Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

NICOSULFURON

1-(4,6-dimethoxypyrimidin-2-yl)-3-(3-dimethylcarbamoyl-2-pyridylsulfonyl)urea

2022

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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 1999 onward, the development of FAO specifications follows the **New Procedure**, described first in the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products" and later in the 1st edition of "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (2002) - currently available as 3rd revision of the 1st edition (2016) - , which is available only on the internet through the FAO and WHO web sites.
This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPM, rather than the JMPS.]

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

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

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

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

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

* NOTE: PUBLICATIONS ARE AVAILABLE ON THE INTERNET AT (Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at:
http://www.fao.org/pest-and-pesticide-management/guidelines-standards/faowho-joint-meeting-on-pesticide-specifications-jmps/pesticide-specifications/pesticide-specifications-list/en/

OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.

PART ONE

SPECIFICATIONS

NICOSULFURON

PART ONE

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NICOSULFURON

INFORMATION

ISO common name

Nicosulfuron (E-ISO, BSI, ANSI)

Synonyms

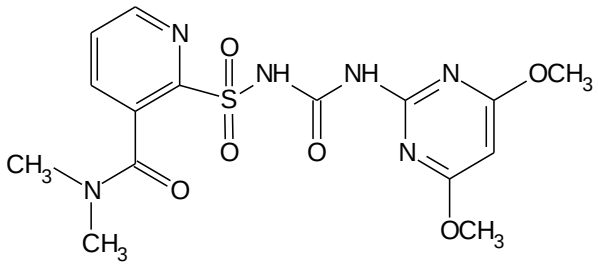
None

Chemical names

IUPAC 1-(4,6-dimethoxypyrimidin-2-yl)-3-(3-dimethylcarbamoyl-2-pyridylsulfonyl)urea

CA 2-[[[[(4,6-dimethoxyl-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-*N*,*N*-dimethyl-3-pyridinecarboxamide

Structural formula



Empirical formula

$C_{15}H_{18}N_6O_6S$

Relative molecular mass

410.4

CAS Registry number

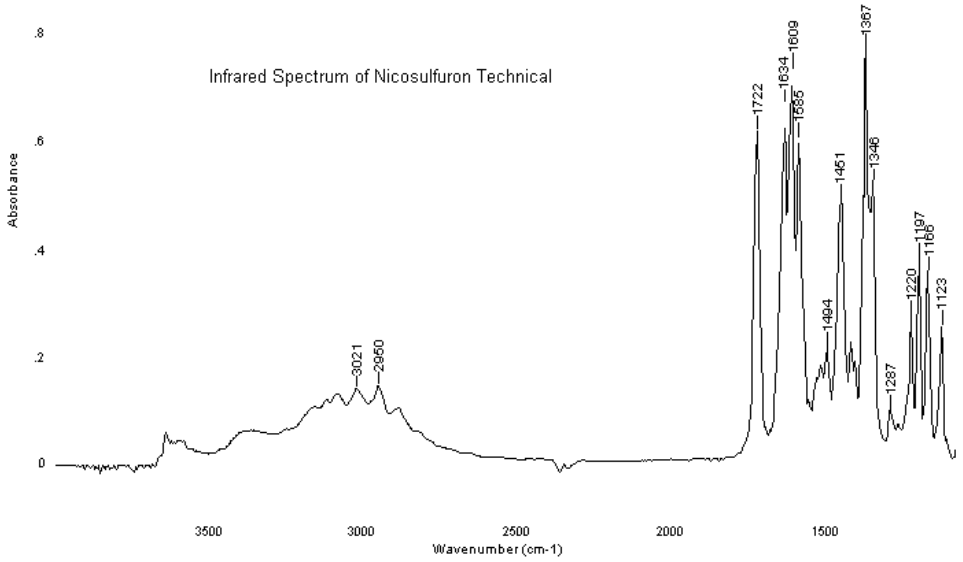
111991-09-4

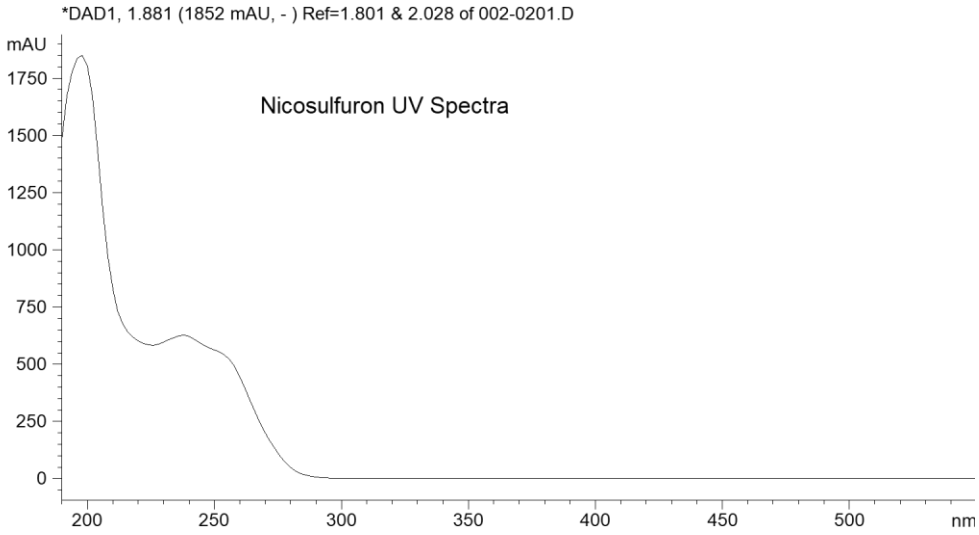
CIPAC number

709

Identity tests

HPLC retention time; IR spectrum; UV spectrum


Infrared Spectrum of Nicosulfuron Technical
Absorbance
.8
.6
.4
.2
0
3500
3000
2500
2000
1500
Wavenumber (cm-1)
3021
2950
1722
1634
1609
1585
1494
1451
1367
1346
1287
1220
1197
1166
1123


*DAD1, 1.881 (1852 mAU, -) Ref=1.801 & 2.028 of 002-0201.D
Nicosulfuron UV Spectra
mAU
1750
1500
1250
1000
750
500
250
0
200
250
300
350
400
450
500
nm

NICOSULFURON TECHNICAL MATERIAL

FAO Specification 709 / TC (January 2022*)

*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 (*709/2005*,* 709/2010, 709/2013 and 709/2021.1*). 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 (*709/2005*,* 709/2010, 709/2013 and 709/2021.1*) as PART TWO form an integral part of this publication.*

1 **Description**

The material shall consist of nicosulfuron together with related manufacturing impurities and shall be a homogeneous white crystalline or powder solid, free from visible extraneous matter and added modifying agents.

2 **Active ingredient**

2.1 **Identity test**s (709/TC/M/2, CIPAC Handbook M, p.122, 2009)

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 **Nicosulfuron content** (709/TC/M/3, CIPAC Handbook M, p.122, 2009)

The nicosulfuron content shall be declared (not less than 910 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/pest-and-pesticide-management/guidelines-standards/faowho-joint-meeting-on-pesticide-specifications-jmps/pesticide-specifications/pesticide-specifications-list/en/

NICOSULFURON WATER DISPERSIBLE GRANULES

FAO Specification 709 / WG (January 2022*)

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 (709/2005 & 709/2021.1*). 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 (709/2005 &* 709/2021.1*) as PART TWO form an integral part of this publication.*

1 Description

The material shall consist of a homogeneous mixture of technical nicosulfuron, complying with the requirements of the FAO specification 709/TC (December 2021), together with carriers and any other necessary formulants. It shall be in the form of granules for application after disintegration and dispersion in water. The formulation shall be dry, free-flowing, essentially non-dusty, and free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 **Identity tests** (709/WG/M/2, CIPAC Handbook M, p.125, 2009)

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 **Nicosulfuron content** (709/WG/M/3, CIPAC Handbook M, p.125, 2009)

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

Declared content, g/kg	Tolerance
above 500	± 25 g/kg

3 Physical properties

3.1 **Wettability** (MT 53.3, CIPAC Handbook F, p.165, 1995)

The formulation shall be completely wetted in 20 sec without swirling.

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

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

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

Dispersibility: minimum 70% after 1 min stirring.

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

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

A minimum of 70% 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 2)

Maximum: 60 ml after 1 min.

3.6 **Dustiness** (MT 171.1, CIPAC Handbook P, p.235, 2021) (Note 3)

Essentially non-dusty.

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

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

4 Storage stability

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

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower that 95% relative to the determined average content found before storage (Note 4) and the formulation shall continue to comply with the clauses for:

- wet sieve test (3.2),
- degree of dispersion (3.3),
- suspensibility (3.4),
- dustiness (3.6),
- flowability (3.7).

Note 1 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, the simpler gravimetric method, MT 168, 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 2 The mass of sample to be used in the test should be at the highest application rate of use recommended by the supplier.

Note 3 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 method 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 method shall be used.

Note 4 Analysis of the formulation, before and after the storage stability test, may be carried out concurrently (i.e. after storage) to reduce analytical error.

NICOSULFURON OIL DISPERSION

FAO specification 709 / OD (January 2022*)

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 reports (709/2013 & 709/2021.1). 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 (709/2013 & 709/2021.1) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of a stable suspension of fine particles of technical nicosulfuron, complying with the requirements of FAO specification 709 / TC (January 2022), in the form of an off-white viscous liquid, in a non-aqueous fluid together with suitable formulants. After shaking or stirring of the sample, the material shall be homogeneous (Note 1).

2 Active ingredient

2.1 **Identity tests** (709/OD/M/2, CIPAC Handbook O, p.79, 2017)

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

2.2 **Nicosulfuron content** (709/OD/M/3, CIPAC Handbook O, P.79, 2017)

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

Declared content in g/kg or g/l at 20± 2 °C	Permitted tolerance
above 25 up to 100 Note: the upper limit is included in each range	±10% of the declared content

3 Physical Properties

3.1 **Pourability** (MT 148.1, CIPAC Handbook F, p. 348, 1995)

Maximum “residue”: 5%.

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

3.2 **Dispersion Stability** (MT 180, CIPAC Handbook H, p. 310, 1998) (Note 3)

The formulation, when diluted at 30 ± 2°C with CIPAC Standard waters A and D, shall comply with the following:

Time after allowing the dispersion to stand	Limits of stability
0 h	initial dispersion complete
0.5 h	"cream", maximum: trace "free oil", maximum: trace "sediment", trace
24 h	re-dispersion complete
24.5 h	"cream", maximum: trace "free oil", maximum: trace "sediment", trace

3.3 **Wet sieve test** (MT 185, CIPAC Handbook K, p.148, 2003) (Note 4)

Maximum: 2% of the formulation shall be retained on a 75 μm test sieve.

3.4 **Persistent foam** (MT 47.3, CIPAC Handbook O, p.177, 2017) (Note 5)

Maximum: 25 ml after 1 min.

4 **Storage Stability**

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

After storage at 0 ± 2°C for 7 days, the formulation shall continue to comply with the clauses for:

- dispersion stability (3.2),
- wet sieve test (3.3),

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

After storage at 40 ± 2°C for 8 weeks, 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:

- pourability (3.1),
- dispersion stability (3.2),
- wet sieve test (3.3)

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

tests must be carried out on a laboratory sample taken after the recommended homogenisation procedure.

Note 2 Unless homogenisation is carried out carefully, it is possible for the sample to become aerated. This can lead to errors in the determination of the mass per millilitre, and in the calculation of the active ingredient content (in g/l), if methods other than OECD 109 are used. If the buyer requires both g/kg and g/l at 20 ± 2 °C, then in case of dispute the analytical results shall be calculated as g/kg.

Note 3 The formulation should be tested at 2% dilution or, alternatively, at the highest and lowest rates of use recommended by the supplier.

Note 4 This test detects coarse particles (e.g. caused by crystal growth) or agglomerates (crust formation) or extraneous materials which could cause blockage of spray nozzles or filters in the spray tank.

Note 5 The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 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

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2021.1 **FAO/WHO Evaluation report** on nicosulfuron based on submission of information from Corteva Agriscience **12**

2013 **FAO/WHO Evaluation report** on nicosulfuron based on submission of information from Rotam Agrochemical Co., Ltd. (TC) and Jiangsu Rotam Chemistry Co., Ltd (OD) **14**

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NICOSULFURON

FAO/WHO EVALUATION REPORT 709/2021.1

Recommendations

The Meeting recommended the following:

i) the change of manufacturer of the FAO reference specifications for nicosulfuron TC and WG from E.I. DuPont to Corteva Agriscience should be noted by FAO

ii) the editorially updated and confirmed FAO specifications for nicosulfuron TC and WG, submitted by Corteva Agriscience should be adopted by FAO

Appraisal

The Meeting noted, that Corteva Agriscience (Corteva) has been formed from the merger of Dow and DuPont in 2017 and became a standalone company in June 2019[2]. The intellectual property rights for nicosulfuron and its formulations previously owned by E.I. DuPont (DuPont) then was integrated into the portfolio of Corteva Agriscience. Its predecessor company, E.I. DuPont, had been the proposer and holder of the FAO reference specifications for nicosulfuron TC and WG (FAO/WHO Evaluation Report 709/2005).

As such a transition may raise certain concerns on the continued validity of the FAO specification for nicosulfuron technical material and formulations (see also FAO/WHO Manual, Section 2.7 on revision of specifications), Corteva was contacted by FAO and a statement on the support of the reference specifications and possible changes therein was requested.

Corteva later on provided a confirmation in writing (Corteva, 2021[3]) to FAO confirming the continued support for the FAO reference specifications for nicosulfuron TC, and WG. Corteva explained, that both manufacturing site and -process for nicosulfuron were not affected by the transition from DuPont to their company and confirmed the continued validity of the published specifications and stewardship for them.

Corteva also communicated to FAO, that a certain intermediate used in the synthesis of nicosulfuron and previously produced in-house is now procured from another supplier. The company explained that the quality of the intermediate sourced from the new supplier meets all quality standard of the former product and that neither the minimum purity nor the impurity profile of the finished nicosulfuron TC are adversely affected by this change of supplier. The Meeting concluded, that this confirmation is acceptable and noted the change of supplier for that intermediate.

The Meeting also noted, that the specifications needed some editorial update with regard to analytical and physical-chemical test methods.

[2] https://www.corteva.ca/en/about-corteva/our-history.html
[3] e-mail Dr. J. Jones, Corteva to FAO, dated Dec 14, 2021

For this reasons, the Meeting recommended that Corteva should be noted as new holder of the reference specifications for nicosulfuron and its formulations produced by Corteva should be considered as the new reference specification.

The FAO specifications for nicosulfuron WG (now Corteva) and OD (holder: Jiangsu Rotam Chemistry Co., Ltd) were considered to require an editorial update as follows

- WG specification: certain CIPAC Methods like suspensibility (MT 14.1), persistent foam (MT 47.3), dustiness (MT 171.1) and stability at elevated temperature (MT 46.4) are available in newer versions that provide equivalent results and are published in recent Handbooks. For these methods, the newer versions are referenced, but no limits were changed.
- OD specification: The version from 2014 carries the designation "Oil Based Suspension Concentrate" which is no longer supported by the 2017 version of the CropLife Monograph Nr. 2[4] - the correct description is now "Oil dispersion". Beside that, the extension of the CIPAC method for determination of nicosulfuron in OD formulations is now published in Handbook O and, similar as for the WG specification, the method to determine the stability at elevated temperature was updated to MT 46.4.

[4] TECHNICAL MONOGRAPH n° 2, 7th Edition Revised March 2017, available through https://croplife.org/wp-content/uploads/2017/04/Technical-Monograph-2-7th-Edition-Revised-March-2017.pdf (October 2021)

NICOSULFURON

FAO/WHO EVALUATION REPORT 709/2013

Recommendations

The Meeting recommended the following:

(i) that the nicosulfuron TC proposed by Rotam Agrochemical Co., Ltd. (Rotam) be accepted as equivalent to the nicosulfuron reference profile

(ii) the existing FAO specification for nicosulfuron TC should be extended to encompass the technical material manufactured by Rotam.

(iii) the new specification for the nicosulfuron OD formulation, proposed by Jiangsu Rotam Chemistry Co., Ltd and as amended, should be adopted by FAO

Appraisal

Data packages for nicosulfuron TC and OD were provided in 2012 in support of an equivalence determination with the TC reference profile and to establish a new specification for an oil based suspension concentrate (OD).

The data submitted were in accordance with the requirements of the revised (second revision, November 2010) 1st edition of the Manual on development and use of FAO and WHO specifications for pesticides [FAO/WHO Manual, 2010] and supported the existing specification.

Rotam's nicosulfuron is currently registered in Argentina, Brazil, Chile, Serbia, Ukraine, USA and European countries.

The confidential data on the manufacturing process of nicosulfuron and the 5-batch analysis results submitted to FAO are identical to those provided to Italy for registration purposes. The impurities and QC limits for nicosulfuron TC produced by Rotam agree exactly between the information submitted to FAO and to Italy, with the following exceptions: the maximum declared content for two of the impurities were set at the LOQ of the methods used for the determination of those impurities, i.e. to < 0.33 g/kg and < 0.01 g/kg respectively. [Santilio, 2012] Italy has registered both TC materials – that of DuPont and Rotam, and considered them equivalent based on the European Union rules [Sanco GD].

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on nicosulfuron and all impurities present at or above 1 g/kg and their manufacturing limits in the TC. Mass balances were 99.63 – 100.01 % in the 5-batch data. The declared minimum active ingredient content was somewhat higher than that of the published FAO specification. The Company confirmed that their product complies with the existing specification, however based on the Rotam's data even a higher value could have been proposed.

Manufacturing limits for impurities identified in the technical material did not exceed the limits in the reference profile. Two new impurities were identified, both with manufacturing QC limits of 1 g/kg, with measured values in the 5-batches below the respective LOQs of the analytical methods used (< 0.33 g/kg and < 0.01 g/kg respectively).

The first impurity is an organic solvent, the second a reagent both with well known toxicological profiles. The Meeting considered that the WHO air quality guideline for the first new impurity is not exceeded from worker exposure to nicosulfuron. For the second new impurity, the lowest concentration at which effects (irritation of nasal mucosa and hepatic enzyme induction) have been reported is 5 ppm (~2 mg/m^3), which translates into 0.8 mg/kg bw.

The default uncertainty factor of JMPR to derive an ADI from a NOAEL (No Observed Adverse Effect Level) is 100, and from a LOAEL (Lowest Observed Adverse Effect Level) the uncertainty factor is usually increased to 300. This leads to an estimate of 0.003 mg/kg bw as an acceptable daily dose for the second impurity. The estimated exposure to impurity 2 at its maximum concentration in nicosulfuron TC (1 g/kg) at EFSA AOEL (Admissible Operator Exposure Level) exposure to nicosulfuron (0.8 mg/kg) [SANCO/3780/07–rev. 1] would be 30% of the derived ADI. Furthermore, the actual concentration of this impurity 2 in the nicosulfuron TC is < 1% of the manufacturing QC limit. For these reasons, the two new impurities were not deemed as relevant in nicosulfuron TC produced by Rotam.

A mutagenicity test (Ames test) on Rotam's nicosulfuron technical has been conducted as Tier-1 data. The study concluded that the test material did not induce mutation under the conditions of the study.

The analytical method for the active ingredient, nicosulfuron, was reversed-phase HPLC with UV detection [CIPAC M]. Impurities were also determined by HPLC-UV. Validation data were provided for nicosulfuron and the impurities. Methods for the impurities were validated to LOQs of 0.01 g/kg - 0.33 g/kg in the TC. [Study 0490]

Toxicity data were available for reverse mutation in *Salmonella typhimurium,* for *in vivo* micronucleus test in Swiss mice, for rat acute oral, rat acute dermal, rat acute inhalation, rabbit eye irritation, rabbit skin irritation and guinea-pig skin sensitization. The ratings were equivalent to those of the reference material.

The Meeting concluded that the nicosulfuron TC produced by Rotam was equivalent to the nicosulfuron reference TC based on Tier-1 evaluation. This is supported by the data on the sensitization capacity (not sensitizing) of the Rotam product, and also by the acute oral and dermal toxicity figures – which however belong to the Tier-2.

The difference in melting point range is due to the difference in purity of the test materials. (97.9% versus 98.1%)

Physical property data were provided for nicosulfuron OD formulation as a new type of formulation. For the OD, data were available on: pourability, spontaneity of dispersion, wet sieve test, persistent foam, particle size distribution, viscosity, stability at low temperature and accelerated storage testing (40˚C).

The Meeting noted that the OD is not based on mineral oil, which would not be miscible with acetonitrile used in the CIPAC method. Instead, a semipolar water immiscible continuous phase is used that mixes well with the extraction solvent acetonitrile.

The OD formulation complied with all specification clauses before and after accelerated storage, where appropriate. [Study 0898]

The Meeting recommended amendment of the pourability specification clause and to replace MT 148 with MT 148.1.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 709/2013

Table 1: Chemical composition and properties of nicosulfuron 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 99.63 – 100.01 % and percentages of unknowns were 0.23 – 0.45 %.
Declared minimum nicosulfuron content	910 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities **<** 1 g/kg and maximum limits for them:	None
Stabilisers or other additives and maximum limits for them:	None

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC and/or TK	172 °C	98.1	EEC A1	R A4201 02
Solubility in organic solvents	heptane: 0.8 mg/l; xylene: 141 mg/l; 1,2-dichloroethane: 16.5 g/l methanol: 356 mg/l; acetone: 14.9 g/l; ethyl acetate: 2.23 g/l octanol: 376 mg/l (all at 25 °C)	98.1	EEC A6	R A4201 08

METHODS OF ANALYSIS AND TESTING

The analytical method for the active ingredient (including identity tests) is the CIPAC method 709/TC/M/3 published in Handbook M (TC, WG). The extension of the method to OD formulations was provisionally adopted by CIPAC in 2013 in Kiev and is available under the prepublishment scheme of CIPAC. Briefly, nicosulfuron is determined by HPLC using a reverse phase column (C8) and detected by UV. Quantification is performed using internal standard method. The method(s) for determination of impurities are based on validated HPLC-PDA and HPLC-UV method at 254nm according to SANCO 3030/99 rev.4.Test methods for determination of physico-chemical properties of the technical active ingredient and formulation were OECD, EEC and CIPAC where appropriate.

CONTAINERS AND PAKCKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The active ingredient is expressed as nicosulfuron.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

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

Table 1. Mutagenicity profile of nicosulfuron technical material based on in vitro and in vivo tests

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium	*In vitro* bacterial gene mutation assay	97.1	OECD 471 (1997), OPPTS 870.5100 (1998), EC B13/14 (2000) Technical nicosulfuron was tested in concentrations ranging from 0 to 5000 µg/plate in the absence and presence of S-9 in five strains of *Salmonella typhimurium*	Negative	RL6959/2008 – 2.0AM-B
Mus musculus (Swiss mice)	*In vivo* micronucleus test	97.1	EC directive 2000/32 No L136, B.12 tris (2000), OECD 474 (1997), OPPTS 870.5395 (1998). Oral dosing, 2000 mg/kg bw	Negative	RL6959/2008 – 3.0MN-B

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

Table 2. Toxicology profile of nicosulfuron technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Purity % Note[6]	Guideline, duration, doses and conditions	Result	Study number
Albino rat (f)	Acute oral	98.13	14 d, OPPTS.870.1100	LD_{50} > 5000 mg/kg bw	8809-04
Albino rat (m, f)	Acute dermal	98.13	14 d, OPPTS.870.1200	LD_{50} > 5050 mg/kg bw	8810-04
Sprague-Dawley rat (m, f)	Acute inhalation	98.13	4 d, OPPTS.870.1300	LC_{50} > 2.36 mg/L	8811-04
Rabbit, New Zealand white (m, f)	Skin irritation	98.13	72 h, OPPTS.870.2500	Non-Irritant	8813-04
Rabbit, New Zealand white (m, f)	Eye irritation	98.13	24 h, OPPTS.870.2400	Non-Irritant	8812-04
Guinea pig, Hartley-Albino (m, f)	Skin sensitisation	98.13	48 h, OPPTS.870.2600	Not a sensitizer	8814-04

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

ACUTE TOXICITY AND MUTAGENICITY

Nicosulfuron has not been evaluated by the WHO IPCS or FAO/WHO JMPR.
The IPCS hazard classification of nicosulfuron is: None (unlikely to present acute hazard in normal use). The EU classification of the product according to 67/548/EEC as amended: N - Dangerous for the environment; R51/53 - Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

GHS classification according to UN edition 2005 is: Hazards to the aquatic environment: Category Chronic 1. Nicosulfuron does not meet the criteria established in the UN Recommendations on the Transport of Dangerous Goods (published by the United Nations Committee of Experts on the Transport of Dangerous Goods) and therefore, is not considered as dangerous or hazardous for transportation purposes. [WHO, 2005]

ANNEX 2

REFERENCES

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
CD, 2008		2008	Commission Directive 2008/40/EC – OJ L87, 29.03.2008. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:087:0005:0008:EN:PDF
FAO, 2006		2006	http://www.fao.org/ag/AGP/AGPP/Pesticid/Specs/docs/Pdf/new/nicosulfuron06.pdf
FAO/WHO Manual, 2010		2010	Manual on development and use of FAO and WHO specifications for pesticides, November 2010 second revision of the First Edition http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/PestSpecsManual.pdf
Santilio, 2012		2012	E-mail from Angela Santilio, National Institute of Health (Istituto Superiore di Sanità), Sent on 01 February 2013 14:45 [From: angela.santilio@iss.it to laszlo.bura@efsa.europa.eu]
SANCO/3780/07 – rev. 1	European Commission	2008	Review report for the active substance nicosulfuron
Sanco GD	European Commission	2012	Guidance Document on the Assessment of the Equivalence of Technical Materials of Substances Regulated under Council Directive 91/414/EEC. SANCO/10597/2003 – rev. 10.1, 13 July 2012
CIPAC, M	Martijn A and Dobrat W, Edts.	2009	CIPAC Handbook Volume M. Analysis of Technical and Formulated Pesticides, p.122
Study 0490		2008	Purity profile for five batches of nicosulfuron technical. RRL Study No 0490. RRL Report No 0490. GLP. Rotam Research Laboratory. Unpublished
Study 0898		2012	Study on the physico-chemical properties of nicosulfuron 40 g/l suspension concentrate. . Study No 0898. Rotam Agrochem International Co., Ltd. Unpublished.
R A4201 02		2006	Determination of Physical and Chemical Properties of Nicosulfuron Technical – Melting point. Study No A4201. Report No R A4201 02. GLP. ANADIAG S.A. Unpublished.
R A4201 08		2006	Determination of Physical and Chemical Properties of Nicosulfuron Technical – Solubility in organic solvents. Study No A4201. Report No R A4201 08. GLP. ANADIAG S.A. Unpublished.
WHO, 2005		2005	The WHO recommended classification of pesticides by hazard and guidelines to classification: 2004, p.27. WHO, Geneva

RL6959/2008 – 2.0AM-B	2008	Nicosulfuron Technical: Bacterial Reverse Mutation Test (Ames Test). Study No 6959/2008 – 2.0AM. Report No RL6959/2008 – 2.0AM-B. GLP.
RL6959/2008 – 3.0MN-B	2009	Nicosulfuron Technical: Mammalian Erythrocyte Micronucleus Test. Study No 6959/2008 – 3.0MN. Report No RL6959/2008 – 3.0MN-B. GLP.
8809-04	2005	Nicosulfuron Technical: Acute oral toxicity study (UDP) in rats. Study No 8809-04. GLP.
8810-04	2005	Nicosulfuron Technical: Acute dermal toxicity study in rats. Study No 8810-04. GLP.
8811-04	2005	Nicosulfuron Technical: Acute inhalation toxicity study in rats. Study No 8811-04. GLP.
8813-04	2005	Nicosulfuron Technical: Acute dermal irritation study in rabbits. Study No 8813-04. GLP.
8812-04	2005	Nicosulfuron Technical: Acute eye irritation study in rabbits. Study No 8812-04. GLP.
8814-04	2005	Nicosulfuron Technical: Skin sensitization study in guinea pigs. Study No 8814-04. GLP.

NICOSULFURON

FAO/WHO EVALUATION REPORT 709/2010

Recommendations

The Meeting recommended:

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

(ii) to extend the existing FAO specification for nicosulfuron to encompass the technical material produced by Cheminova A/S.

(iii) the necessary editorial changes like updated references to CIPAC physical-chemical and analytical methods in the nicosulfuron TC and WG specifications, respectively, be made when incorporating the evaluation report for the Cheminova A/S materials into the existing specifications and evaluations.

Appraisal

Nicosulfuron was under patent in Canada until 2012.

Nicosulfuron has not been evaluated by the FAO/WHO JMPR and WHO/IPCS. Nicosulfuron was evaluated and reviewed 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 2008. It was included in Annex I with a minimum purity of 930 g/kg. [CD, 2008]

The data for nicosulfuron 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 2004. The FAO full specifications for nicosulfuron were published in 2006. [FAO, 2006]

Supporting data on nicosulfuron TC were provided by Cheminova A/S in support of an equivalence determination with the reference profile that supports the existing nicosulfuron FAO specification 709/TC (May 2006).

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 specification.

Cheminova A/S nicosulfuron is currently registered in the United States of America.

The confidential data provided on the manufacturing process of nicosulfuron are identical to those submitted for registration in the United States of America. The 5-batch analysis results submitted to FAO are similar to those provided to the US EPA for registration purposes. The impurities and QC limits for nicosulfuron TC produced by Cheminova agree exactly between the information submitted to FAO and to the US EPA, with the exception for water and the active substance, which 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 99.1 – 101.8 % in the 5-batch data.

The declared minimum active ingredient content (910 g/kg) agrees with that of the existing FAO specification.

Manufacturing limits for impurities identified in the technical material did not exceed the limits in the reference profile, except for water. The water content was considered not being a reason for non-equivalence. One new impurity was identified. No evidence was found that this impurity or its likely metabolites were more toxic or that their toxicity would be qualitatively different from the active ingredient. US EPA has registered both the original, and this new product, and accepted both, thus apparently considering the Cheminova product not to be significantly worse than the original. A mutagenicity test (Ames test) on Cheminova nicosulfuron technical has been conducted as tier-1 data. The study concluded that the test material did not induce mutation under the conditions of the study.

The analytical method for the active ingredient, nicosulfuron, was reversed-phase HPLC with UV detection. Impurities were also determined by HPLC-UV. Validation data were provided for nicosulfuron and the impurities. Methods for the impurities were validated to LOQs of 0.084% - 0.092% in the TC.

The analytical method for determination of nicosulfuron in nicosulfuron technical used by Cheminova was developed in 2005 before the CIPAC method was published. The Meeting requested Cheminova to carry out a bridging study comparing the in-house method with the CIPAC method published in Handbook M to ensure that the results in the 5-batch study were valid and the CIPAC method can be applied to the material produced by the company. The bridging study was provided (L. Mathiasen, 2014) and allowed the conclusion, that the results produced by the in-house method were statistically indistinguishable from those elaborated by the CIPAC method on the same batches of nicosulfuron 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 end points and scorings, respectively, were the same as those of the reference material.

The Meeting concluded that the Cheminova A/S nicosulfuron TC was equivalent to the nicosulfuron reference TC based on Tier-1 evaluation outlined in the FAO and WHO Manual (FAO and WHO, 2010). This is supported by the data on the sensitization capacity (not sensitizing) of the Cheminova product, and also by the acute oral and dermal toxicity figures – which however belong to the Tier 2. As the data package for nicosulfuron was prepared before the 2010 revision of the FAO/WHO Manual with the two-tiered equivalence process became available, the hazard data were kept in the supporting information section.

The difference in melting point range is due to the difference in purity of the test materials. (97.9% versus 95.91%).

References Appraisal

Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
JMPS	2010	Manual on development and use of FAO and WHO specifications for pesticides November 2010 - second revision of the First Edition, Rome, 2010
L. Mathiasen	2014	Cheminova's response to question from JMPS concerning the analytical method for Nicosulfuron TC.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 709/2010

Table 1: Chemical composition and properties of nicosulfuron 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 99.1 – 101.8 % and percentages of unknowns were 0.0 – 0.9 %.
Declared minimum [a.i.] content	910 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities **<** 1 g/kg and maximum limits for them:	None
Stabilisers or other additives and maximum limits for them:	None

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC and/or TK	166.8 – 168.3 °C. Decomposition occurs (endothermic reaction).	95.91	OECD 102	CHA Doc. No.: 45 NIS
Solubility in organic solvents	0.96 g/l methanol at 20 °C 16.0 g/l acetone at 20 °C	95.91	OECD 105	CHA Doc. No.: 47 NIS

USES

Nicosulfuron is a herbicide affecting sensitive weeds through inhibition of the enzyme acetolactate synthase (ALS). Inhibition of ALS, which catalyzes the biosynthesis of branched amino acids in plants, leads to the cessation of cell division and subsequent growth processes in plants. Rapid growth inhibition is followed by plant death. It is used post-emergence in forage maize against a variety of annual grasses and weeds.

FORMULATIONS

Cheminova's nicosulfuron SC and OD formulations are registered and sold in a range of countries throughout the world, including Brasil, Member States of the EU and USA

METHODS OF ANALYSIS AND TESTING

The analytical method for nicosulfuron TC and WG (including identity tests) is a full CIPAC method published in Handbook M.

The methods for determination of impurities are based on HPLC using a reverse phase column (C_{18}), UV detection and external standard method [Pedersen, 2008] and titration based on CIPAC. [Hinz, 2008]

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 nicosulfuron.

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 nicosulfuron having impurity profiles similar to those referred to in Table 1, above

Table 2. Mutagenicity profile of technical nicosulfuron based on in vitro tests

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium	*In vitro* test. Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium.*	95.7	OECD 471 Technical nicosulfuron was tested in a concentration range from 0.0032 to 50 µg/plate in the absence and presence of S-9 (metabolic activation via rat liver post-mitochondrial fraction). The plates were incubated at 37 °C for 3 days.	The sensitivity of the assay was validated. Technical nicosulfuron did not induce mutations in five strains of *Salmonella typhimurium* when tested in concentrations up to the lower limit of toxicity.	CHA Doc. No.: 154 NIS

Table 3. Toxicology profile of technical nicosulfuron based on acute toxicity, irritation and sensitization.

Species	Test	Purity %	Guideline, duration, doses and conditions	Result	Study number
Sprague-Dawley derived, albino rats, female	oral	95.0	OECD 425, OPPTS 870.1100 Three animals received a single oral administration of technical nicosulfuron at a dose of 5000 mg/kg bw. The animals were then observed for 14 days.	LD_{50} > 5000 mg/kg bw No mortality or other signs of toxicity were observed in the treatment group.	CHA Doc. No.: 13 NIS
Sprague-Dawley derived,	dermal	95.0	OECD 402, OPPTS 870.1200 Animals were administered a single 24-hour dermal application of technical	LD_{50} > 2000 mg/kg bw	CHA Doc.

albino rats, male and female			nicosulfuron at a dose level of 2000 mg/kg bw. Animals were then observed for 14 days.	No mortality was seen in the study and there were no signs of systemic toxicity.	No.: 11 NIS
Sprague-Dawley derived, albino rats, male and female	inhalation	95.0	OECD 403, OPPTS 870.1300 Animals were exposed to technical nicosulfuron at 2.04 mg/L via an inhalation chamber for a 4-hour period. Animals were then observed daily for 14 days.	LC_{50} > 2.04 mg/L No mortality or other signs of toxicity were observed in the treatment group.	CHA Doc. No.: 14 NIS
Albino Rabbits (New Zealand), female	skin irritation	95.0	OECD 404, OPPTS 870.2500 Animals received a single 0.5 g dose of technical nicosulfuron applied to an area of clipped skin for 4 hours. Animals were observed for signs of irritation for up to 72 hours.	Technical nicosulfuron was classified as slightly irritating to skin. No mortality was recorded during the study and no signs of edema were observed. Within one hour of test substance administration, all three animals exhibited very slight erythema at the treated sites. No dermal irritation in any of the animals was apparent after 24 hrs. Dermal irritation was evaluated according to the method of Draize. The Primary Dermal Irritation Index was 0.3.	CHA Doc. No.: 10 NIS
Albino Rabbits (New Zealand), female	eye irritation	95.0	OECD 405, OPPTS 870.2400 A single dose of technical nicosulfuron (0.05 g) was applied to the conjunctival sac of one eye of three animals. Animals were then observed for 72 hrs.	Technical nicosulfuron was classified as minimally irritating to the eye. No corneal opacity or iritis were observed. Within one hour of test substance administration, all three treated eyes exhibited conjunctivitis. All animals were free of ocular irritation by 48 hrs. Ocular irritation	CHA Doc. No.: 12 NIS

				was evaluated according to the method of Draize. After one hour, the Maximum Mean Total Score was 6.0.	
Hartley albino Guinea pigs, male and female	skin sensitisation	95.0	OECD 406, OPPTS 870.2600 Animals received three dermal induction applications (0.4 g 60% w/w mixture, 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 nicosulfuron was not considered to be a contact sensitizer. Both test animals (seven of twenty) and control animals (four of ten) exhibited very faint erythema 24 hrs after the challenge application. In the test animals, irritation persisted at one site for 48 hrs, in the control animals, irritation had cleared after 48 hrs.	CHA Doc. No.: 15 NIS

ACUTE TOXICITY AND MUTAGENICITY

Nicosulfuron 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 nicosulfuron 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, 2008	2008	Commission Directive 2008/40/EC – OJ L87, 29.03.2008. http://eur-lex.europa.eu/ LexUriServ/LexUriServ.do?uri=OJ:L:2008:087:0005:0008:EN:PDF
	FAO, JMPS	2006	http://www.fao.org/ag/AGP/AGPP/Pesticid/Specs/docs/Pdf/new/nicosulfuron06.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]
CIPAC, M	Martijn A and Dobrat W, Edts.	2009	CIPAC Handbook Volume M. Analysis of Technical and Formulated Pesticides, p.121
45 NIS		2006	Melting Point and range of Nicosulfurom Técnico Cheminova. CHA Doc. No.: 45 NIS. RF-0265.005.123.06. GLP. BIOAGRI Laboratórios Ltda., Brazil. Unpublished.
47 NIS		2006	Solubility of Nicosulfurom Técnico Cheminova in water and organic solvents. CHA Doc. No.: 47 NIS. RF-0265.008.432.06. GLP. BIOAGRI Laboratórios Ltda., Brazil. Unpublished.
		2005	Determination of Nicosulfuron (CAS No. 111991-09-4) in Nicosulfuron Technical and 240 g/l SC Formulation. Cheminova A/S. Unpublished report, CHA Doc. No.: VAM 081-01.
		2008	Determination of REF 225, REF 208 and REF 363 in Nicosulfuron, technical. CHA Doc. No.: VAM 088-01. Cheminova A/S, Denmark. Unpublished.
		2008	Determination of water in technical pesticide or its formulations. CHA Doc. No.: VAM 022-02. Cheminova A/S, Denmark. Unpublished report.
	WHO, 2005	2005	The WHO recommended classification of pesticides by hazard and guidelines to classification: 2004, p.27. WHO, Geneva
154 NIS		2009	Reverse Mutation in Five Histidine-requiring Strains of Salmonella typhimurium. CHA Doc. No.: 154 NIS. 676/135. GLP. Unpublished.
13 NIS		2006a	Acute Oral Toxicity Up and Down Procedure in Rats. CHA Doc. No.: 13 NIS. 19526. GLP. Unpublished.
11 NIS		2006b	Acute Dermal Toxicity Study in Rats : Limit Test. CHA Doc. No.: 11 NIS. 19527. GLP. Unpublished.
14 NIS		2006c	Acute Inhalation Toxicity Study in Rats : Limit Test. CHA Doc. No.: 14 NIS. 19528. GLP. Unpublished.

10 NIS	2006d	Primary Skin Irritation Study in Rabbits. CHA Doc. No.: 10 NIS. 19530. GLP. Unpublished.
12 NIS	2006e	Primary Eye Irritation Study in Rabbits. CHA Doc. No.: 12 NIS. 19529. GLP. Unpublished.
15 NIS	2006f	Dermal Sensitization Study in Guinea Pigs (Buehler Method). CHA Doc. No.: 15 NIS. 19531. GLP. Unpublished.

NICOSULFURON

FAO/WHO EVALUATION REPORT 709/2005

Recommendations

The Meeting recommended that the specifications for nicosulfuron TC and WG, proposed by Du Pont, should be adopted by FAO.

Appraisal

The Meeting considered data on nicosulfuron, submitted by E.I. du Pont de Nemours, in support of proposed new FAO specifications for TC and WG. The data submitted were in accordance with the requirements of the manual (FAO/WHO 2002) and supported the draft specifications.

Nicosulfuron is a herbicide, used post-emergence in forage maize to control various annual grasses and other weeds. It is under patent in Belgium, Chile, Greece, Luxembourg and Sweden until 2007, in the USA until 2006 and in Canada until 2012.

Nicosulfuron is acidic (pKa = 4.22) and its water solubility is very dependent upon pH (407, 7100 and 46000 mg/kg at 25°C at pH 5, 7 and 9 respectively). It is stable to hydrolysis at pH 7 and 9, but hydrolyses with a half-life of 15 days at pH 5. Photolysis of nicosulfuron is quite slow.

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. The process typically produces nicosulfuron having a minimum assay of 910 g/kg. Analyses of 5 batches of nicosulfuron produced in 1998 and 1999 accounted for 99.2-99.89 % of the material (nicosulfuron 91.9-93.95%, water 4.1-4.19%, total other impurities 1.79-3.60%). These data were stated to be similar, though not identical, to those submitted for registration in the USA. For reasons beyond the control of the manufacturer and FAO, it was not possible to obtain independent confirmation from the USA authorities but the manufacturer provided details of all variations between the two sets of data (Du Pont 2006). The 5-batch analysis data provided to FAO were from a later study than the corresponding data submitted to USEPA. The proposed minimum nicosulfuron content of the TC (910 g/kg) was higher than the minimum declared for registration in the USA (885 g/kg). Four additional impurities, all <1 g/kg (and hence non-relevant) and identified in the data submitted to FAO, did not appear in the data submitted to USEPA. The manufacturing specification originally submitted to FAO was replaced with one identical to that submitted to USEPA, which was only slightly different.

The Meeting agreed that none of the impurities should be designated as relevant.

The analytical method for determination of nicosulfuron relies on reversed-phase HPLC-UV and internal standardization with diphenylmethylurea. The method was adopted by CIPAC in 2005, for the analysis of TC and WG. The HPLC method provides one identity test, with IR and UV spectrophotometry for further identification.

The draft specifications for nicosulfuron TC and WG complied with the requirements of the manual (FAO/WHO 2002).

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 709/2005

Uses

Nicosulfuron is a herbicide, which affects sensitive weeds through inhibition of the enzyme acetolactate synthase (ALS). Inhibition of ALS leads to the cessation of cell division and subsequent growth processes in plants. Rapid growth inhibition is followed by plant death. It is used post-emergence in forage maize against a variety of annual grasses and weeds.

Identity of the active ingredient

ISO common name

Nicosulfuron (E-ISO, BSI, ANSI)

Synonyms

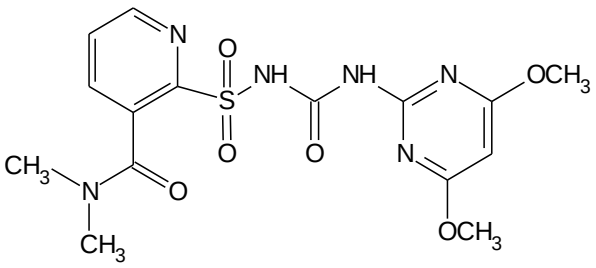
None

Chemical names

IUPAC 1-(4,6-dimethoxypyrimidin-2-yl)-3-(3-dimethylcarbamoyl-2-pyridylsulfonyl)urea

CA 2-[[[[(4,6-dimethoxyl-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-*N*,*N*-dimethyl-3-pyridinecarboxamide

Structural formula



Empirical formula

$C_{15}H_{18}N_6O_6S$

Relative molecular mass

410.4

CAS Registry number

111991-09-4

CIPAC number

709

Identity tests

HPLC retention time; IR spectrum (page 4); UV spectrum (page 4)

Physico-chemical properties of nicosulfuron

Table 1. Physico-chemical properties of pure nicosulfuron

Parameter	Value(s) and conditions	Purity %	Method	References
Vapour pressure	1.6×10^{-14} Pa at 25ºC (extrapolated from measurements at 136.6ºC to 165.9ºC)	Not known	Knudsen gas effusion Method US EPA Pesticide Assessment Guidelines Subdivision D, Series 63-9	Knudsen 1909 USEPA 1982a AMR 1263-88
Melting point, temperature of decomposition	Melting point: 183.3 ± 0.3ºC Decomposition temperature: (colour changes) 180-190ºC	97.9	OECD 102 OPPTS 830.7200	USEPA 1996a DuPont-13183
Density	1.4222 g/cm^3 at 20ºC	97.9	OECD 109 pycnometer method OPPTS 830.7300	USEPA 1996b DuPont-13183
Solubility in water	All in buffered solutions at 25ºC* 407 mg/kg at pH 5 7.1 g/kg at pH 7 46 g/kg at pH 9	92 (mono-hydrate)	U.S. EPA Pesticide Assessment Guidelines Subdivision D, Series 63-8	USEPA 1982b V9360.D
	All in buffered solutions at 28ºC** 370 mg/l at pH 5 (4.6) 390 mg/l at pH 5 (5.1-5.6) 9.0 g/l at pH 7 (6.3) 15.0 g/l at pH 7 (6.6) 18.0 g/l at pH 9 (7.2) >250 g/l at pH 9 (9)	97.3 (mono-hydrate)	U.S. EPA Pesticide Assessment Guidelines Subdivision D, Series 63-8	AMR-1333-88

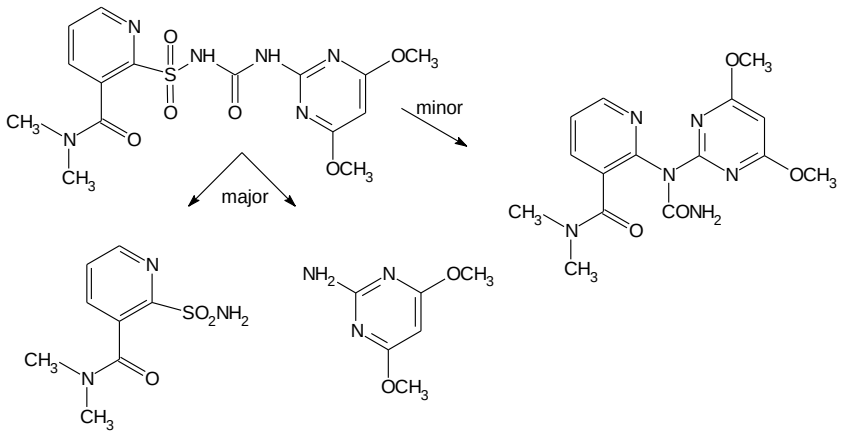
* Test compound was the monohydrate but results are expressed as nicosulfuron. Densities of pH 7 and 9 buffer solutions of test compound were 1.11 and 1.05 g/ml, respectively. Density of pH 5 solution not measured.

** Test compound was the monohydrate but results are expressed as nicosulfuron. Initial pH value of buffer shown, with final measured pH value in parentheses.

Table 1. Physico-chemical properties of pure nicosulfuron

Parameter	Value(s) and conditions	Purity %	Method	References
Octanol/water partition coefficient (at 25ºC)	log P K_{OW} = -0.36 at pH 5 (5.3) log P K_{OW} = -1.7 at pH 7 (7.0) log P K_{OW} = -2.2 at pH 9 (8.7)	99***	U.S. EPA Pesticide Assessment Guidelines Subdivision D, Series 63-11, shake flask method	USEPA 1982c AMR-827-87
Hydrolysis characteristics (at 25ºC, 30 d test, see also Figure 1)	Half-life = 15 days at pH 5 Stable at pH 7 Stable at pH 9	95/97 ****	U.S. EPA Pesticide Assessment Guidelines Subdivision N, Series 161-1	USEPA 1996c AMR 1104-88
Photolysis characteristics (at 25ºC, 30 d test, simulated sunlight)	Half-life = 14-19 days at pH 5 (dark control approx. 18 days) Half-life = 190-250 days at pH 7 (dark control stable) Half-life = 180-200 days at pH 9 (dark control stable)	99/98.8 *****	U.S. EPA Pesticide Assessment Guidelines Subdivision N, Series 161-2	USEPA 1996d AMR 1173-88
Dissociation characteristics	pKa = 4.22 at 25ºC	97.9	OECD 112, spectrophotometric method, OPPTS 830.7370	USEPA, 1996e. DuPont-13182

Figure 1. Hydrolysis of nicosulfuron at pH 5 (McFetridge, 1988)



*** Radiopurity, pyrimidine label.

**** Radiopurity, 95% pyridine label, 97% pyrimidine label.

***** Radiopurity, 99% pyridine label, 98.8% pyrimidine label.

Table 2 Chemical composition and properties of technical nicosulfuron (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 99.21-99.88% and no unknowns were reported
Declared minimum nicosulfuron content	910 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 temperature of the TC	183.3°C, decomposition occurs during melting

Hazard summary

Nicosulfuron has not been evaluated by the FAO, JMPR or WHO/IPCS. A mini-dossier was submitted to Greece in 2004 and is currently under review. Nicosulfuron was submitted to the USEPA in 1990 and is currently registered in the USA.

The WHO classification of nicosulfuron is U: unlikely to cause acute hazard in normal use (WHO 2002).

Nicosulfuron does not meet the criteria established in the UN Recommendations on the Transport of Dangerous Goods (published by the United Nations Committee of Experts on the Transport of Dangerous Goods) and therefore, is not considered as dangerous or hazardous for transportation purposes.

Formulations

The main formulation type is WG, which registered and sold in several countries, worldwide. Nicosulfuron is not co-formulated with other active ingredients.

Methods of analysis and testing

Nicosulfuron is determined in the TC or WG by reversed-phase HPLC-UV, using a C_8 column and a mobile phase of water/acetonitrile, adjusted to pH 2.5 with phosphoric acid. Samples are prepared for analysis by dissolution in acetonitrile, with the addition of diphenylmethylurea as an internal standard. Nicosulfuron and the internal standard are detected at 245 nm. The method was adopted by CIPAC in 2005, following validation for analysis of the TC and both paste-extruded and dry flowable WG formulations.

Nicosulfuron may be identified by its retention volume in the HPLC method and by its UV and IR[1] spectra.

[1] A typical potassium disc should contain 0.15-0.35% by weight of nicosulfuron from the sample and the IR spectrum should not differ significantly from that of reference nicosulfuron prepared in the same way.

Physical properties

The physical properties, the methods for testing them and the limits proposed for the WG formulation, comply with the requirements of the manual (FAO/WHO 2002). The data in Table 7 were presented in support of the proposed specification.

Table 1. Physical testing of nicosulfuron 75 % WG prepared in April 2002 (DuPont-11469)

Test	Method	Result	
Appearance	-	Colour: light beige Odour: very slight acrid odour.	
pH of 1% aq. dispersion	CIPAC MT 75	4.5	
Bulk density (tap density)	CIPAC MT 169	0.62 g/ml	
Wettability	CIPAC 53.3.1	1 second	
Flowability	CIPAC MT 172	Product flowed spontaneously	
Storage stability at 54°C, 14 days	CIPAC MT 46.3	Ambient	After 54ºC storage, 14 d
Assay	-	75.1% ai	75.3% ai
pH	CIPAC MT 75	4.5	4.6
Wet sieve.	CIPAC MT 182	0%	0%
Suspensibility. Note 1.	CIPAC MT 168	83.4%	84.2%
Dispersibility	CIPAC MT 174	98.4%	97.6%
Persistent foam	CIPAC MT 47.2	39 ml at 1 minute	35 ml at 1 minute
Attrition resistance	CIPAC MT 178	99.3%	99.3%
Dust	CIPAC MT 171	5.7 mg (0.019%)	7.1 mg (0.02%)
Dry sieve	CIPAC MT 170	retain >90% on ~500 µm and <10% on 1410 µm	retain >90% on ~500 µm and <10% on 1410 µm

Note 1. Suspensibility: by analytical determination.

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as nicosulfuron, in g/kg.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

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

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

Species	Test	Duration and conditions or guideline adopted	Purity %	Result	Reference
Rat (m,f)	Acute oral	14 d, USEPA Subdivision F, 81-1 (USEPA, 1982d)	90.6	LD_{50} >5000 mg/kg bw	HLR 737-88 RV1; HLR 737-88 RV1 AD1
Rabbit, New Zealand white (m,f)	Acute dermal	14 d, USEPA Subdivision F, 81-2 (USEPA, 1982e)	90.6	LD_{50} >2000 mg/kg bw	HLR 582-87 RV1; HLR 582-87 RV1 AD1
Rat, Crl:CD BR (m,f)	Acute inhalation	4 h, ,USEPA Subdivision F, 81-3 (USEPA, 1982f)	90.6	LC_{50} >5.9 mg/l	HLR 81-88 AD1; HLR 81-88 SU1
Rabbit, New Zealand white (m)	Acute skin irritation	72 h, USEPA Subdivision F, 81-5 (USEPA, 1982g).	90.6	Non-irritant	HLR 647-87; HLR 647-87 AD1
Rabbit, New Zealand white (m)	Acute eye irritation	24 h, EEC Method B5, USEPA Subdivision F, 81-4 (USEPA, 1982h)	90.4	Non-irritant	HLR 146-87 RV1 AD1; HLR 146-87 RV1 AD2
Guinea pig, Duncan Hartley albino (m,f)	Acute skin sensitization	48 h; Buehler Method (Buehler, 1965), US EPA Subdivision F, 81-6 (USEPA, 1982i)	90.4	Not a sensitizer	HLR 429-87 RV1; HLR 429-87 RV1 AD1

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

Species	Test	Duration and conditions or guideline adopted	Purity %	Result	Reference
Rat, Cr1:CD BR (m,f)	Oral and reproductive toxicity (one generation)[1]	90 d, USEPA Subdivision F, 83-5	90.6	NOEL = 20,000 ppm (1495 and 1830 mg/kg bw/d, m & f, respectively) [2]	HLR 15-88; HLR 15-88 AD1
Mouse, Cr1:CD-1 (ICR)BR (m,f)	Oral	90 d, USEPA Subdivision F, 82-1	90.6	NOEL = 300 ppm (43.9 and 62.3 mg/kg bw/d, m&f, respectively) [2]	HLR 16-88; HLR 16-88 AD1
Dog, beagle (m,f)	Oral	90 d, USEPA Subdivision F, 83-1	90.6	NOEL = 20,000 ppm (710 and 689 mg/kg bw/d, m&f, respectively) [2]	HLR 332-88; HLR 332-88 AD1
Rat, Cr1:CD BR (m,f)	Oral	24 months, USEPA Subdivision F, 83-5	90.6	NOEL = 20,000 ppm (786 and 1098 mg/kg bw/d m&f, respectively) [2]	HLR 637-89; HLR 637-89 SU AP1
Mouse, Crl/CD-1 (1CR) BR, (m,f)	Oral oncogenicity	18 months, USEPA Subdivision F, 83-2	90.6	NOEL = 7500 ppm (993 and 1312 mg/kg bw/d, m&f, respectively) [2]	HLR 645-89; HLR 645-89 SU1
Dog, beagle (m,f)	Oral feeding	1 year, USEPA Subdivision F, 83-1	90.6	NOAEL(m) = 5,000 ppm (147 mg/kg bw/d; NOAEL(f) = 20,000 ppm (587 mg/kg bw/d) [2]	HLR 390-89
Rat, Crl:CD BR (m,f)	Reproductive toxicity (2 generations)	USEPA Subdivision F, 83-4	90.6	NOEL (parental and offspring) = 5,000 ppm (289 and 370 mg/kg bw/d m&f, respectively) [2]	HLR 429-89

[1] The minimum requirements of USEPA guidelines were met but the study also included a 45-day clinical pathology examination and a satellite group of 10 rats/sex/dose as a one-generation reproductive range-finding study. Following the 90-day feeding phase, these animals were mated and allowed to deliver offspring, which were observed through weaning.

[2] Mean daily intake values are based on diets prepared using a purity value of 94.5%. Subsequent purity analysis by the project sponsor found the purity to be 90.6%.

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

Species	Test	Duration and conditions or guideline adopted	Purity %	Result	Reference
Rat, Crl:CD BR (f)	Teratogenicity study	16 d, U.S. EPA FIFRA Guideline, Subdivision F, 83-3	90.6	Non teratogenic (NOAEL) at up to 5581 mg/kg bw/day [1]	HLR 611-88; HLR 611-88 AD1

[1] Mean daily intake values were recalculated based on diets prepared using the new purity value of 90.6 %

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

Species	Test	Conditions	Purity %	Result	Reference
Salmonella typhimurium	Mutagenicity	U.S. EPA Pesticide Assessment Guidelines, Subdivision F, 84-2	90.6	Negative [1]	HLR 734-88; HLR 734-88 AD1
Chinese Hamster ovary cells	CHO/HRPT gene mutation	U.S. EPA Pesticide Assessment Guidelines, Subdivision F, 84-2	90.6	Negative with and without activation [1]	HLR 429-88; HLR 429-88 AD1
Rat hepatocytes	*In vitro* Unscheduled DNA synthesis (UDS)	U.S. EPA Pesticide Assessment Guidelines, Subdivision F, 84-2	90.6	UDS not observed [1]	HLR 302-88; HLR 302-88 AD1
Human lymphocytes	*In vitro* gene mammalian cytogenetics	U.S. EPA Pesticide Assessment Guidelines, Subdivision F, 84-2	90.6	Negative with and without activation [1]	HLR 470-88; HLR 470-88 AD1

[1] Subsequent reanalysis by the project sponsor found the test substance purity to be 90.6 %, not the original 94-97% as originally reported. Test results were not recalculated but this has no effect on the reported results as these were based on nominal concentration, not corrected for sample purity.

Table D. Ecotoxicology profile of nicosulfuron technical material

Species	Test	Duration and conditions	Purity %	Result	Reference
Lepomis macrochirus (bluegill sunfish)	Acute	96 h, static, U.S. EPA Pesticide Assessment Guidelines, Subdivision E, 72-1	90.6	LC_{50} >1000 mg/l *	HLR 185-88; HLR 185-88 AD1
Oncorhynchus mykiss (rainbow trout)	Acute	96 h, static, U.S. EPA Pesticide Assessment Guidelines, Subdivision E, 72-1	90.6	LC_{50} >1000 mg/l *	HLR 726-8; HLR 726-87 AD1
Daphnia magna (water flea)	Acute toxicity	48 h, static, U.S. EPA Pesticide Assessment Guidelines, Subdivision E, 72-2	90.6	EC_{50} >1000 mg/l *	HLR 121-88; HLR 121-88 AD1
Daphnia magna (water flea)	Chronic toxicity	21 d, static renewal, OECD Guideline 202, U.S. EPA Pesticide Assessment Guidelines, Subdivision E, 72-4	95.2	NOEC = 43 mg/l MATC = 61 mg/l LOEC = 86 mg/l EC_{50} >710 mg/l	HL-1997-01004
Lemna gibba	Growth and reproduction	14 d, FIFRA, Subdivision J, 122-2 & 123-2	92.9	Frond density: EC_{50} = 6.7 µg/l NOEC = 2.5 µg/l (Williams Test) Mean growth rate: EC_{50} = 9.0 µg/l NOEC = 2.5 µg/l (Williams Test) Biomass: EC_{50} = 7.3 µg/l NOEC = 5.0 µg/l (Kruskal-Wallis Test)	Williams 1971; Williams 1972; Sokal & Rohif 1981; AMR 2178-91

* Subsequent reanalysis by the project sponsor found the test substance purity to be 90.6 %, not the original 94-97% as originally reported. Test results were not recalculated but this has no effect on the reported results as these were based on nominal concentration, not corrected for sample purity.

Table D. Ecotoxicology profile of nicosulfuron technical material

Species	Test	Duration and conditions	Purity %	Result	Reference
Selenastrum capricornutum (green alga)	Growth and reproduction	120 h, FIFRA, Subdivision J, 122-2 Draft Guidelines for Nontarget Plant Testing for Registration of Pesticides in Canada, Tier I	91.4	NOEC = 30 µg/l	AMR 2321-92
Eisenia foetida andrei earthworm	Acute toxicity	14 d, OECD Guideline 207	90.6	LC_{50} >1000 ppm	HUK 269/32
Apis mellifera (honey bee)	Acute oral and contact toxicity	48 h, FIFRA Subdivision L, Series 141-1, hazard evaluation: non-target insects	92.9 (oral) 97.4 (contact)	LC_{50} oral >1000 ppm (oral) LC_{50} contact >20 µg/bee	HLO 468-91 (Oral) ABM 87-3 (Contact)
Colinus virginianus bobwhite quail	Acute oral toxicity	14 days Nicosulfuron technical (90.6 % purity) Pesticide Assessment Guidelines, FIFRA Subdivision E, Hazard Evaluation: Wildlife and Aquatic Organisms, 71-1		LD_{50} = >2250 mg/kg NOEC = 2250 mg/kg	HLO 730-8; HLO 730-87 AD1
Colinus virginianus bobwhite quail	Dietary toxicity	5 d, Pesticide Assessment Guidelines, FIFRA Subdivision E, Hazard Evaluation: Wildlife and Aquatic Organisms, 71-2	Not known	LC_{50} > 5620 ppm NOEC = 1780 ppm	HLO 729-87; HLO 729-87 AD1
Anas platyrhynchos Mallard duck	Dietary toxicity	5d, Pesticide Assessment Guidelines, FIFRA Subdivision E, Hazard Evaluation: Wildlife and Aquatic Organisms, 71-2	90.6	LC_{50} > 5620 ppm NOEC = 5620 ppm	HLO 728-87; HLO 728-87 AD1

ANNEX 2. REFERENCES

Du Pont document number or other reference	Year and title of report or publication details
ABM 87-3	1987. Acute contact LD50 study of DPX-V9360-27 on honey bees (*Apis mellifera* L).
AMR 1104-88	1988. Hydrolysis of [pyrimidine-2-^{14}C] DPX-V9360 and [pyridine-2-^{14}C] DPX-V9360 in buffer solutions of pH 5, 7, and 9.
AMR 1173-88	1989. Photodegradation of [pyrimidine-2-^{14}C] DPX-V9360 and [pyridine-2-^{14}C] DPX-V9360 in water.
AMR 1263-88	1988. Vapor pressure of DPX-V9360.
AMR 2178-91	1992. Acute toxicity of DPX-V9360 to *Lemna gibba* G3 (final report).
AMR 2321-92	1992. DPX-V9360: toxicity to *Selenastrum capricornutum.*
AMR-1333-88	1988. Determination of the solubiltiy of DPX-V9360 in various organic solvents and buffered aqueous solutions.
AMR-827-87	1988. *n*-Octanol/water partition coefficient of [pyrimidine-2-^{14}C]DPX-V9360.
Buehler 1965	Buehler E.V., 1965. Delayed Contact Hypersensitivity in the Guinea Pig, *Archives of Dermatology*, **91**:171-177.
Du Pont 2006	Re: FW: (Nicosulfuron) (Dupont) Report of the 4th JMPS Closed Meeting, Utrecht, The Netherlands, 1-7 June 2005 PL 32/9. E-mail from Dr T Woods to Dr G Vaagt (FAO), 6 February 2006, with attachments.
DuPont-11469	2002. Nicosulfuron 75WG water-dispersible granular herbicide formulation: laboratory study of physical and chemical properties.
DuPont-13182	2003. Nicosulfuron (DPX-V9360): Determination of the dissociation constant.
DuPont-13183	2003. Nicosulfuron (DPX-V9360): Determination of color, physical state, odour, density, melting point, and thermal analysis.
FAO/WHO 2002	Manual on development and use of FAO and WHO specifications for pesticides, 1st edition. FAO plant production and protection paper 173. FAO, Rome, 2002.
HL-1997-01004	1997. Nicosulfuron technical: 21-day chronic, static-renewal toxicity to *Daphnia magna.*
HLO 468-91	1991. A dietary LC50 toxicity study with the honey bee.
HLO 728-87 & HLO 728-87 AD1	1989. A dietary LC50 study with the Mallard (Addendum 1).
HLO 729-87; HLO 729-87 AD1	1989. A dietary LC50 study with the Bobwhite (Addendum 1).

Du Pont document number or other reference	Year and title of report or publication details
HLO 730-87 & HLO 730-87 AD1	1989. An acute oral toxicity study with the Bobwhite quail (Addendum 1).
HLR 121-88 & HLR 121-88 AD1	1989. *Daphnia magna* static acute 48-hour EC50a of IN V9360-27 (Addendum 1)
HLR 146-87 RV1 AD1 & HLR 146-87 RV1 AD2	1991. Primary eye irritation study with INV-9360-7 in rabbits (Revision 1 Addendum 2)
HLR 15-88 & HLR 15-88 AD1	1989. Subchronic oral toxicity: 90-day study with IN V9360-7 feeding study and one-generation reproduction study in rats (Addendum 1).
HLR 16-88 & HLR 16-88 AD1	1989. Subchronic oral toxcity: 90-day study with IN V9360-7 feeding study in mice (Addendum 1).
HLR 185-88 & HLR 185-88 AD1	1989. Static acute 96-hour LC50a of IN V9360-27 to Bluegill sunfish (Addendum 1).
HLR 302-88 & HLR 302-88 AD1	1989. Assessment of IN V9360-27 in the *In vitro* unscheduled DNA synthesis assay in rat primary hepatocytes.
HLR 332-88 & HLR 332-88 AD1	1989. Subchronic oral toxicity: 90-Day study with IN-V9360-27 feeding study in dogs (Addendum 1).
HLR 390-89	1989. Chronic toxicity study with IN V9360-27 one-year feeding study in dogs.
HLR 429-87 RV1 & HLR 429-87 RV1 AD1	1989. Closed-patch repeated insult dermal sensitization study (Buehler method) with INV60-7 in guinea pigs (Addendum 1/ Revision 1). DuPont Haskell Laboratory.
HLR 429-88 & HLR 429-88 AD1	1989. Mutagenicity evaluation of IN V9360-27 in the CHO/HPRT assay (Addendum 1).
HLR 429-89	1989. Reproductive and fertility effects with IN V9360-27 multigeneration reproduction study in rats (2 volumes).
HLR 470-88 & HLR 470-88 AD1	1989. *In vitro* evaluation of IN V9360-27 for chromosome aberrations in human lymphocytes (Addendum No 1).
HLR 582-87 RV1 & HLR 582-87 RV1 AD1	1989. Acute dermal toxicity study of IN V9360-27 in rabbits (Revision 1/Addendum 1).
HLR 611-88 & HLR 611-88 AD1	1989. Teratogenicity study of IN V9360-27 rats (Addendum 1).

Du Pont document number or other reference	Year and title of report or publication details
HLR 637-89 & HLR 637-89 SU AP1	1990. Combined chronic toxicity/oncogenicity study with IN V9360 two-year feeding study in rats (Supplemental Appendix I).
HLR 645-89 & HLR 645-89 SU1	1990. Oncogenicity study with IN V9360-27 eighteen-month feeding study in mice (Supplemental Appendix 1).
HLR 647-87 & HLR 647-87 AD1	1989. Primary dermal irritation study with IN V 9360-27 in rabbits (Addendum 1).
HLR 726-87 & HLR 726-87 AD1	1989. Static acute 96-hour LC50a of IN V9260-27 to Rainbow trout (*Salmo gairdneri*) (Addendum 1).
HLR 734-88 & HLR 734-88 AD1	1989. Mutagenicity testing of IN V9360-7 in the *Salmonella typhimurium* plate incorporation assay (Addendum 1).
HLR 737-88 RV1 & HLR 737-88 RV1 AD1	1989. Acute oral toxicity study with in V9360-27 in male and female rats (Addendum 1/Revision 1)
HLR 81-88 AD1 & HLR 81-88 SU1	1989. Acute inhalation toxicity study with IN V9360-27 in rats (Supplement 1).
HUK 269/32	1991. DPX-V9360: Determination of toxicity to the earthworm *Eisenia foetida.*
Knudsen 1909	Knudsen M., 1909. *Ann. Physik* **28**, 75.
NICO/PCH 6	1992. The Henry's Law constant for nicosulfuron.
Sokal & Rohif 1981	Sokal R.R. and Rohif F.J., 1981. *Biometry*. 2nd Edition. W.H. Freeman and Co., New York. 859 pp.
USEPA. 1982a	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 63-9, Vapor Pressure, Pesticide Assessment Guidelines, Subdivision D: Product Chemistry, EPA Report 540/9-82-018.
USEPA. 1982b	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 63-8, Solubility, Pesticide Assessment Guidelines, Subdivision D: Product Chemistry, EPA Report 540/9-82-018.
USEPA. 1982c	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 63-11, Octanol/Water Partition Coefficient, Pesticide Assessment Guidelines, Subdivision D: Product Chemistry, EPA Report 540/9-82-018.
USEPA. 1982d	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 81-1, Acute Oral Toxicity, Pesticide Assessment Guideline, Subdivision F: Hazard Evaluation; Human and Domestic Animals, EPA Report 540/09-82-025.

Du Pont document number or other reference	Year and title of report or publication details
USEPA. 1982e	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 81-2, Acute Dermal Toxicity, Pesticide Assessment Guideline, Subdivision F: Hazard Evaluation; Human and Domestic Animals, EPA Report 540/09-82-025.
USEPA. 1982f	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 81-3, Acute Inhalation Toxicity-Rat, Pesticide Assessment Guideline, Subdivision F: Hazard Evaluation; Human and Domestic Animals, EPA Report 540/09-82-025.
USEPA. 1982g	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 81-5, Primary Dermal Irritation, Pesticide Assessment Guideline, Subdivision F: Hazard Evaluation; Human and Domestic Animals, EPA Report 540/09-82-025.
USEPA. 1982h	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 81-4, Acute Eye Irritation, Pesticide Assessment Guideline, Subdivision F: Hazard Evaluation; Human and Domestic Animals, EPA 712-C-96-195, EPA, Washington, D.C.
USEPA. 1982i	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 81-6, Dermal Sensitization, Pesticide Assessment Guideline, Subdivision F: Hazard Evaluation; Human and Domestic Animals, EPA Report 540/09-82-025.
USEPA. 1996a	United States Environmental Protection Agency (U.S. EPA). August 1996. Office of Prevention, Pesticides, and Toxic Substances (OPPTS). Product Properties Test Guidelines, OPPTS 830.7200, Melting Point/Melting Range, EPA 712-C-95-033. EPA, Washington, D.C.
USEPA. 1996b	United States Environmental Protection Agency (U.S. EPA). August 1996. Office of Prevention, Pesticides, and Toxic Substances (OPPTS). Product Properties Test Guidelines, OPPTS 830.7300, Density/Relative Density/Bulk Density, EPA 712-C-96-035, 3p. EPA, Washington, D.C.
USEPA. 1996c	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 161-1, Hydrolysis, Pesticide Assessment Guidelines, Subdivision N: Chemistry: Environmental Fate, EPA Report 712-C-98-057.
USEPA. 1996d	United States Environmental Protection Agency (U.S. EPA); OPP Guideline 161-2, Photolysis, Pesticide Assessment Guideline, Subdivision N: Chemistry: Environmental Fate, EPA Report 712-C-96-060.
USEPA. 1996e	United States Environmental Protection Agency (U.S. EPA). August 1996. Office of Prevention, Pesticides, and Toxic Substances (OPPTS). Product Properties Test Guidelines, OPPTS 830.7370, Dissociation Constants in Water, EPA 712-C-96-036, EPA, Washington, D.C.

Du Pont document number or other reference	Year and title of report or publication details
V9360.D	1988. Determination of the water solubility of DPX-V9360 monohydrate, 2-[[[[(4,6-dimethoxypyrimidin-2-yl)amino]carbonyl]-amino]sulfonyl]-N,N-dimethyl-3-pyridine carboxamide monohydrate.
WHO 2002	The WHO recommended classification of pesticides by hazard and guidelines to classification 2000-2002. WHO, Geneva, 2002.
Williams 1971	Williams D.A., 1971. A test for differences between treatment means when survival dose levels are compared with a zero dose control. *Biometrics* **27**: 103-117.
Williams 1972	Williams D.A., 1972. A comparison of several dose levels with a zero control. *Biometrics* **28**: 519-531.