in the figure below. At alkaline pH, thifensulfuron-methyl hydrolysed to thifensulfuron, which was slowly transformed by sulfonylurea bridge cleavage and demethylation of the methoxy group.

Table of hydrolysis rates of thifensulfuron-methyl in sterile buffer solutions at 28°C in the dark (Cambon and Bastide, 1996).

pH	k_{obs}, h^{-1}	half-life (h)
4	0.0241	28.8
5	0.0025	277.3
9	0.0071	97.6
10	0.1155	6.0

Figure: proposed acidic hydrolysis pathway of thifensulfuron-methyl in aqueous buffer solutions (pH 4 and 5) at 28°C (Cambon and Bastide, 1996).

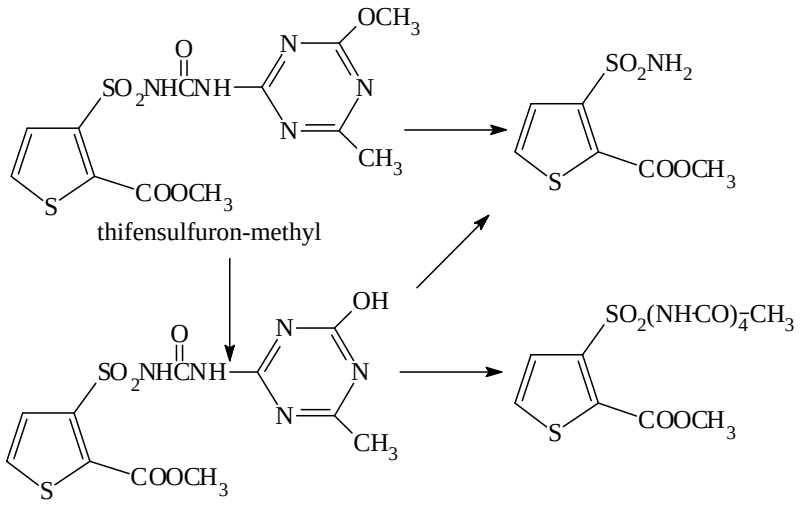

Table 2. Chemical composition and properties of thifensulfuron-methyl TC

Manufacturing process, maximum limits for impurities ≥1 g/kg, 5 batch analysis data	Confidential information was supplied and held on file by FAO. Mass balances for the technical materials were high.
Declared minimum thifensulfuron-methyl content	960 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

Hazard Summary

Thifensulfuron-methyl has not been reviewed by the FAO/WHO JMPR.

WHO/IPCS classification of the active ingredient: "Unlikely to present acute hazard in normal use". The WHO/IPCS reference is to thifensulfuron but will change to thifensulfuron-methyl (A Aitio, WHO/PCS, letter dated 22 May 2000).

Formulations

Thifensulfuron-methyl is usually formulated as water dispersible granules (75% WG). Thifensulfuron-methyl formulations are registered and sold in Australia, Austria, Canada, Nordic countries, Germany, Ireland, Spain and USA.

Methods of Analysis and Testing

The CIPAC method for determination of thifensulfuron-methyl in TC and WG is published in Handbook K. It is a reversed phase HPLC method using a C_{18} column and UV detection at 280 nm and external standardization. The identity tests are based on retention time comparison in HPLC and IR spectroscopy.

Physical properties

The proposer declared that thifensulfuron-methyl formulations produced and commercialized by E.I. DuPont de Nemours and Company comply with the proposed FAO specifications (Woods, 2000).

Containers and packaging

No special requirements needed for thifensulfuron-methyl WG.

Expression of the active ingredient

The active ingredient content is expressed as thifensulfuron-methyl.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: the proposer provided written confirmation that the toxicological data included in the following summary were derived from thifensulfuron-methyl having impurity profiles similar to those referred to in Table 2, above.

Table 1 Toxicological profile of thifensulfuron-methyl technical material, based on acute toxicity, irritation and sensitization.

Route or test	Species	Result	Purity
Oral ra	t	LD_{50}>5000 mg/kg bw	96.5%
Oral rab	bit	ALD>2600 mg/kg bw[1] 97	.1%
Dermal, 24 hours	rabbit	LD_{50}>2000 mg/kg bw	96.5%
Inhalation, 4 hours	rat	LC_{50}>7.9 mg/l air	96.5%
Skin irritation	rabbit	Not irritant	95.6%
Eye irritation	rabbit	Not irritant	95.6%
Skin sensitization	guinea pig	Not sensitizing	98.2%

The acute toxicity of technical thifensulfuron-methyl is low.

Table 2 Toxicological profile of thifensulfuron-methyl technical material, based on repeated administration (sub-chronic, multiple batches of test material were used in some studies)

Study type	Species	NOEL, feed level ppm	Purity
Ten-dose oral study	rat	N/A	93.4%
90-day feeding study	rat	100	94.6%, 93.6%, 95.6%
90-day feeding study	mouse	7500	95.6%, 98.0%
90-day feeding study	dog	1500	95.6%

[1] Approximated lethal dose (ALD). Note: no animals died at the highest dose tested.

Table 3 Toxicological profile of thifensulfuron-methyl technical material, based on repeated administration (chronic, multiple batches of test material were used in long-term studies)

Study type	Species	NOEL, feed level ppm	Purity
18-month feeding study	mouse	7500	95.6%, 98.0%
2-year feeding study	rat	M 500 F 25	95.6%, 98.0%, 98.2%
1-year feeding study	dog	M 750 F 750	98.2%, 94.8%

Table 4 Toxicological profile of thifensulfuron-methyl technical material, based on reproduction toxicity (multiple batches of test material were used in long-term studies)

Study	Species	NOEL, feed level ppm	Purity
One-generation reproduction toxicity study	rat	7500	94.6%, 93.6%, 95.6%
Multi-generation reproduction toxicity study	rat	2500	95.6%, 98.0%

Table 5 Mutagenicity profile of thifensulfuron-methyl technical material, based on in vitro and in vivo tests

Test Te	st organism	Test result	Purity
in vitro			
mutagenicity Ames assay	*Salmonella typhimurium*	negative 93	.4%
mutagenicity CHO/HPRT assay	Chinese hamster ovary cells	negative 96	.9%
chromosome aberration	human lymphocytes	negative 96	.9%
unscheduled DNA synthesis	rat primary hepatocytes	negative 95	.6%
in vivo			
micronuclei induction	mouse (bone marrow cells)	negative 95	.6%
micronuclei induction	rat (bone marrow cells)	negative 95	.6%

Table 6. Ecotoxicology profile of thifensulfuron-methyl technical material

Species R	esult	Purity %
Bobwhite Quail	1524	97.1%
Mallard oral acute	>2510	97.1%
Apis mellifera, 48 h ours LD_{50} topical exposure	>100 µg/bee	98.2%
Apis mellifera, L D_{50} oral exposure	>7.1 µg/bee	98.2%
Eisenia foetida, 14 days contact exposure in soil	LC_{50} > 2000 m g ai /kg s oil NOEC >2000 mg ai/kg soil	95.0%
Chrysoperla carnea, survi vorship or fecundity	no ad verse effects - classified as 'har mless' Clas s 1 und er laboratory conditions	74.4%
Aphidius rhopalosiphi, survi vorship or fecundity	no ad verse effects - classified as 'har mless' Clas s 1 und er laboratory conditions	74.4%
Typhlodromus pyri, mortality and reproduction	classified as 'harmless' Class 1 under w orse c ase e xposure conditions in the laboratory	74.4%
Soil respiration (c arbon mineralization)	NOEC >0.53 mg ai/ kg soil	75.0%
Soil nitrification	NOEC >0.53 mg ai/ kg soil	75.0%