Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS

FOR PLANT PROTECTION PRODUCTS

METSULFURON-METHYL

methyl 2-(4-methoxy-6-methyl-1,3,5-triazin-2-ylcarbamoylsulfamoyl)benzoate

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METSULFURON-METHYL

DISCLAIMER[1]

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

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

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

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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.

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

INTRODUCTION

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

From 2002, the development of WHO specifications follows the **New Procedure**, described in the 1st edition of "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (2002) - 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 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.

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

PART ONE

SPECIFICATIONS

METSULFURON-METHYL

METSULFURON-METHYL

INFORMATION

ISO common name

Metsulfuron-methyl (modified ISO 1750, published)

Chemical names

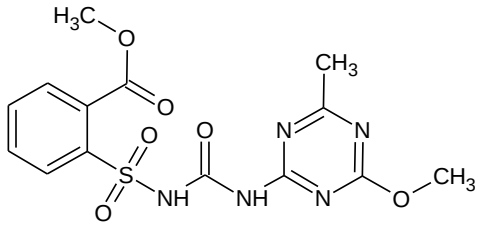
IUPAC methyl 2-(4-methoxy-6-methyl-1,3,5-triazin-2-yl carbamoylsulfamoyl)benzoate

CA methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]= sulfonyl]benzoate

Synonyms

none

Structural formula



Molecular formula

$C_{14}H_{15}N_5O_6S$

Relative molecular mass

381.36

CAS Registry number

74223-64-6

CIPAC number

441

Identity tests

HPLC with UV detection and IR

METSULFURON-METHYL TECHNICAL MATERIAL

FAO Specification 441 / TC (February 2018*)

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 (441/2001, 441/2010 and 441/2017). 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 (441/2001, 441/2010 and 441/2017) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of metsulfuron-methyl together with related manufacturing impurities and shall be an off-white to beige, homogenous, crystalline solid, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (441/TC/M/2, CIPAC Handbook H, p. 205, 1998)

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

2.2 **Metsulfuron-methyl methyl content** (441/TC/M/3, CIPAC Handbook H, p.205, 1998)

The metsulfuron-methyl content shall be declared (not less than 960 g/kg) and, when determined, the average 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/thematic-sitemap/theme/pests/jmps/ps-new/en/

METSULFURON-METHYL WATER DISPERSIBLE GRANULES

FAO Specification 441 / WG (February 2018*)

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 (441/2001, 441/2010 and 441/2017). 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 (441/2001, 441/2010 and 441/2017) as PART TWO form an integral part of this publication.

1. Description

The material shall consist of a homogeneous mixture of technical metsulfuron-methyl, complying with the requirement of FAO Specification 441/TC (February 2018), together with fillers 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** (441/WG/M/2, CIPAC Handbook H, p 207, 1998)

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

2.2 **Metsulfuron-methyl content** (441/WG/M/3, CIPAC Handbook H, p. 207, 1998)

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

Declared content	Permitted tolerance
above 100 up to 250 g/kg	± 6% of declared content
above 250 up to 500 g/kg	± 5% of declared content
above 500 g/kg	± 25 g/kg

* 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/thematic-sitemap/theme/pests/jmps/ps-new/en/

3. Physical properties

3.1 **Wettability** (MT 53.3.1, CIPAC Handbook F, p.165, 1995) (Note 1)

The formulation shall be completely wetted in 60 seconds.

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

Maximum: 2.0% retained on a 75 µm test sieve.

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

Minimum: 70% after 1 minute of stirring.

3.4 **Suspensibility** (MT 184, CIPAC Handbook K, p.142, 2003) (Notes 2 and 3)
A minimum of 75% of the metsulfuron-methyl found under 2.2 shall be in suspension after 30 min in CIPAC Standard Water D at 30±2°C.

3.5 **Persistent foam** (MT 47.3, CIPAC Handbook O, p. 177, 2017) (Note 4)

Maximum: 25 ml after 1 minute.

3.6 **Dustiness** (MT 171.1) (Notes 5 & 6)

Essentially non-dusty.

3.7 **Flowability** (MT 172.1, CIPAC Handbook O, p. 187, 2017) (Note 7)

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: 98% attrition resistance.

4. Storage stability

4.1 **Stability at elevated temperature** (MT 46.3, CIPAC Handbook J, p.129, 2000)

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

- wet sieve test (3.2),
- degree of dispersion (3.3),
- suspensibility (3.4) and
- dustiness (3.6).

Note 1 The product should be tested using 0.5 g. Although this amount of test substance is well below the 5.0 gram sample size required by the MT 53.3.1, it is still far in excess of the maximum concentration recommended for use and does constitute sufficient quantity to enable an accurate visual determination of wettability.

Note 2 MT 184 test shall be conducted using 0.1 g of the formulation. Alternatively, if the buyer requires other CIPAC Standard Waters or temperatures to be used, then this shall be specified.

Note 3 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, simpler methods such as gravimetric and solvent extraction determination may be used on a routine basis provided that these methods have been shown to give equal results to those of chemical assay. In case of dispute, chemical assay shall be the "referee method".

Note 4 The mass of sample to be used in the test should be 0.1g

Note 5 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 171.1, 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 submethod shall be used.

Note 6 MT 171.1 is the corrected and amended version of MT 171. Prior to its publication in a next Handbook, the method can be downloaded from http://www.cipac.org/index.php/methods-publications/errata

Note 7 The data for the test were generated following storage at 45°C ± 2°C for six weeks. However the product has been successfully used in hot climates.

Note 8 Analysis of the formulation, before and after the storage stability test, may be carried out concurrently (i.e. after storage) to reduce analytical error.

METSULFURON-METHYL WETTABLE POWDERS

FAO Specification 441 / WP (January 2018*)

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 (441/2001). It should be applicable to relevant products of 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 the products of other manufacturers. The evaluation report (441/2001) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist of a homogeneous mixture of technical metsulfuron-methyl complying with the requirement of FAO Specification 441/TC (February 2018), together with fillers and any other necessary formulants. It shall be in the form of a fine powder free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 Identity tests: (441/WP/M/2, CIPAC Handbook K, 2003, p.95)
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 Metsulfuron-methyl content (441/WP/M/3, CIPAC Handbook K, 2003, p.95)
The metsulfuron-methyl content shall be declared in g/kg and, when determined, the average content measured shall not differ from that declared by more than the following amounts:

Declared content in g/kg	Permitted Tolerance
above 25 up to 100	± 10% of the declared content
above 100 up to 250	± 6% of the declared content
above 250 up to 500	± 5% of the declared content
above 500	± 25% g/kg

3 Physical properties

3.1 **Wet sieve test** (MT 185, CIPAC Handbook K, p.149, 2003)
Maximum: 2 % retained on a 75 µm test sieve.

3.2 **Suspensibility** (MT 184, CIPAC Handbook K, p.142, 2003) (Notes 1, 2 and 3)

* 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/thematic-sitemap/theme/pests/jmps/ps-new/en/

A minimum of 65 % of the metsulfuron-methyl found under 2.2 shall be in suspension after 30 min in CIPAC Standard Water D at 30 ± 2°C.

3.3 **Persistent foam** (MT 47.3, CIPAC Handbook O, p. 177, 2017) (Note 4)

Maximum: 25 ml after 1 minute

3.4 **Wettability** (MT 53.3.1, CIPAC Handbook F, p.165, 1995) (Note 5)
The formulation shall be completely wetted in 60 seconds without swirling

4 Storage stability

4.1 **Stability at elevated temperature** (MT 46.3, CIPAC Handbook J, p.129, 2000)

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 95 % relative to the determined average content found before storage (Note 6) and the formulation shall continue to comply with the clauses for:

- wet sieve test (3.1),
- suspensibility (3.2) and
- wettability (3.4)

Note 1 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, simpler methods such as gravimetric and solvent extraction determination may be used on a routine basis provided that these methods have been shown to give equal results to those of chemical assay. In case of dispute, chemical assay shall be the "referee method".

Note 2 The mass of sample to be used in the test should be 0.1g.

Note 3 This test will normally only be carried out after the heat stability test

Note 4 The mass of sample to be used in the test should be 0.1g.

Note 5 The product should be tested using 0.5 g. Although this amount of test substance is well below the 5.0 gram sample size required by the MT 53.3.1, it is still far in excess of the maximum concentration recommended for use and does constitute sufficient quantity to enable an accurate visual determination of wettability.

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

PART TWO

EVALUATION REPORTS

[2] Note added in editing, February 2018: Cheminova A/S was acquired by FMC in April 2015. Without further notice from FMC, the conclusions in the Evaluation report 441/2010 continue to be valid.

[3] Note added in editing, February 2018: DuPont sold the intellectual property rights for metsulfuron-methyl to FMC in 2017. Without further notice from FMC, the conclusions in the Evaluation report 441/2001 continue to be valid.

METSULFURON-METHYL
FAO/WHO EVALUATION REPORT 441/2017

Recommendations

The Meeting recommended the following:

(i) the metsulfuron-methyl TC proposed by Rotam Agrochemical Co., Ltd. should be accepted as equivalent to the metsulfuron-methyl reference profile

(ii) the existing FAO specification for metsulfuron-methyl TC should be extended to the material produced by Rotam Agrochemical Co., Ltd.

(iii) the existing FAO specification for metsulfuron-methyl WG should be extended to the material produced by Jiangsu Rotam Chemistry Co., Ltd.

(iv) the existing FAO specifications for metsulfuron-methyl WG and WP should be amended and editorially updated

Appraisal

The data for metsulfuron-methyl were provided by Rotam Agrochemical Co., Ltd. in support of the extension of the existing FAO specifications for TC and by Jiangsu Rotam Chemistry Co., Ltd in support of extension of the existing FAO specifications for WG (2011).

Metsulfuron-methyl is no longer under patent protection. Metsulfuron-methyl has not been evaluated by the FAO/WHO JMPR and WHO/IPCS.

The data for metsulfuron-methyl were evaluated in support of new FAO specifications based on the draft specifications and the supporting data provided by E.I. du Pont de Nemours in 2000. The FAO full specifications for metsulfuron-methyl were initially published in 2001 for TC, WG and WP formulations and extended in 2011 based on the supporting data provided by Cheminova A/S for the TC and WG formulations. [FAO, 2011].

The data package submitted by Rotam was broadly in accordance with the requirements of the 3rd revision of the 1st edition of the Manual on development and use of FAO and WHO specifications for pesticides [FAO/WHO Manual, 2016] and supported the existing specifications.

Rotam's metsulfuron-methyl is currently registered in Ecuador, Indonesia and EU.

The confidential data provided on the manufacturing process of metsulfuron-methyl are the same as those submitted for registration in France. The 5-batch analysis results submitted to FAO are the same as those provided to France for registration purposes. [Six, 2017]

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on all impurities present at or above 1 g/kg and their manufacturing limits in the TC. Mass balances were 99.02 – 99.36 % in the 5-batch data. The declared minimum active ingredient content (980 g/kg) is higher than that of the FAO specification (960 g/kg)

The manufacturing limits for impurities identified in the technical material did not exceed the limits in the reference profile. One new impurity was identified. The new impurity in the Rotam's metsulfuron-methyl TC is well known as a primary metabolite in mammals, and thus unlikely to be differently toxic than the a.i. It was considered not relevant based on the mutagenicity test conducted using a technical batch of metsulfuron-methyl with a content of the respective impurity at the level specified. The study concluded that the test material did not induce mutation under the conditions of the study [RL1720/2007] Therefore the Meeting concluded that this new impurity was considered as non-relevant.

The analytical method for the active ingredient, metsulfuron-methyl, was reversed-phase HPLC with UV detection, identical to CIPAC method 441/TC/M/3. Impurities were also determined by HPLC-UV. Validation data were provided for metsulfuron-methyl and the impurities. Methods for the impurities were validated to LOQs of 0.02 -0.13 g/kg in the TC.
Toxicity data were available for *in vitro* reverse mutation in *Salmonella typhimurium* strains, and *in vivo* micronucleus test in Swiss mice.

The Meeting concluded that the TC produced by Rotam was equivalent to the metsulfuron-methyl reference TC based on Tier-1 evaluation. Rotam also submitted a data package on acute toxicity. The evaluation of the toxicity studies confirms the Tier-1 equivalence finding, in that the toxicological end points and scorings are similar and do not indicate a significant increase or extension of hazard in the Rotam TC.

A data package on physical-chemical properties was provided for metsulfuron-methyl WG formulations showed, that the WG produced by Rotam fully complies with the existing WG specification before and after accelerated storage. The data package also included a study on resistance tested by MT 178.2 - a clause not yet included in the model specifications prior to 2016.

The Meeting therefore recommended the amendment of the WG specification for metsulfuron-methyl with a clause for attrition resistance, subject to agreement of the holder of the reference specification (DuPont) and the equivalent product (Cheminova) for inclusion of the new clause and the proposed limit (attrition resistance minimum 98 %).

FAO therefore contacted DuPont with the request to consider the possible amendment of the reference specification for metsulfuron-methyl WG with a clause for attrition resistance and a limit of 98 % minimum. Cheminova was concurrently contacted to state whether, in case of an amendment, their WG would also comply with the amended WG

specification. Short time later, DuPont responded with the information, that the metsulfuron-methyl rights have been sold to FMC. This company in turn confirmed in writing, that FMC welcomes the amendment of the WG specification and agrees with the proposed limit of minimum 98 % when tested using MT 178.2.

As FMC has acquired Cheminova in 2015, the positive response of FMC is also considered valid for the equivalent products produced by former Cheminova.

The Meeting also recommended an editorial update of the metsulfuron-methyl WG and WP formulations as follows:

- clause for suspensibility: to replace the obsolete MT 168 with MT 184 which is a harmonisation of methods MT 15, MT 161 and MT 168.
- persistent foam clause: to replace MT 47.2 by MT 47.3 now published in Handbook O
- to refer to the amended and corrected MT 171.1 for determination of dustiness of the WG formulation

As these newer methods are judged to lead to equivalent results, the limits are not expected to be affected in any way by referring to these actual CIPAC methods.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 441/2017

Table 1: Chemical composition and properties of metsulfuron-methyl 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 99.02 – 99.36 % and percentages of unknowns were 0.64 – 0.98 %.
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

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC	156.7 °C-159.8 °C	98.03	OECD 102	R A1147 02
Solubility in organic solvents	heptane: 0.0013 g/l; xylene: 0.84 g/l; 1,2-dichloroethane: 28.2 g/l; methanol:10.5 g/l; acetone: 41.6 g/l; ethyl acetate: 12.3 g/l; 1-octanol: 0.57 g/l (all at 25 °C)	98.03	EEC A6	R A1147 08

FORMULATIONS

The main formulation types available are WG and WP.

Rotam's metsulfuron-methyl WG formulations are registered and sold in Ecuador and Indonesia.

METHODS OF ANALYSIS AND TESTING

The analytical method for the active ingredient (including identity tests) is CIPAC method 441/TC/(M)/-. [CIPAC H] 'Metsulfuron-methyl'. The metsulfuron-methyl content is determined by HPLC on a reversed phase column (C_8) with UV detection at 254 nm and phenyl sulphone as internal standard.

The method(s) for determination of impurities are based on HPLC-DAD method validated according to SANCO/3030/99 rev.4.

Test methods for determination of physico-chemical properties of the technical active ingredient were EEC and OECD, while those for the formulations were CIPAC, OPPTS, as indicated in the specifications. [CIPAC F, CIPAC J, CIPAC K, CIPAC O]

PHYSICAL-CHEMICAL PROPERTIES

The physical-chemical properties, the methods for testing them and the limits proposed for the WG formulation comply with the requirements described in the existing FAO specification for metsulfuron-methyl WG formulation (FAO Specification 441/WG (2011)).

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The active ingredient content is expressed as metsulfuron-methyl.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: Rotam Agrochemical provided written confirmation that the toxicological data included in the following summary were derived from metsulfuron-methyl having impurity profiles similar to those referred to in Table 1, above

Table 2. Toxicology profile of the metsulfuron-methyl technical material, based on acute toxicity, irritation and sensitization.

Species	**Test**	**Purity %**	**Guideline, duration, doses and conditions**	**Result**	**Study number**
Sprague-Dawley, Albino Rat (m, f)	Acute oral	97.58	Guideline: OPPTS 870.1100 Duration: Single gavage Dose: 5050 mg/kg Condition: Observations for mortality and clinical/behavioral signs of toxicity were made at least three times on the day of dosing (Day 0) and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing and on Days 7 and 14.	$LD_{50} \geq$ 5050 mg/kg	6531-01
New Zealand White, Albino Rabbit (m, f)	Acute dermal	97.58	Guideline: OPPTS 870.1200 Duration: 24 h Dose: 2020 mg/kg Condition: Observations for mortality and clinical/behavioral signs of toxicity were made at least three times on the day of dosing (Day 0) and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing and on Days 7 and 14; Observations for evidence of dermal irritation were made at approximately 60 minutes after removal of wrappings, and on Days 4, 7, 11 and 14.	$LD_{50} \geq$ 2020 mg/kg	6533-01
Sprague-Dawley Rat (m, f)	Acute inhalation	97.58	Guideline: OPPTS 870.1300 Duration: 4 h Dose: 6.22 mg/l Condition: Observations for mortality and signs of pharmacologic and/or toxicologic effects were made frequently on the day of exposure and at least once daily thereafter for 14 days (Day 0 is day of exposure). Individual body weights were recorded just prior to the inhalation exposure and on Days 7 and 14.	$LC_{50} \geq$ 6.22 mg/L	6534-01
New Zealand White, Albino Rabbit (m, f)	Skin irritation	97.58	Guideline: OPPTS 870.2500 Duration: 4 h Dose: 0.5 g of test substance moistened with 0.8 mL of deionized water was applied to each test site and covered with a surgical gauze patch measuring 2.5 x 2.5 cm and four single layers thick. Condition: The test sites were observed for erythema and edema formation, and any other dermal defects or irritation at 1, 24, 48 and 72 hours after unwrap.	Non-irritating	6535-01

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number
New Zealand White, Albino Rabbit (m, f)	Eye irritation	97.58	Guideline: OPPTS 870.2400 Duration: 30 seconds Dose: 0.1 ml by volume (0.029 g) Condition: The grades of ocular reaction were recorded at 1, 24, 48 and 72 hours after treatment. The corneas of all treated eyes were examined immediately after the 24-hour observation with a fluorescein sodium ophthalmic solution. Any of the corneas which exhibited fluorescein staining at the 24-hour observation were re-examined with the fluorescein sodium ophthalmic solution at each consecutive observation until fluorescein staining of the cornea no longer occurred.	Minimally irritating	6532-01
Hartley-Albino Guinea pig (m, f)	Skin sensitisation	97.58	Guideline: OPPTS 870.2600 Duration: 6 h Dose: the test group were treated with 400 mg of test substance moistened with 0.9 mL of deionized water. The animals were treated once weekly for three weeks, for a total of three treatments. After a two week rest period, all animals were challenged at a virgin test site with an application of 400 mg of test substance moistened with 0.9 mL of deionized water. Condition: Observations for skin reactions at each test site were made approximately 24 hours after each treatment. In addition, observations for skin reactions were made approximately 48 hours after the first induction treatment and 48 hours after the challenge treatment.	Non-sensitizer	6536-01

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

Species	**Test**	**Purity %**	**Guideline, duration, doses and conditions**	**Result**	**Study number**
Salmonella typhimurium	*In vitro* Bacterial Reverse Mutation Test (Ames Test)	98.56	OECD 471; OPPTS 870.5100; EC B13/14 (2000) Metsulfuron-methyl technical was evaluated for its possible mutagenic effect in five strains of *Salmonella typhimurium* at the dose levels of 0.3, 0.5, 0.9, 1.5 and 2.5 µg/plate both in the presence (5% v/v S9 mix) and in the absence of metabolic activation.	Negative	RL1720/2007 – 3.0AM-B
Salmonella typhimurium (TA100, TA102, TA1535, TA98, TA1537)	*In vitro* Bacterial Reverse Mutation Test (Ames Test)	98.32	OECD 471; Metsulfuron-methyl technical was evaluated for its possible mutagenic effect in five strains of *Salmonella typhimurium* at the dose levels of 4.89, 9.77, 19.54, 39.07 and 78.13 µg/plate both in the presence and in the absence of metabolic activation.	Negative	13260
Mus musculus (Swiss mice)	*In vivo* Micronucleus Test	98.56	OECD 474; OPPTS 870.5395; EC B12 tris (2000). One group of Swiss male mice was treated by oral administration (gavage) at a dose selected after a tolerability test 2000 mg/kg bw. Two concurrent control groups, negative and positive received the vehicle (deionised water, 5 mL/kg bw) and cyclophosphamide (75 mg/kg bw), respectively. Animals were treated twice at 0 and 24 h (two treatments at 24 hours interval) and sampled approximately 24 hours following the final treatment.	Negative	RL1720/2007 – 4.0MN-B
Human lymphocytes	*In* vitro Mammalian Cell Micronucleus Test	98.32	OECD 487, In all three treatment regimes (3 hours, +/-S9 and continuous, -S9), treatment of cultures resulted in an acceptable (14.29 to 41.24%) dose related inhibition in % cytostasis. The % micronucleated binucleate cells of all technical treated cultures fell within or close to the historical control values and were not significantly different from the current solvent control cultures..	non genotoxic	13261

ANNEX 2
REFERENCES

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
	FAO, 2011	2011	http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/Metsulfuron-methyl_2011.pdf
	FAO/WHO Manual, 2016	2016	Manual on development and use of FAO and WHO specifications for pesticides, First edition – third revision, FAO Plant Production and Protection Paper 228 http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/JMPS_Manual_2016/3rd_Amendment_JMPS_Manual.pdf
	Six, 2017	2017	E-mail from Thérèse Six, ANSES, Sent on 24 March 2017 13:33 [From: Therese.SIX@anses.fr to laszlo.bura@efsa.europa.eu]
RL1720/2007–3.0AM-B		2008	Bacterial Reverse Mutation Test (Ames Test) for METSULFURON-METHYL TECHNICAL. Study No. RL1720/2007 – 3.0AM-B. GLP. Unpublished
RL1720/2007 – 4.0MN-B		2008	Mammalian Erythrocyte Micronucleus Test for METSULFURON-METHYL TECHNICAL. Study No 1 RL1720/2007 – 4.0MN-B. GLP. Unpublished
13260		2013	Mutagenicity evaluation of Metsulfuron-methyl Technical by Ames *Salmonella typhimurium* –Reverese Mutation Assay, Study No. 13260, GLP, Unpublished
13261		2013	Genotoxicity evaluation of Metsulfuron-methyl Technical by cytokinesis-block micronucleus assay in human peripheral blood, Study No. 13261, GLP, Unpublished
R A1147 02		2003	Determination of Physical and Chemical Properties of METSULFURON METHYL TECHNICAL-MELTING POINT. Study No R A1147 02. GLP. Unpublished
R A1147 08		2003	Determination of Physical and Chemical Properties of METSULFURON METHYL TECHNICAL-SOLUBILITY IN ORGANIC SOLVENTS. Study No R A1147 08. GLP. Unpublished
CIPAC, H	Martijn A and Dobrat W	1998	CIPAC Handbook Volume H. Analysis of Technical and Formulated Pesticides, p.204
CIPAC, F	Martijn A and Dobrat W	1995	CIPAC Handbook Volume F. Physico-chemical Methods for Technical and Formulated Pesticides
CIPAC, J	Martijn A and Dobrat W	2000	CIPAC Handbook Volume J. Analysis of Technical and Formulated Pesticides
CIPAC, K	Martijn A and Dobrat W	2003	CIPAC Handbook Volume K. Analysis of Technical and Formulated Pesticides

CIPAC, O	Cardeal de Oliveira MC and Garvey J	2017	CIPAC Handbook Volume O. Analysis of Technical and Formulated Pesticides
6531-01		2001	Metsulfuron Methyl Technical-ACUTE ORAL TOXICITY STUDY IN RATS. Study No. 6531-01. GLP. Unpublished.
6532-01		2001	Metsulfuron Methyl Technical-ACUTE EYE IRRITATION STUDY IN RABBITS. Study No. 6532-01.GLP. Unpublished.
6533-01		2001	Metsulfuron Methyl Technical-ACUTE DERMAL TOXICITY STUDY IN RABBITS. Study No. 6533-01. GLP. Unpublished.
6534-01		2001	Metsulfuron Methyl Technical-ACUTE INHALATION TOXICITY STUDY IN RATS. Study No. 6534-01. GLP. Unpublished.
6535-01		2001	Metsulfuron Methyl Technical-ACUTE DERMAL IRRITATION STUDY IN RABBITS. Study No. 6535-01. GLP. Unpublished.
6536-01		2001	Metsulfuron Methyl Technical-SKIN SENSITIZATION STUDY IN GUINEA PIGS. Study No. 6536-01. GLP. Unpublished.

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Recommendations

The Meeting recommended that

(i) the metsulfuron-methyl TC as proposed by Cheminova A/S be accepted as equivalent to the metsulfuron-methyl reference profile

(ii) the existing FAO specifications for metsulfuron-methyl TC and WG, should be extended to encompass the products of Cheminova A/S.

(iii) the necessary editorial changes like correct ISO common name, updated references to CIPAC physical and chemical test and analytical methods for metsulfuron-methyl and formulations, respectively, be made when incorporating the evaluation report for the Cheminova A/S materials into the existing specifications and evaluations.

Appraisal

The data for metsulfuron-methyl were evaluated in support of the extension of the existing FAO specification for TC and WG (2001).

Metsulfuron-methyl is under patent in Latvia and Lithuania until 2013.
Metsulfuron-methyl has not been evaluated by the FAO/WHO JMPR and WHO/IPCS.

It was evaluated by the European Commission as part of the EU review of existing active substances for inclusion in Annex I of the Council directive 91/414/EEC in 2000. It was included in Annex I with a minimum purity of 960 g/kg. [CD, 2000]
The data for metsulfuron-methyl were evaluated in support of new FAO specifications based on the draft specifications and the supporting data provided by E.I. du Pont de Nemours in 2000. The FAO specifications for metsulfuron-methyl TC, WG and WP were published in 2001. [FAO, 2001]

Supporting data on metsulfuron-methyl TC and WG formulation were provided by Cheminova A/S in support of an equivalence determination with the reference profile that supports the existing metsulfuron-methyl FAO specifications 441/TC (2001) and 441/WG (2001).
The data submitted were in accordance with the requirements of the revised (revision June 2009) 1st edition of the Manual on development and use of FAO and WHO specifications for pesticides [FAO/WHO Manual, 2006] and supported the existing specifications.
Cheminova A/S metsulfuron-methyl is currently registered in the United States of America, Canada, as well as a range of other countries.
The confidential data provided on the manufacturing process of metsulfuron-methyl are identical to those submitted for registration in the United States of America. The 5-batch analysis results submitted to FAO are the same as those

provided to the US EPA for registration purposes. The impurities and QC limits for metsulfuron-methyl TC produced by Cheminova A/S agree exactly between the information submitted to FAO and to the US EPA, with the exception for the active substance, where the specified minimum is higher in the US than in the FAO submission. This discrepancy is noted in the Cheminova submission to FAO. [Funk, 2010]

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on all impurities present at or above 1 g/kg and their manufacturing limits in the TC. Mass balances were 98.7 to 99.4 % in the 5-batch data.
The declared minimum active ingredient content (960 g/kg) agrees with that of the reference specification. Manufacturing limits for impurities identified in the technical material did not exceed the limits in the reference profile.

One new impurity was identified. The new impurity in the Cheminova A/S metsulfuron-methyl technical seems to be an *O*-demethylation product of the active ingredient, and thus seemed unlikely to significantly extend or increase the hazard in the TC. This assumption was supported by results of the *in-vitro* mutagenicity assay using a technical batch of metsulfuron-methyl with a content of the respective impurity of more than twice the manufacturing limit proposed. The study concluded that the test material did not induce mutation under the conditions of the study [236MEM]. Therefore the Meeting concluded that this new impurity was considered as non-relevant.

The analytical method for the active ingredient, metsulfuron-methyl, was reversed-phase HPLC with UV detection, identical to CIPAC method 441/TC/M/3. Impurities were also determined by HPLC-UV. Validation data were provided for metsulfuron-methyl and the impurities. Methods for the impurities were validated to LOQs of 0.6 -1.6 g/kg in the TC.

Toxicity data were available for reverse mutation in *Salmonella typhimurium,* for rat acute oral, rat acute dermal, rat acute inhalation, rabbit eye irritation, rabbit skin irritation and guinea-pig skin sensitization. The scorings were the same as those of the reference material.

The Meeting concluded that the Cheminova A/S metsulfuron-methyl TC was equivalent to the metsulfuron-methyl reference TC based on Tier 1 evaluation. As the submission of the data package was in 2009, when the second revision of the First Edition was not yet available, Cheminova A/S also submitted a data package on acute toxicity. The evaluation of the toxicity studies (cf. Table 2) confirm the Tier 1 equivalence finding, in that the toxicological end points and scorings are similar and do not indicate a significant increase or extension of hazard in the Cheminova TC.

Physical property data were provided for metsulfuron-methyl WG formulations for comparison with the existing specification.

For the WG, data were available on: wettability, wet sieve test, degree of dispersion, suspensibility, persistent foam, dustiness, flowability and accelerated

storage testing (54˚C). The WG formulation complied with all specification clauses before and after accelerated storage, where appropriate.

The Meeting recommended amendment of the wet sieve test specification clause for metsulfuron-methyl WG and to replace MT 167 with MT 185 which is the preferred method (a revision of the methods MT59.3 and MT 167).
The Meeting also recommended amendment of the suspensibility clause for metsulfuron-methyl WG, and to replace MT 168 with MT 184 which is a harmonisation of methods MT 15, MT 161 and MT 168.

SUPPORTING INFORMATION

FOR

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Table 1: Chemical composition and properties of metsulfuron-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 98.7 – 99.4 % and percentages of unknowns were 0.6 – 1.3 %.
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

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC	160.2 – 160.5 °C. Decomposition occurs (endothermic reaction).	97.8	OECD 102	CHA Doc. No.: 91 MEM
Solubility in organic solvents	7.68 g/l methanol at 20°C 51.1 g/l acetone at 20°C 0.528 g/l xylene at 20°C 35.2 g/l 1,2-dichloroethane at 20°C 11.0 g/l ethyl acetate at 20°C 0.000548 g/l n-heptane at 20°C 0.454 g/l n-octanol at 20 °C	98.9	EEC Method A6	CHA Doc. No.: 150 MEM

USES

Metsulfuron-methyl is a selective herbicide that inhibits the biosynthesis of branched amino acids in sensitive plants by competitively binding to the enzyme system which catalyzes the formation of these amino acids, the acetolactate synthase (ALS). It is used in cereals for the control of broadleafed weeds.

FORMULATIONS

The formulation available is WG. Metsulfuron-methyl may be formulated alone or co-formulated with other sulfonylureas, such as thifensulfuron-methyl.
Cheminova's metsulfuron-methyl WG formulations are registered and sold in many countries, including among others Argentina and United States of America.

METHODS OF ANALYSIS AND TESTING

Metsulfuron-methyl is determined according to CIPAC Method published in Handbook H by HPLC using a reverse phase column (C_8) and UV detection. Quantification is performed using external standard method. The methods for

determination of impurities are based on HPLC using a reverse phase column (C_8), UV detection and external standard method.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, 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 metsulfuron-methyl.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: Cheminova A/S provided written confirmation that the toxicological data included in the following summary were derived from metsulfuron-methyl having impurity profiles similar to those referred to in Table 1, above

Table 2: Toxicology profile of the metsulfuron-methyl technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Purity %	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
Wistar rats, male and female	oral	96.3	OECD 401 Animals received a single oral administration of technical metsulfuron-methyl at a dose of 2000 mg/kg bw. The animals were then observed for 14 days.	LD_{50} > 2000 mg/kg bw No mortality or other signs of toxicity were observed in the treatment group.	CHA Doc. No.: 59 MEM
Wistar rats, male and female	dermal	96.3	OECD 402 Animals were administered a single 24-hour dermal application of technical metsulfuron-methyl at a dose level of 4000 mg/kg bw. Animals were then observed for 14 days.	LD_{50} > 4000 mg/kg bw No mortality was seen in the study and there were no signs of systemic toxicity.	CHA Doc. No.: 49 MEM
Wistar rats, male and female	inhalation	96.3	OECD 403 Animals were exposed to technical metsulfuron-methyl at 5.29 mg/L via an inhalation chamber for a 4-hour period. Animals were then observed daily for 14 days.	LC_{50} > 5290 mg/m^3 LC_{50} > 5.29 mg/L No mortality or other signs of toxicity were observed in the treatment group.	CHA Doc. No.: 48 MEM
Albino Rabbits (New Zealand), male	skin irritation	96.3	OECD 404 Animals received a single 0.5 ml dose of technical metsulfuron-methyl applied to an area of clipped skin for 4 hours. Animals were observed for signs of irritation for up to 72 hours.	Technical metsulfuron-methyl was classified as non-irritant No mortality was recorded during the study and no signs of erythema and oedema were observed at 24 hrs.	CHA Doc. No.: 50 MEM

Albino Rabbits (New Zealand), male	eye irritation	96.3	OECD 405 A single dose of technical metsulfuron-methyl (0.1 g) was applied to the conjunctival sac of one eye of the animals. Animals were then observed for 72 hrs.	According to the guidelines of INCQS, technical metsulfuron-methyl was classified as a slight eye irritant No corneal or iridal effects were observed. Slight conjunctival effects were noted in two animals after 24 hrs, however, the effects were reversible as all the animals showed full recovery after 48 hrs.	CHA Doc. No.: 60 MEM
Albino Guinea pigs, male and female	skin sensitisation	96.3	OECD 406 Animals received three dermal induction applications (0.5 ml, duration 6 hrs) one week apart. Four weeks after the first application, the animals received the challenge application and were then observed for 48 hrs.	Technical metsulfuron-methyl was not considered a potential sensitiser No skin reaction was observed in any of the animals after 24 and 48 hrs.	CHA Doc. No.: 51 MEM

According to Directive 2001/59/EC technical metsulfuron-methyl does not require classification as an eye irritant, as the mean scores of the eye irritation test concerning redness of the conjunctivae is less than 2,5 and as the ocular lesions had decreased to a score of 0 after 24 hrs.

Table 3: Mutagenicity profile of technical metsulfuron-methyl based on *in vitro* and *in vivo* tests

Species	Test	Purity %	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.*	97.8	OECD 471, Method B13/14 (EC), OPPTS 870.5100 Technical metsulfuron-methyl was tested in concentrations ranging from 0.15 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 metsulfuron-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 metsulfuron-methyl was considered to be non-mutagenic under the conditions of this test.	CHA Doc. No.: 236 MEM

ACUTE TOXICITY AND MUTAGENICITY

Metsulfuron-methyl was found to be of low acute oral, dermal and inhalation toxicity, was found to be slightly irritating in the albino rabbit but was not a sensitizer in the maximization test. The TC was found to be non-mutagenic in the in-vitro tests with *S. typhimurium* and *E. coli* without and with metabolic activation.

The GHS classification according to UN version 2005 is: Hazards to the aquatic environment: Category Chronic 1 [WHO, 2005]

ECOTOXICITY

No information was available on ecotoxicity of the metsulfuron-methyl technical material produced by Cheminova A/S, as this is not a data requirement in the 2010 revision of the Manual.

ANNEX 2

REFERENCES

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
	CD, 2000	2000	Commission Directive 2000/49/EC of 26 July 2000 – OJ L 197, 3.8.2000 p. 32–34. http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=32000L0049&model=guichett
	FAO, 2001	2001	http://www.fao.org/ag/AGP/AGPP/Pesticid/Specs/docs/Pdf/new/metsulfu.pdf
	FAO/WHO Manual, 2006	2009	Manual on development and use of FAO and WHO specifications for pesticides, June 2009 revision of the First edition http://www.fao.org/agriculture/crops/core-themes/theme/pests/pm/jmps/manual/en/
	Funk, 2010	2010	E-mail from Steven Funk, EPA, Sent on 26 February 2010 15:51 [From: Funk.Steve@epamail.epa.gov to laszlo.bura@efsa.europa.eu]
236 MEM		2009	Metsulfuron-methyl Technical: Reverse Mutation Assay "Ames Test" using *Salmonella typhimurium* and *Escherichia coli*. CHA Doc. No.: 236 MEM. 0545-0757. GLP. Unpublished.
91 MEM		2004	Metsulfuron-methyl technical: Determination of melting point / melting range. CHA Doc. No.: 91 MEM. 545/285. GLP. Unpublished.
150 MEM		2005	Metsulfuron-methyl (Technical Grade) Physico-Chemical Properties. CHA Doc. No.: 150 MEM. CHV 118/053295. GLP. Unpublished.
Pedersen, 2004		2004	Determination of Metsulfuron-methyl (CAS No. 74223-64-6) in Metsulfuron-methyl Technical and Metsulfuron-methyl WG Formulations. Cheminova A/S. Unpublished report, CHA Doc. No.: VAM 062-01.
CIPAC, H	Martijn A and Dobrat W	1998	CIPAC Handbook Volume H. Analysis of Technical and Formulated Pesticides, p.204
CIPAC, F	Martijn A and Dobrat W	1995	CIPAC Handbook Volume F. Physico-chemical Methods for Technical and Formulated Pesticides
CIPAC, K	Martijn A and Dobrat W	2003	CIPAC Handbook Volume K. Analysis of Technical and Formulated Pesticides
PED1		2005	Determination of storage stability for 14 days at 54°C of Metsulfuron-methyl 600 g/kg WG formulation in commercial packaging, Cheminova A/S, Study No.: PYC 126, Unpublished report, CHA Doc. No.: 171 MEM Determination of flowability of metsulfuron-methyl 600 g/kg WG formulation, batch No. 673-DJØ-170, Cheminova A/S, Study No.: PYC 122, Unpublished report, CHA Doc. No.: 128 MEM

PED2		2005	Determination of storage stability for 14 days at 54°C of metsulfuron-methyl 200 g/kg WG formulation in commercial packaging, Cheminova A/S, Study No.: PYC 125, Unpublished report, CHA Doc. No.: 143 MEM Determination of flowability of metsulfuron-methyl 200 g/kg WG formulation, batch No. 843-DJØ-14, Cheminova A/S, Study No.: PYC 121, Unpublished report, CHA Doc. No.: 127 MEM
	WHO, 2005	2005	The WHO recommended classification of pesticides by hazard and guidelines to classification: 2004, WHO, Geneva
59 MEM		2003 a	Acute oral toxicity test for CHA 170. CHA Doc. No.: 59 MEM. RL0410-03TO-B. GLP. Unpublished.
49 MEM		2003 b	Rat acute dermal toxicity test for CHA 170. CHA Doc. No.: 49 MEM. RL0410-03TC-B. GLP. Unpublished.
48 MEM		2003 c	Acute inhalation toxicity test for CHA 170. CHA Doc. No.: 48 MEM. RL0410-03TI-B. GLP. Unpublished.
50 MEM		2003 d	Rabbits acute dermal irritation / corrosion test for CHA 170. CHA Doc. No.: 50 MEM. RL0410-03IC-B. GLP. TECAM - Unpublished.
60 MEM		2003 e	Acute eye irritation / corrosion test for CHA 170. CHA Doc. No.: 60 MEM. RL0410-03IO-B. GLP. Unpublished.
51 MEM		2003 f	Skin sensitization test for CHA 170. CHA Doc. No.: 51 MEM. RL0410-03SE-B. GLP. Unpublished.

METSULFURON-METHYL

FAO/WHO EVALUATION REPORT 441/2001

Explanation

The data for metsulfuron-methyl were evaluated in support of the review of existing FAO specifications for the technical material (TC), and Water Dispersible Granules (WG) published in 1998 (AGP:CP/349), to include specifications for Wettable Powders (WP) as reviewed by the FAO in 1999.

Metsulfuron-methyl is under patent in New Zealand, Latvia, and Lithuania until 2001, 2013, and 2013, respectively.

Metsulfuron-methyl has not been evaluated by the FAO/WHO JMPR and WHO/PCS. It was evaluated/reviewed by the European Commission and was included in Annex I, according to Directive 91/414, on July 1, 2000 (Reference 1). The Annex I listing lasts for 10 years and expires on 30 June 2011.

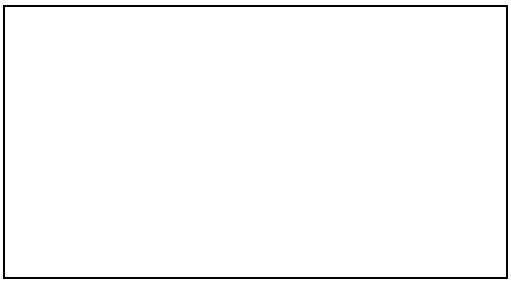
The draft specification and the supporting data were provided by E. I. du Pont de Nemours and Company in 2000. The EU review report and supporting monograph were available for the evaluation.

Uses

Metsulfuron-methyl is a herbicide that inhibits the formation of branched amino acids by competitively binding to the enzyme acetolactate synthase (ALS inhibitor). It is used in cereals, rice, and plantation crops for the control of broadleaf weeds.

Identity

ISO common name:	metsulfuron-methyl
Chemical name(s):	
IUPAC	methyl 2-(4-methoxy-6-methyl-1,3,5-triazin-2-ylcarbamoylsulfamoyl)benzoate
CA	methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]benzoate
Synonyms	None

Structural formula	
Molecular formula	$C_{14}H_{15}N_5O_6S$
Relative molecular mass	381.36
CAS Registry number	74223-64-6
CIPAC number	441
Identity tests	HPLC retention time, IR

Physico-chemical properties of pure metsulfuron-methyl (*Table 1*)

Parameter	Value(s) and conditions	Purity % (nominal)	Method reference (and technique if the reference gives more than one)
Vapour pressure	$3.3X10^{-10}$ Pa at 25 °C (extrapolated)	99%	OECD 104, by extrapolation
Melting point, boiling point and/or temperature of decomposition	Melting point: 158-162 °C Boiling point: not applicable Decomposition temperature: decomposes upon melting	97.4%	OECD 102
Solubility in water	0.5 g/L at 25 °C at pH 5 2.8 g/L at 25 °C at pH 7 213 g/L at 25 °C at pH 9	99.4%	CIPAC MT157, Part 2, Flask Method
Octanol/water partition coefficient	log P_{OW} = 0.28 at 25 °C at pH 5 log P_{OW} = -1.74 at 25 °C at pH 7 log P_{OW} = - 2.35 at 25 °C at pH 9	97.45%	EEC A8, OECD 107, EPA OPPTS 830.7550
Hydrolysis characteristics	Half-life = 22 days at 25 °C at pH 5 Half-life = 85 days at 15 °C at pH 5 Half-life = stable for 30 days at 25 °C at pH 7 & 9 (Reference 2)	99%	EPA Pesticide Assessment Guidelines, Subdivision N, Chemistry: Environmental Fate 161-1

Photolysis characteristics	No photolysis was observed in aqueous solutions under environmental conditions (Reference 3)	99%	EPA Pesticide Assessment Guidelines, Subdivision N, Chemistry: Environmental Fate 161-2
Dissociation characteristics	pKa = 3.75	97.6 %	OECD 112, OPPTS 830.7370, spectrophoto-metric titration

Chemical composition and properties of metsulfuron-methyl methyl technical materials (TC) (*Table 2*)

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 100.3 – 100.6%.
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
Melting range	158–162 °C - decomposition/gas evolution then occurs

Toxicological summaries

Notes.

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from metsulfuron-methyl methyl 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.

The EU review of metsulfuron-methyl methyl established the following toxicological reference doses:

ADI 0 – 0.22 mg/kg bw/day

AOEL systemic 0.7 mg/kg bw/day

AOEL dermal 20 mg/kg bw/day

Table 3. Toxicology profile of metsulfuron-methyl methyl technical material, based on acute toxicity, irritation and sensitisation.

Species	Test	Duration and conditions or guideline adopted	Result
Male and Female Rat Crl:CD®	oral	US EPA proposed guidelines for Pesticide regulation 40 CFR 163.8101 metsulfuron-methyl technical (92.9% a.i.)	LD_{50} = >5000 mg/kg bw No deaths or clinical signs were observed.
Male and Female mouse (Crj:CD-1)	Oral	OECD Test Guideline 401 (1987) metsulfuron-methyl technical (94.8% a.i.)	LD_{50} = >5000 mg/kg bw No deaths or clinical signs were observed.
Male and Female Rabbit (New Zealand White rabbits)	Dermal adsorption	US EPA Proposed Guidelines for Pesticide Registration 40 CFR 163.81-2 metsulfuron-methyl technical (92.9% a.i.)	LD_{50} = >2000 mg/kg bw No deaths or clinical signs were observed.
Male and Female Rat Crl:CD®	inhalation	Haskell modified EPA guideline (24, 48, and 72 hours) metsulfuron-methyl technical (95.8% a.i.)	LD_{50} = >5.0 mg/L No deaths occurred during the study.
Male and Female Rabbit (New Zealand White rabbits)	skin irritation	EPA Proposed Guidelines for Pesticide Registration 40 CFR 163.81-2 U.S. EPA metsulfuron-methyl technical (92.9% a.i.)	Non-irritant (according to EEC Directive 93/21.)
Female Rabbit (New Zealand White rabbits)	eye irritation	Nov. 1983. "Primary Eye Irritation Study." Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Humans and Domestic Animals (revised) 81-4. U.S. EPA. metsulfuron-methyl technical (95.8% a.i.)	Ocular non-irritant (EEC guidance [Directive 93/21])
Male and Female Guinea Pig (Duncan-Hartley albino)	skin sensitisation	U.S. EPA Pesticide Assessment Guidelines, Subdivision F, 81-6. metsulfuron-methyl technical (95.8% a.i.)	No delayed hypersensitivity or allergic reactions

Table 4. Toxicology profile of the technical material based on repeated administration (subacute to chronic)

Species	Test	Duration and conditions or guideline adopted	Result [(isomer/form)]
Male and Female Rat	Subchronic 90-day feeding study	Meets requirements of US EPA FIFRA, 82-1 and EEC Directive 87/302/EEC Part B. metsulfuron-methyl technical (97% a.i.)	NOEL & NOAEL = 1000 ppm (68 mg/kg bw/d for males, 84 mg/kg bw/d for females)
Male and Female Beagle dog	Subchronic 90-day feeding study	Meets requirements of US EPA, FIFRA 82-1 and ECC Directive 87/302/EEC Part B. metsulfuron-methyl technical (92.9% a.i.)	NOEL = 5000 ppm (134 mg/kg/day for males and 129 mg/kg/day for females. Subchronic NOAEL > 5000 ppm (highest dose tested)
Male and Female Rat (Crl:COBS® CD® (SD)BR rats)	Chronic toxicity and potential oncogenicity	24 months metsulfuron-methyl technical (93 and 95.8% a.i.)	metsulfuron-methyl was not oncogenic in male or female rats. NOEL and NOAEL for chronic toxicity was 500 ppm (22.76 mg/kg/day for male and 29.97 mg/kg/day for female rats)
Male and Female Beagle dog	Chronic toxicity	52 weeks metsulfuron-methyl technical (93-95.8% a.i.)	Chronic NOEL 500 ppm in males (13.28 mg/kg/day) based on decreased food consumption and 5000 ppm for females (137 mg/kg/day), the highest dose tested. The NOAEL for male and female dogs was > 5000 ppm (127 and 137 mg/kg/day, respectively) (highest dose tested)
Male and Female Rat	Effect of metsulfuron-methyl on reproductive and lactation of male and female rats over two generations.	2 generation metsulfuron-methyl technical (96% a.i.)	NOEL and NOAEL 500 ppm (34 and 35 mg/kg/body weight for F_O and F_{1B} males and females respectively; and 39 and 43 mg/kg body weight for F_O and F_{1B} males and females respectively, based on decreased body weights in both parental male and female rats.
Female rat (Crl:COBS®C	teratogenicity and developmental toxicity	EPA Pesticide Programs Proposed Guidelines for	Maternal NOAEL was 40 mg/kg/day and developmental NOAEL

Species	Test	Duration and conditions or guideline adopted	Result [(isomer/form)]
D®(SD)BR rats)	in rat	Registering Pesticides in the U.S.; Hazard Evaluation:Humans and Domestic Animals, Federal Register Section Series 163.3, Subpart F. metsulfuron-methyl technical (92.9% a.i.)	was 1000 mg/kg/day or higher. (highest dose tested)

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

Species	Test	Conditions	Result [(isomer/form)]
Salmonella typhimurium	*In vitro* Mutagenicity Ames Assay	Activated and non-activated rat liver (S9) metabolic systems metsulfuron-methyl technical (100% a.i.)	Non-mutagenic in Salmonella typhmurium HLR
CHO cells	Mutagenicity CHO/HGPRT Assay	Study conducted prior to OECD guideline No. 476 and US EPA Guideline 40 CFR 798.5300, but study meets current guidelines with the exception that CO cells were used rather than LY5178Y mouse lymphoma metsulfuron-methyl technical (92.9% a.i.)	metsulfuron-methyl was not mutagenic in the CHO/HGPRT Assay for Gene Mutation when tested at the approximate limit of solubility, 2670 mg/L in culture medium.
Chinese hamster ovary (CHO) Cells	*In vitro* Cytogenetics Assay	The study was conducted prior to OECD guidelines. metsulfuron-methyl technical (92.9% a.i.)	metsulfuron-methyl induced chromosome aberrations in CHO cells exposed *in vitro* at concentrations > 1000mg/L. (highest dose tested)
Rat Primary Hepatocytes	*In vitro* Unscheduled DNA Synthesis (UDS)	Study is scientifically valid; however there is no data requirement for the in vitro assessment of UDS. metsulfuron-methyl technical (92.9% a.i.)	metsulfuron-methyl did not induce unscheduled DNA synthesis in rat hepatocytes under the conditions of the study at concentrations of 381 mg/L or less. (highest dose tested)
Mouse (bone	*In vivo* Micronucleus	Complied with OECD	metsulfuron-methyl did

Species	Test	Conditions	Result [(isomer/form)]
marrow cells)	Assay	No. 474. metsulfuron-methyl technical (92.9% a.i.)	not induce micronuclei in mouse bone marrow polychromatic erythrocytes when administered orally at 5000 mg/kg of body weight
Rat (bone marrow cells)	*In vivo* Cytogenetic Assay	Study conducted prior to OECD guidelines but meets the principles of current guidelines. metsulfuron-methyl technical (92.9% a.i.)	metsulfuron-methyl did not induce chromosome aberrations in rat bone marrow when administered by oral intubation at dose rates up to 5000 mg/kg body weight.

Table 6. Ecotoxicology profile of the technical material

Species	Test	Duration and conditions	Result [(isomer/form)]
Daphnia magna (water flea)	Acute toxicity	OECD Guideline for testing of chemicals 202, U.S. EPA Pesticide Assessment Guidelines Subdivision E, 72-2. metsulfuron-methyl 20% WG (21.0% a.i.)	48hr EC_{50} > 200mg a.i./L
Lepomis macrochirus (bluegill)	Acute toxicity	OECD Guideline for testing of chemicals 203 metsulfuron-methyl technical, (93.74% a.i.)	96 hr. LC_{50} > 119 mg No mortality concentration 119mg/L
Oncorhynchus mykiss (rainbow trout)	Acute toxicity	OECD Guideline for testing of chemicals 203 metsulfuron-methyl technical (93.74% a.i.)	96 hr. LC_{50} > 113 mg No mortality concentration 113mg/L
Salmo gairdneri (rainbow trout)	Flow though 21 day toxicity test	OECD Guideline for testing of chemicals 204 metsulfuron-methyl technical (98.8% a.i.)	21 day EC_{50} & LC_{50}, > 150mg/L NOEC 68mg/L
[insert species, e.g. *Salenastrum* (green alga)	Effect on growth and cell count	[EU Commission Directive 92/69/EEC, Method C3 metsulfuron-methyl technical (97.21% a.i.)	**Healthy Cell Count** EC_{50} 165 µg/L NOEC 50 µg/L Area Under the Growth Curve EC_{50} 157 µg/L NOEC 50 µg/L Growth Rate EC_{50} 875 µg/L NOEC 50 µg/L
Eisenia foetida (Earthworm)	Acute toxicity	OECD 207 metsulfuron-methyl technical (100% a.i.)	14 day LC_{50} > 1000mg/kg
Apis mellifera (honey bee)	Acute oral, and contact toxicity	EPPO Guideline No. 170(1992) metsulfuron-methyl technical (97.4% a.i.)	Acute oral LD_{50} >44.3 µg a.i./bee Acute contact LD_{50} >50 µg a.i./bee
Colinus virginianus (Bobwhite quail chicks)	Short term toxicity	Pesticide Assessment Guidelines, FIFRA, EPA-540-9-82-024 metsulfuron-methyl technical (98% a.i.)	LC_{50} > 5620 ppm NOEL 3160 ppm

Anas platyrhynchos (Mallard ducklings)	Short term toxicity	Pesticide Assessment Guidelines, FIFRA, EPA-540-9-82-024 metsulfuron-methyl technical (98% a.i.)	LC_{50} > 5620 ppm NOEL 562 ppm
Chrysoperla carnea (Green lacewing)	Effects on beneficial arthropods	Bigler, 1988 & ESCORT, 1994 metsulfuron-methyl 20% WG (19.9% a.i.)	Classified as 'harmless' Class 1 of the IOBC Categorisation (Hassan, 1992) when tested under laboratory conditions.
Aphidius rhopalosiphi Parasitic wasp	Effects on beneficial arthropods	Mead-Briggs, M., 1992 metsulfuron-methyl 20% WG (19.9% a.i.)	Classified as 'harmless' Class 1 of the IOBC Categorisation (Hassan, 1992) when tested under laboratory conditions.
Typhlodromus pyri Predatory mite	Effects on beneficial arthropods	Overmeer, 1988, Lowes & Ufer, 1995 ESCORT, 1994 metsulfuron-methyl 20% WG (19.9% a.i.)	Classified as 'harmless' Class 1 of the IOBC Categorisation (Hassan, 1992) when tested under laboratory conditions.
Poecilius cupreus Ground beetle	Effects on beneficial arthropods	IOBC Guidelines, Heimback, 1992 ESCORT 1994 metsulfuron-methyl 20% WG (19.9% a.i.)	Classified as 'harmless' Class 1 of the IOBC Categorisation (Hassan, 1992) when tested under laboratory conditions.

Hazard summary

Metsulfuron-methyl has not been evaluated by the WHO/PCS or by the FAO/WHO JMPR.

Metsulfuron-methyl has not been classified according to WHO/PCS hazard.

N R 50/53 ECB, very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Classification is driven by the algae toxicity endpoint according to Annexes I, II, III, IV to Commission Directive 93/21/EEC of 27 April 1993 adapting to technical progress for the 18th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging, and labelling of dangerous substances.

Formulations

The main formulation types available are water dispersible granules (WG) and wettable powders (WP).

These formulations are registered and sold in many countries throughout the world.

Methods of analysis and testing
The analytical methods for the determination of the active ingredient (including identity tests) are full CIPAC methods and published in Handbook H (TC, WG) and in Handbook K for the WP (References 4 and 5). The metsulfuron-methyl is determined by reversed phase HPLC, using UV detection at 254 nm and internal standardisation with phenyl sulfone. The methods for determination of impurities are based on reversed phase HPLC, using UV detection at 235 nm and external standardisation.

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

Physical properties
The proposer has stated 'The physical properties, the methods for testing them and the limits proposed for the WG and WP formulations, comply with the requirements of the FAO Manual (5th edition). The wettability test (CIPAC MT 53.3.1) should be conducted using a sample of 0.5 grams. Although this amount of test substance is well below the 5.0 gram sample size required by the method, it is still far in excess of the maximum concentration recommended for use and does constitute sufficient quantity to enable an accurate visual determination of wettability.'

Containers and packaging
No extraordinary container or packaging issues need to be considered special requirements.

Expression of active ingredient
The active ingredient is expressed as metsulfuron-methyl.

Appraisal
Metsulfuron-methyl is included in Annex 1 of Council Directive 91/414, and an agreed evaluation monograph, including a review report and the conditions of Annex 1 listing, was available for consultation.

Metsulfuron-methyl is a post-emergence, selective sulfonyl urea herbicide acting through foliar and root uptake. It affects sensitive plants through inhibition of the enzyme acetolactate synthase. Metsulfuron-methyl provides selective control over annual weeds in small grain cereals, rice, and pasture. The application rate of the substance is low, with typical application rates between 4 and 6 g ai/ha and the maximum recommended application rate in Europe of 8 g a i/ha. The application timing depends on the geographical area and crop but typically ranges between the 2 leaf stage of the crop and emergence of the flag leaf.

Metsulfuron-methyl TC is an off-white to beige crystalline solid with a faint odour. The water solubility is pH dependent, with the highest solubility at higher pH values (0.548 g/l at pH 5 and 213 g/l at pH 9), due to the formation of the salts. The octanol/water partition coefficient is low, indicating a low potential for bio accumulation and metsulfuron-methyl exhibits low vapour pressure. The technical material is not classified for explosive, oxidising or flammable properties.

The data summary submitted by the proposer in support of the physico-chemical, toxicological and ecotoxicological properties were in accordance with those evaluated as part of the EU review of metsulfuron-methyl. The Proposer confirmed that all studies submitted for this evaluation were also submitted in support of the EU review of metsulfuron-methyl. Metsulfuron-methyl was found to be of low acute, sub chronic and chronic toxicity. Metsulfuron-methyl is rapidly eliminated from mammalian systems, mainly as the parent compound. The active substance and metabolites do not accumulate in tissues. The compound was not teratogenic and was considered by the EU review not to be genotoxic, although one test result was questioned.

Confidential information on the method of manufacture, the technical specification and data from the analysis of production batches was presented to the meeting. The proposer stated that the confidential data presented were identical to those submitted for registration in the European Union, with France as the rapporteur. Mass balances were 100.3 – 100.6% and the minimum purity of the technical material of 960 g/kg was in accordance with that considered in the EU review. Although a number of production batches showed purities close to that of the minimum specified, the Proposer has confirmed that the figure of 960 g/kg minimum purity is appropriate to the overall production quality. The meeting considered this to be acceptable.

The data supporting the technical material supported the TC specification as proposed.

Specifications for the WG and WP formulations were published in 1997 and 1999 respectively. The proposer has confirmed all physical properties conform to the requirements of the Manual.

Recommendations
Subject to amendments of the specifications for the water dispersible granules and wettable powders in accordance with the 5th Edition of the Manual, the meeting recommended adoption of the specifications for the technical material, water dispersible granule and wettable powder.

ANNEX 1

REFERENCES

1	Official Journal of the European Communities, 3 August 2000 (No. L 197, pp 32-34) Commission Directive 2000/49/EC
2	EPA Guidelines: Hitch, R. K., "Hydrolysis Studies", Pesticide Assessment Guidelines, Subdivision N, Chemistry: Environmental Fate 161-1, pp 44-46; October 1982; National Technical Service Information No. PB83-153973.
3	EPA Guidelines: Hitch, R. K., "Photodegradation Studies in Water", Pesticide Assessment Guidelines, Subdivision N, Chemistry: Environmental Fate 161-2, pp 46-49; October 1982; National Technical Service Information No. PB83-153973.
4	CIPAC Handbook H, p. 204 - 211, 1998.
5	CIPAC Handbook K, p. 95, 2003.