WHO SPECIFICATIONS AND EVALUATIONS FOR PUBLIC HEALTH PESTICIDES

DIFLUBENZURON

1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea

World Health Organization

TABLE OF CONTENTS

DIFLUBENZURON

Page

DISCLAIMER **4**

INTRODUCTION **5**

PART ONE

SPECIFICATIONS FOR DIFLUBENZURON

DIFLUBENZURON INFORMATION **7**

DIFLUBENZURON TECHNICAL MATERIAL (MAY 2020) **8**

DIFLUBENZURON TECHNICAL CONCENTRATE (MAY 2020) **9**

DIFLUBENZURON WETTABLE POWDER (MAY 2020) **11**

DIFLUBENZURON GRANULES (MAY 2020) **14**

DIFLUBENZURON TABLETS FOR DIRECT APPLICATION (MAY 2020) **17**

PART TWO

EVALUATIONS OF DIFLUBENZURON

2019.2 FAO/WHO EVALUATION REPORT ON DIFLUBENZURON **21**
SUPPORTING INFORMATION **23**
ANNEX 1: HAZARD SUMMARY PROVIDED BY PROPOSER **26**
ANNEX 2: REFERENCES **28**

2019.1 FAO/WHO EVALUATION REPORT ON DIFLUBENZURON **29**

2018 FAO/WHO EVALUATION REPORT ON DIFLUBENZURON **31**
SUPPORTING INFORMATION **33**
ANNEX 1: HAZARD SUMMARY PROVIDED BY PROPOSER **36**
ANNEX 2: REFERENCES **38**

2016.2 FAO/WHO EVALUATION REPORT ON DIFLUBENZURON **40**
SUPPORTING INFORMATION **42**
ANNEX 1: HAZARD SUMMARY PROVIDED BY PROPOSER **44**
ANNEX 2: REFERENCES **46**

2016.1 FAO/WHO EVALUATION REPORT ON DIFLUBENZURON **47**
ANNEX 1: REFERENCES **49**

2004 FAO/WHO EVALUATION REPORT ON DIFLUBENZURON **50**

Disclaimer[1]

WHO 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.

WHO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may be 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, WHO 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.

WHO 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, WHO does not in any way warrant or represent that any pesticide claimed to comply with a WHO specification actually does so.

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

INTRODUCTION

WHO establishes and publishes specifications* for technical material and related formulations of public health 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 Manual for Development and Use of FAO and WHO Specifications for Pesticides. This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by WHO and the experts of the "FAO/WHO Joint Meeting on Pesticide Specifications" (JMPS).

WHO specifications now only apply to products for which the technical materials have been evaluated. Consequently, from the year 2002 onwards the publication of WHO specifications under the **New Procedure** has changed. Every specification consists now of two parts, namely the specifications and the evaluation report(s):

Part One: The Specification of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the above-mentioned manual.

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

WHO specifications under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. WHO 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.

* Footnote: The publications are available on the Internet under the WHO Prequalification Team - Vector control products (PQT-VC) website.

PART ONE

SPECIFICATIONS

DIFLUBENZURON

	Page
DIFLUBENZURON INFORMATION	**7**
DIFLUBENZURON TECHNICAL MATERIAL (MAY 2020)	**8**
DIFLUBENZURON TECHNICAL CONCENTRATE (MAY 2020)	**9**
DIFLUBENZURON WETTABLE POWDER (MAY 2020)	**11**
DIFLUBENZURON GRANULES (MAY 2020)	**14**
DIFLUBENZURON TABLETS FOR DIRECT APPLICATION (MAY 2020)	**17**

DIFLUBENZURON

INFORMATION

ISO common name

Diflubenzuron (E-ISO, (m) F-ISO, ANSI, ESA)

Chemical names

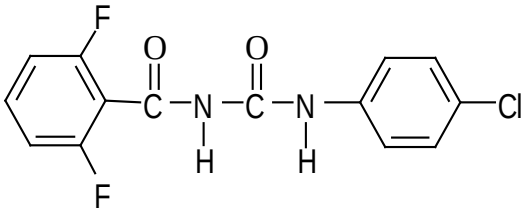
IUPAC 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea

CA *N*-[[(4-chlorophenyl)amino]carbonyl]-2,6-difluorobenzamide

Synonyms

Dimilin, Micromite, Adept, DU 112307, PH 60-40, TH 6040, ENT-29054, OMS 1804 (Crompton tradenames and/or past development codes).

Structural formula



Molecular formula

$C_{14}H_9ClF_2N_2O_2$

Relative molecular mass

310.7

CAS Registry number

35367-38-5

CIPAC number

339

Identity tests

HPLC retention time; IR spectrum

DIFLUBENZURON TECHNICAL MATERIAL

WHO specification 339/TC (May 2020*)

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 (339/2016.1, 339/2016.2, 339/2018, 339/2019.1, 339/2019.2). It should be applicable to TC produced by these manufacturers but it is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for TC produced by other manufacturers. The evaluation reports (339/2016.1, 339/206.2, 339/2018, 339/2019.1, 339/2019.2), as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of diflubenzuron, together with related manufacturing impurities, and shall be an off-white, fine powder, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (339/TC/M/2, CIPAC Handbook N, p.38, 2012)

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 **Diflubenzuron content** (339/TC/M/3, CIPAC Handbook N, p.38, 2012)

The diflubenzuron content shall be declared (not less than 950 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

3 **Relevant impurities** (Note 1)

Note 1 There are no relevant impurities to be controlled in diflubenzuron products of the manufacturers identified in evaluation reports 339/2016.1, 339/2016.2, 339/2018, 339/2019.1 and 339/2019.2. However, 4-chloroaniline could occur as a result of certain manufacturing processes. If 4-chloroaniline occurs at ≥ 0.1 g/kg (of diflubenzuron) in the products of other manufacturers, it would be designated as relevant impurity and a clause would be required to limit its concentration.

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* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Team - Vector control products (PQT-VC) website.

DIFLUBENZURON TECHNICAL CONCENTRATE

WHO specification 339/TK (May 2020*)

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 (339/2004, 339/2016.1, 339/2019.1). 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 specification. The specification may not be appropriate for the products of other manufacturers. The evaluation reports (339/2004, 339/2016.1, 339.2019.1) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of diflubenzuron, together with related manufacturing impurities, and shall be an off-white, fine powder, free from visible extraneous matter and added modifying agents except for the diluent.

2 Active ingredient

2.1 **Identity tests** (339/TK/M/2, CIPAC Handbook H, p.142, 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 **Diflubenzuron content** (339/TK/M/3, CIPAC Handbook H, p.142, 1998)

The diflubenzuron content shall be declared (900 g/kg) and, when determined, the average measured content shall not differ from that declared by more than ± 25 g/kg.

3 Relevant impurities (Note 1)

4 Physical properties

4.1 **Particle size** (MT 187, CIPAC Handbook K, p.153, 2003) (Note 2)

Particles smaller than 5 µm: not less than 70% w/w.

Average particle size: not more than 3.75 µm.

Note 1 There are no relevant impurities to be controlled in diflubenzuron products of the manufacturer identified in evaluation reports 339/2004, 339/2016.1 and 339/2019.1. However, 4-chloroaniline could occur as a result of certain manufacturing processes. If 4-chloroaniline occurs at ≥ 0.1 g/kg (of diflubenzuron) in the products of other manufacturers, it would be designated as relevant impurity and a clause would be required to limit its concentration.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Team - Vector control products (PQT-VC) website.

Note 2 Control of particle size is required to ensure efficacy of the formulated products.

DIFLUBENZURON WETTABLE POWDER

WHO specification 339/WP (May 2020*)

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 (339/2004, 339/2016.1, 339/2018, 339/2019.1). 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 specification. The specification may not be appropriate for the products of other manufacturers. The evaluation reports (339/2004, 339/2016.1, 339/2018, 339/2019.1) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of a homogeneous mixture of technical diflubenzuron, complying with the requirements of WHO specification 339/TC (May 2020) or 339/TK (May 2020), together with filler(s) and any other necessary formulants. It shall be in the form of a fine, white to yellowish-brown powder, free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 Identity tests (339/WP/M/2, CIPAC Handbook N, p.40, 2012)

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 Diflubenzuron content (339/WP/M/2, CIPAC Handbook N, p.40, 2012)

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

Declared content, g/kg	Tolerance
above 100 up to 250 Note: the upper limit is included in the range	± 6% of the declared content

3 Relevant impurities (Note 1)

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Team - Vector control products (PQT-VC) website.

4 Physical properties

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

Maximum: 1% retained on a 75 µm test sieve.

4.2 **Suspensibility** (MT 184.1) (Notes 2, 3, 4 & 5)

A minimum of 60% of the diflubenzuron content found under 2.2 shall be in suspension after 30 min in CIPAC Standard Water D at 25 ± 5°C (Note 5).

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

Maximum: 50 ml after 1 min.

4.4 **Wettability** (MT 53.3.1, CIPAC Handbook F, p.164, 1995)

The formulation shall be completely wetted in 2 min without swirling.

5 Storage stability

5.1 **Stability at elevated temperature** (MT 46.4) (Note 7)

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 mean content found before storage (Note 8) and the formulation shall continue to comply with the clauses for:

- wet sieve test (4.1),
- suspensibility (4.2),
- wettability (4.4).

Note 1 There are no relevant impurities to be controlled in diflubenzuron products of the manufacturer identified in evaluation reports 339/2004, 339/2016.1, 339/2018 and 339/2019.1. However, 4-chloroaniline could occur as a result of certain manufacturing processes. If 4-chloroaniline occurs at ≥ 0.1 g/kg (of diflubenzuron) in the products of other manufacturers, it would be designated as relevant impurity and a clause would be required to limit its concentration.

Note 2 The revision of CIPAC method MT 184, Suspensibility of formulations forming suspensions on dilution with water (CIPAC/5156) was accepted as full CIPAC method in 2019. Prior to its publication in the next Handbook, copies of the method can be obtained through the CIPAC website, http://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 3 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in method MT 184.1.

Note 4 This test will normally only be carried out after the heat stability test, 5.1.

Note 5 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 6 The CIPAC method MT 47.1 published in Handbook O was erroneously codified. The correct method number is MT 47.3 – see erratum at http://www.cipac.org/index.php/methods-publications/errata The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier.

Note 7 The harmonized accelerated storage procedure for all formulation types (MT 46.4, CIPAC/5217) was accepted as provisional CIPAC method in 2019. MT 46.4 supersedes all previous versions of MT 46 for accelerated storage. Prior to its publication in the next Handbook, copies of the method can be obtained through the CIPAC website, http://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 8 Samples of the formulation taken before and after the storage stability test should be analyzed concurrently after the test in order to reduce the analytical error.

DIFLUBENZURON GRANULES (Note 1)

WHO specification 339/GR (May 2020*)

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 (339/2004, 339/2016.1, 339/2018, 339/2019.1). 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 (339/2004, 339/2016.1, 339/2018, 339/2019.1) as PART TWO form an integral part of this publication.

1 **Description**

The material shall consist of creamy-grey granules containing technical diflubenzuron, complying with the requirements of WHO specification 339/TC (May 2020) or 339/TK (May 2020), together with suitable carriers and any other necessary formulants. It shall be dry, free from visible extraneous matter and hard lumps, free-flowing, essentially non-dusty and intended for application manually or by machine.

2 **Active ingredient**

2.1 **Identity tests** (339/GR/M/2, CIPAC Handbook N, p.42, 2012)

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 **Diflubenzuron content** (339/GR/M/3, CIPAC Handbook N, p.42, 2012)

The diflubenzuron content shall be declared (20 g/kg) and, when determined, the average content measured shall not differ from that declared by more than ±25%.

3 **Relevant impurities** (Notes 2 & 3)

3.1 **Water** (MT 30.6)

Maximum: 20 g/kg.

4 **Physical properties**

4.1 **Acidity** (MT 191, CIPAC Handbook L, p.143, 2005)

Maximum acidity: 500 g/kg calculated as H_2SO_4.

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* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Team - Vector control products (PQT-VC) website.

4.2 **Bulk density** (MT 186, CIPAC Handbook K, p.151, 2003)

Pour density: 0.80 to 0.90 g/ml.

Tap density: 0.85 to 0.95 g/ml.

4.3 **Nominal size range** (MT 170, CIPAC Handbook F, p.420, 2007)

Nominal size range: 500 to 2000 µm. Not less than 850 g/kg of the formulation shall be within the nominal size range.

4.4 **Dustiness** (MT 171.1) (Note 4)

The formulation shall have a maximum collected dust of 30 mg by the gravimetric method.

4.5 **Attrition resistance** (MT 178, CIPAC Handbook H, p.304, 1998)

Minimum: 95% attrition resistance.

5 Storage stability

5.1 **Stability at elevated temperature** (MT 46.4) (Note 5)

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:

- acidity (4.1),
- pour and tap density (4.2),
- nominal size range (4.3),
- dustiness (4.4),
- attrition resistance (4.5)

Note 1 The specification does not include encapsulated granules (formerly CG), microgranules (formerly MG), or macrogranules (formerly GG). The granules contain a water-soluble acid carrier and an effervescent system, so the water content must be kept low prior to application. The granules are not intended for dispersion in water prior to application.

Note 2 There are no other relevant impurities to be controlled in diflubenzuron products of the manufacturer identified in evaluation report 339/2004, 339/2016.1, 339/2018 and 339/2019.1). However, 4-chloroaniline could occur as a result of certain manufacturing processes. If 4-chloroaniline occurs at ≥ 0.1 g/kg (of diflubenzuron) in the products of other manufacturers, it would be designated as relevant impurity and a clause would be required to limit its concentration.

Note 3 The revision of CIPAC method MT 30.5, Karl Fischer method using pyridine-free reagents (CIPAC/5154) was accepted as full CIPAC method in 2019. Prior to its publication in the next Handbook, copies of the method can be obtained through the CIPAC website, http://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 4 The optical method of MT 171.1, usually shows good correlation with the gravimetric method and can, therefore, be used as an alternative where the equipment is available. Where the correlation is in doubt, it must be checked with the formulation to be tested. In case of dispute the gravimetric method shall be used. The revised and corrected MT 171.1 - before being reprinted in one of the next Handbooks - is available under http://www.cipac.org/index.php/methods-publications/errata

Note 5 The harmonized accelerated storage procedure for all formulation types (MT 46.4, CIPAC/5217) was accepted as provisional CIPAC method in 2019. MT 46.4 supersedes all previous versions of MT 46 for accelerated storage. Prior to its publication in the next Handbook, copies of the method can be obtained through the CIPAC website, http://www.cipac.org/index.php/methods-publications/pre-published-methods

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

DIFLUBENZURON TABLETS FOR DIRECT APPLICATION (Note 1)

WHO specification 339/DT (May 2020*)

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 (339/2004, 339/2016.1, 339/2018, 339/2019.1). 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 (339/2004, 339/2016.1, 339/2018, 339/2019.1) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of a homogeneous mixture of technical diflubenzuron, complying with the requirements of WHO specification 339/TC (May 2020) or 339/TK (May 2020), together with carriers and any other necessary formulants. It shall be in the form of tablets for direct application. The formulation shall be of dry, unbroken, free-flowing tablets, free from visible extraneous matter.

2 Active ingredient (Note 2)

2.1 **Identity tests** (339/TB/M/2, CIPAC Handbook N, p. 43, 2012)

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 **Diflubenzuron content** (339/TB/M/3, Handbook N, p. 43, 2012)

The diflubenzuron content shall be declared (20 g/kg) and, when determined, the average content measured shall not differ from that declared by more than ±25%.

3 Relevant impurities (Notes 2, 3 & 4)

3.1 **Water** (MT 30.6)

Maximum: 40 g/kg.

4 Physical properties

4.1 **Acidity** (MT 191, CIPAC Handbook L, p.143, 2006) (Note 2)

Maximum acidity: 150 g/kg calculated as H_2SO_4.

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* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at the WHO Prequalification Team - Vector control products (PQT-VC) website.

4.2 **Tablet integrity** (Notes 2 & 5)

No broken tablets.

4.3 **Attrition resistance of tablets** (MT 178.2, CIPAC Handbook K, p.140, 2003) (Note 2)

Minimum attrition resistance: 98% (loose-packed tablets).

Maximum attrition resistance : 99% (close-packed tablets).

5 Storage stability

5.1 **Stability at elevated temperature** (MT 46.4) (Notes 2 & 7)

After storage at 54 ± 2°C for 14 days without pressure (Note 6), the determined average active ingredient content must not be lower than 95%, relative to the determined average content found before storage (Note 8), and the formulation shall continue to comply with the clauses for:

- acidity (4.1),
- tablet integrity (4.2),
- Attrition resistance of tablets (4.3).

Note 1 The tablets contain an effervescent system with its water-soluble acid component present in excess, a combination intended to aid gentle dispersion in water after application. The tablets are not intended for dispersion in water prior to application.

Note 2 Sub-samples for analysis (2.1, 2.2, 3.1, 4.1) are prepared as follows.
An appropriate quantity of tablets should be milled to a powder and thoroughly mixed, prior to withdrawing test portions for analysis.

Sub-samples for tests of other physical properties and storage stability are prepared as follows.
To determine attrition of tablets (4.3, MT 178.2), or storage stability (5.1, MT 46.4), tablets must not be broken prior to the test. To determine tablet integrity (4.2), before or after the test of storage stability, at least one pack/package of multiple tablets must be examined.

Note 3 The revision of CIPAC method MT 30.5, Karl Fischer method using pyridine-free reagents (CIPAC/5154) was accepted as full CIPAC method in 2019. Prior to its publication in the next Handbook, copies of the method can be obtained through the CIPAC website, http://www.cipac.org/index.php/methods-publications/pre-published-methods

Note 4 There are no other relevant impurities to be controlled in diflubenzuron products of the manufacturer identified in evaluation reports 339/2004, 339/2016.1, 339/2018 and 339/2019.1. However, 4-chloroaniline could occur as a result of certain manufacturing processes. If 4-chloroaniline occurs at ≥ 1 g/kg (of diflubenzuron) in the products of other manufacturers, it would be designated as relevant impurity and a clause would be required to limit its concentration.

Note 5 By visual examination.

Note 6 Without pressure means that the test is done as specified by method MT 46.4, but no pressure is applied to the sample during its ageing.

Note 7 The harmonized accelerated storage procedure for all formulation types (MT 46.4, CIPAC/5217) was accepted as provisional CIPAC method in 2019. MT 46.4 supersedes all previous versions of MT 46 for accelerated storage. Prior to its publication in the next Handbook, copies of the method can be obtained through the CIPAC website, http://www.cipac.org/index.php/methods-publications/pre-published-methods

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

PART TWO

EVALUATION REPORTS

DIFLUBENZURON

		Page
2019.2	**FAO/WHO evaluation report** based on submission of data from Taizhou Bailly Chemical Co., Ltd. (TC)	**21**
	Supporting Information	**23**
	Annex 1: Hazard summary provided by proposer	**26**
	Annex 2: References	**28**
2019.1	**FAO/WHO evaluation report** based on submission of data from UPL (TC, TK)	**29**
2018	**FAO/WHO evaluation report** based on submission of data from Gharda Chemicals Ltd. (TC, WP, GR, DT)	**31**
	Supporting Information	**33**
	Annex 1: Hazard summary provided by proposer	**36**
	Annex 2: References	**38**
2016.2	**FAO/WHO evaluation report** based on submission of data from Helm AG (TC)	**40**
	Supporting Information	**42**
	Annex 1: Hazard summary provided by proposer	**44**
	Annex 2: References	**46**
2016.1	**FAO/WHO evaluation report** based on submission of data from Arysta LifeScience[1] (TC, TK)	**47**
	Annex 1: References	**49**
2004	**FAO/WHO evaluation report** based on submission of data from Crompton Europe B.V. (TK, GR, WP, DT, SC)	**50**

[1] Crompton Europe B.V is an entity of Arysta LifeScience.

DIFLUBENZURON

FAO/WHO EVALUATION REPORT 339/2019.2

Recommendations

The Meeting recommended that:

(i) The diflubenzuron TC as proposed by Taizhou Bailly Chemical Co., Ltd. should be accepted as equivalent to the diflubenzuron reference profile.

(ii) The FAO specification for diflubenzuron TC should be extended to encompass the material produced by Taizhou Bailly Chemical Co., Ltd.

(iii) The WHO specification for diflubenzuron TC should be extended to encompass the material produced by Taizhou Bailly Chemical Co., Ltd.

Appraisal

The data for diflubenzuron provided by Taizhou Bailly Chemical Co., Ltd. (Taizhou Bailly) were evaluated by the Meeting in support of an equivalence determination of their technical material with the existing FAO and WHO specifications for diflubenzuron TC.

Diflubenzuron is no longer under patent.

Diflubenzuron was last evaluated by the FAO/WHO JMPR in 2002 and 2011 for residues (JMPR, 2002 and 2011) and in 2001 for toxicology (JMPR, 2001). Diflubenzuron has been registered and sold in China.

The supporting data were provided by Taizhou Bailly in 2018, and updated in 2019.

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on all impurities present at or above 1 g/kg and their manufacturing limits in the TC. The manufacturing process provided by Taizhou Bailly is different from that supporting the existing reference FAO and WHO specification for diflubenzuron TC. Mass balances in the 5-batch data ranged from 986 to 990 g/kg. The percentage of unknowns was lower than 14 g/kg. The minimum purity of diflubenzuron in the TC is 980 g/kg and complies with the existing specification (950 g/kg).

Diflubenzuron was determined by reverse phase HPLC on a C_8 column with acetonitrile: water (60/40) as mobile phase, using UV detection at 290 nm, resulting in a retention time of approximately 5 minutes. This in-house method was validated for specificity, linearity, precision and accuracy. A bridging study was submitted by the proposer, and the results using the in-house and CIPAC methods were in good agreement.

All the analytical methods for impurities used in the 5-batch analysis study were validated for their specificity, linearity of response, accuracy, repeatability and limits of detection and quantification.

Test methods for determination of physical-chemical properties of the technical active ingredient were OECD.

It was confirmed that the confidential data submitted to FAO and WHO was the same as those submitted to the Chinese authority (ICAMA) for the registration of diflubenzuron TC.

The Meeting raised some concerns on possible residues of a highly reactive intermediate in the Taizhou Bailly's TC. Taizhou Bailly stated that the intermediate was highly reactive with water, and no residue was expected. They also provided a study on this impurity. The residual level of a potentially toxic solvent was not determined in the 5-batch analysis report. The proposer submitted data on the 2 possible impurities of concern, which shows that their levels were below limit of quantification (0.5 g/kg). The impurity profile of Taizhou Bailly's TC was considered as equivalent to the reference profile. No new relevant impurity and no new impurity at or above 1 g/kg was present in the proposer's product.

The *in vitro* mutagenicity test on *Salmonella typhimurium* strains showed that it was non-mutagenic. However, the batch of sample used, which was also used in the 5-batch analysis study, was expired when the Ames study was conducted, but the purity was re-analysed using another method and showed that the batch used was still valid.

The Meeting concluded that the Taizhou Bailly diflubenzuron TC was equivalent to the diflubenzuron reference TC based on Tier-1 evaluation.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 339/2019.2

Physico-chemical properties of diflubenzuron

Table 1. Chemical composition and properties of diflubenzuron 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 and WHO. Mass balances were 98.6 – 99.0% and percentage of unknows were ≤ 1.4%			
Declared minimum diflubenzuron content	980 g/kg			
Relevant impurities ≥ 1 g/kg and maximum limits for them	None			
Relevant impurities < 1 g/kg and maximum limits for them	None			
Stabilisers or other additives and maximum limits for them	None			
Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC	222.3-222.8°C [no decomposition or gas evolution occurs]	98.7	OECD 102	NC-2014-122
Solubility in organic solvents	1.1 g/l methanol at 20 ± 0.5°C 2.4 mg/l hexane at 20 ± 0.5°C	98.7	OECD 105	NC-2014-122

Hazard summary

Diflubenzuron was evaluated by the JMPR for toxicology in 2001 (JMPR, 2001). The 2004 JMPR established an ADI of 0-0.02 mg/kg bw, and an ARfD was considered unnecessary.

The WHO hazard classification of diflubenzuron is class III, slightly hazardous (WHO 2002), and it is in GHS category 5.

Formulations and co-formulated active ingredients

The current submission is for determination of equivalence of TC only.

Methods of analysis and testing

The active ingredient diflubenzuron in the TC is determined by a fully validated in-house reversed-phase HPLC method, using an Eclipse Zorbax XDB-C8 column and acetonitrile/water mobile phase, with UV detection at 290 nm and external standard quantitative method.

The methods for determination of impurities were based on HPLC-DAD, using external standardization. The methods were full validated with respect to system suitability, specificity, linearity of response, range of linearity, accuracy, precision, LOQ and LOD.

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

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as diflubenzuron, in g/kg in technical material.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

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

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

Table 2. Mutagenicity profile of diflubenzuron technical material based on an *in vitro* test

Species	Test	Purity % (Batch No. 2014030301)	Guideline	Result	Study number
Salmonella Typhimurium strains TA1537, TA1535, TA98, TA 100 and TA102	Ames Test - *in vitro*	98.7	OECD 471; 937.5 µg/mL to 30000 µg/mL; 37 ± 1°C (48h)	Non-mutagenic.	481-1-06-20295

ANNEX 2: REFERENCES

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
	FAO/WHO	2016	Manual on development and use of FAO and WHO specifications for pesticides. 2016. 3rd Revision of First Edition. FAO Plant Production and Protection Paper. Revised.
NC-2014-122	Jing Gao	2014	Physical Characterization of Diflubenzuron TGAI: Colour, Physical State, Odour, Density, Melting Point, Partition Coefficient, Solubility and Vapour Pressure. GLP. Nutrichem.
481-1-06-20295	Deval S. Mehta	2018	Bacterial reverse mutation test of diflubenzuron tech using Salmonella Typhimurium. GLP. JRF.
NC-2014-121	Jing Gao	2014	Preliminary Analysis and Enforcement Analytical Method of Diflubenzuron TGAI. GLP. Nutrichem.
240-2-13-21349	Hiren Patel	2018	Characterisation of Diflubenzuron Tech. GLP. JRF. Unpublished.
NCW-2019-170	Jing Zhang	2019	3-Batch Analysis of Active Ingredient in Diflubenzuron 98% min. Tech with CIPAC Method 339/TC/M/3 and the Diflubenzuron method. Study No. NC2014121A.
NC-2019-038	Jing Zhang	2019	Preliminary Analysis and Validation of Analytical Method of Diflubenzuron Tech.

DIFLUBENZURON

FAO/WHO EVALUATION REPORT 339/2019.1

Recommendations

The Meeting recommended that:

(i) The change of the manufacturer for the reference specifications for diflubenzuron TC and TK from Arysta LifeScience to UPL should be noted by FAO.

(ii) The change of the manufacturer for the reference specifications for diflubenzuron TC, TK, WP, GR and DT from Arysta LifeScience to UPL should be noted by WHO.

Appraisal

The reference FAO specifications for diflubenzuron TK and WHO specifications for TK, WP, GR and DT, respectively, had initially been proposed by Crompton (Europe) in 2003 (FAO/WHO evaluation report 339/2004). In 2016, the Meeting contacted Arysta LifeScience, a successor company of Crompton, with the request of revision of the diflubenzuron TK specification and addition of a TC specification as well (FAO/WHO evaluation report 339/2016.1).

The Meeting noted that in early 2019 UPL Limited, India (UPL) announced the acquisition of Arysta LifeScience Inc. (Arysta)[1] with its portfolio of compounds, among them diflubenzuron. As such a transition may raise some concerns on the continued validity of the FAO and WHO specifications for diflubenzuron technical materials and formulations (see also FAO/WHO Manual, Section 2.7 on revision of specifications), UPL was contacted by FAO and WHO and a statement on the support of the reference specifications and possible changes therein was requested.

UPL later on provided a confirmation in writing (UPL, 2019) to FAO and WHO confirming the continued support of the FAO and WHO reference specifications for diflubenzuron TC, TK and its formulated products[2]. UPL explained that both manufacturing site and process for diflubenzuron were not affected by the transition from Arysta to their company and confirmed the continued validity of the published specifications and stewardship for them.

For this reasons, the Meeting recommended that the transition of the holder of the reference specifications for diflubenzuron TC, TK, WP, GR and DT from Arysta to UPL should be noted by FAO and WHO, and that UPL should be considered as the new holder of the reference specifications for diflubenzuron.

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[1] Press release from UPL dated 1st February 2019, accessible under: https://www.upl-ltd.com/press-release (December 2019).

[2] e-mail from Mrs. C. Moodley, UPL to FAO dated 23 October 2019.

The Meeting also recommended to refer to the CIPAC method MT 46.4 instead of MT 46.3 for the stability at elevated temperature in the WP, GR and DT specifications. This harmonized accelerated storage procedure for all formulation types was accepted as provisional CIPAC method in 2019 and supersedes all previous versions of MT 46 for accelerated storage.

DIFLUBENZURON

FAO/WHO EVALUATION REPORT 339/2018

Recommendations

The Meeting recommended that:

(i) The diflubenzuron TC as proposed by Gharda Chemicals Ltd. should be accepted as equivalent to the diflubenzuron reference profile.

(ii) The FAO specification for diflubenzuron TC should be extended to encompass the material produced by Gharda Chemicals Ltd.

(iii) The WHO specification for diflubenzuron TC should be extended to encompass the material produced by Gharda Chemicals Ltd.

(iv) The WHO specifications for diflubenzuron WP, GR and DT should be extended to encompass the materials produced by Gharda Chemicals Ltd.

Appraisal

The data for diflubenzuron provided by Gharda Chemicals Ltd. were evaluated by the Meeting in support of an equivalence determination of their technical material with the existing FAO and WHO specifications for diflubenzuron TC, and the extension of the existing WHO specifications for diflubenzuron WP, GR and DT.

Diflubenzuron is no longer under patent.

Diflubenzuron was last evaluated by the JMPR in 2002 and 2011 for residues (JMPR, 2002 and 2011) and in 2001 for toxicology (JMPR, 2001). Diflubenzuron has been registered and sold in Australia.

The supporting data were provided by Gharda in 2016, updated in 2017 and 2018.

Diflubenzuron TC is a solid with a melting point of 225-228°C.

The analytical method for the active ingredient (including identity tests) is derived from the CIPAC method published in Handbook N. Diflubenzuron was determined by reverse phase HPLC on a C_{18} column using UV detection at 254 nm, with a retention time of approximately 15 minutes. The differences from the CIPAC method was in the sample preparation and determination and calculation (Gharda: internal standard method; CIPAC: calibration curve). The proposer stated that its method followed the CIPAC method as closely as possible. It was confirmed that the internal standard used for both methods, and the sample preparation is similar. It was also confirmed that chromatographic conditions were similar. The Meeting highlighted that the CIPAC method uses heat to aid solubility, but the in-house method does not. Given the solubility of the active ingredient is 20 g/L, and a clear solution was observed, this would indicate there is no problem. The Meeting concluded that the method is acceptable.

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on all impurities present at or

above 1 g/kg and their manufacturing limits in the TC. The manufacturing process provided by Gharda is similar to those supporting the existing FAO and WHO specification for diflubenzuron TC. Mass balances in the 5-batch data ranged from 991 to 995 g/kg. The percentage of unknowns was no higher than 0.9%. The minimum purity of diflubenzuron in the TC is 960 g/kg and complies with the existing specification (950 g/kg). Based on available information and the criteria as defined in the Manual, the Meeting concluded that none of the impurities in the TC had to be considered as relevant.

All the analytical methods used in the 5-batch analysis study were validated for their specificity, linearity of response, accuracy, repeatability and limits of detection and quantification.

The Meeting was provided with a registration certificate of diflubenzuron from the Australian authorities (APVMA).

The Meeting raised some concerns on possible residues of a highly reactive intermediate in the Gharda's TC. Gharda later submitted an analytical report indicating the levels of this potentially relevant impurity were below limit of quantification (14 mg/kg). The impurity profile of Gharda's TC was considered as equivalent to the reference profile. No new relevant impurity and no new impurity at or above 1 g/kg was present in the proposer's product.

The *in vitro* mutagenicity test in *Salmonella typhimurium* strains showed that it was non-mutagenic.

The Meeting concluded that the Gharda diflubenzuron TC was equivalent to the diflubenzuron reference TC based on Tier-1 evaluation.

The proposer developed a new data package for diflubenzuron WP in 2017, which is in accordance with the existing WHO specification and the revised FAO/WHO Manual.

The methods for diflubenzuron content and physical and chemical properties of WP, GR and DT products were CIPAC methods, and all parameters comply with the clauses of the existing WHO specifications.

The Meeting also recommended an editorial update of the formulation specifications as follows:

- WP specification: to refer to the revised CIPAC method MT 184.1 (instead of MT 184) for suspensibility. MT 184.1 is considered equivalent to to MT 184, therefore no changes in the limit for suspensibility is required;
- GR and DT specifications: to refer to the harmonized CIPAC method MT 30.6 (instead of MT 30.5) for water content;
- DT specification, to refer to the CIPAC method MT 178.2 (instead of MT 193) for attrition resistance of tablets and to adapt the clause accordingly;

in order to be in line with the current CIPAC methods and the last version of the FAO/WHO Manual on pesticide specifications and its amendments.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 339/2018

Uses

Diflubenzuron is a non-systemic insect growth regulator with contact and stomach action. It acts at time of insect moulting, or at hatching of eggs. Diflubenzuron is used in agriculture, horticulture and forestry against larvae of *Lepidoptera, Coleoptera, Diptera, Hymenoptera* and in public health against larvae of mosquitoes and other noxious insects.

It is a chitin synthesis inhibitor, type 0 (Lepidopteran), and so interferes with the formation of the insect cuticle.

Physico-chemical properties of diflubenzuron

Table 1. Chemical composition and properties of diflubenzuron 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 and WHO. Mass balances were 99.1 – 99.5% and percentage of unknows were ≤ 0.9%			
Declared minimum diflubenzuron 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	225-228°C	97.5	OECD 102	4373
Solubility in organic solvents	< 10 g/l methanol, acetone, n-hexane, dichloromethane, toluene and n-octanol	97.5	CIPAC MT 181	4574

Hazard summary

Diflubenzuron was evaluated by the JMPR for toxicology in 2001 (JMPR, 2001). The 2004 JMPR established an ADI of 0-0.02 mg/kg bw, and an ARfD was considered unnecessary.

The WHO hazard classification of diflubenzuron is class III, slightly hazardous (WHO 2002), and it is in GHS category 5.

Formulations and co-formulated active ingredients

The main formulation types available are WP, GR, and DT for public health use.

Methods of analysis and testing

The analytical method for determination of the active ingredient (including identity tests) in the TC, WP, GR and DT is a full CIPAC method (CIPAC N). Diflubenzuron is determined by reversed phase HPLC, using a C_{18} column and acetonitrile/water /dioxan as mobile phase, with UV detection at 254 nm and linuron as the internal standard.

The methods for determination of impurities were based on HPLC-UV and GC, using external standardization.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, EPA and EEC, 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 diflubenzuron, in g/kg in technical material and solid formulations, and in g/kg or g/l at 20 ± 2°C in liquid formulations, as required.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

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

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

Table 2. Mutagenicity profile of diflubenzuron technical material based on an *in vitro* test

Species	Test	Purity %	Guideline	Result	Study number
Salmonella typhimurium Strains: TA 98, TA 100, TA 102, TA 1535 & TA 1537	Ames Test – *in vitro*	97.36	OECD 471 Concentrations: 0.050, 0.158, 0.501, 1.582 and 5 mg/plate, both in presence and absence of metabolic activation (S 9).	No genotoxic potential	4887

ANNEX 2: REFERENCES

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
	FAO/WHO	2016	Manual on development and use of FAO and WHO specifications for pesticides. 2016. Third Revision of First Edition. FAO Plant Production and Protection Paper. Revised. http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/JMPS_Manual_2016/3rd_Amendment_JMPS_Manual.pdf
FAO, 2017	FAO	2017	FAO specifications for diflubenzuron. http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/Diflubenzuron_2017_09_22_.pdf
WHO, 2017	WHO	2016	FAO specifications for diflubenzuron. ww.who.int/neglected_diseases/vector_ecology/pesticide-specifications/Diflubenzuron_eval_specs_WHO_September_2017.pdf
4373	K. Dattatreya Chary	2014	Determination of Melting point of Diflubenzuron. Gharda Report No.: C.DFO.015. GLP. RCC Laboratories India Private Limited. Unpublished.
4574	K. Dattatreya Chary	2014	Determination of Solubility of Diflubenzuron in organic solvents. Gharda Report No.: CDFO.023. GLP. RCC Laboratories India Private Limited. Unpublished.
4887	Veena N	2014	Bacterial Mutation Assay for Diflubenzuron. Gharda Report No.: T.DFO.044. GLP. RCC Laboratories India Private Limited. Unpublished.
SN 1501	S. R. NA YAK	2015	Analysis and certification of limits for diflubenzuron technical. Gharda Report No.: C.DFO.018. GLP. Gharda Chemicals Ltd. Unpublished.
SAL9PC13	Waghmare	1999	Diflubenzuron 25WP Accelerated storage stability. Gharda Report No.: C.DF2.002. GLP. Gharda Chemicals Ltd. Unpublished.
SAL9PC28	Waghmare	1999	Diflubenzuron 25WP Persistent Foaming. Gharda Report No.: C.DF2.005. GLP. Gharda Chemicals Ltd. Unpublished.
SAL9PC30	Waghmare	1999	Diflubenzuron 25WP Suspensibility. Gharda Report No.: C.DF2.006. GLP. GHARDA CHEMICALS LTD. Unpublished.
SAL9PC32	Waghmare	1999	Diflubenzuron 25WP Wet sieving. Gharda Report No.: C.DF2.008. GLP. Gharda Chemicals Ltd. Unpublished.
SAL9PC33	Waghmare	1999	Diflubenzuron 25WP Wetting. Gharda Report No.: C.DF2.010. GLP. Gharda Chemicals Ltd. Unpublished.
17036	S. Pandiselvi	2017	Diflubenzuron 2% GR: Accelerated Storage Stability at 54±2°C for 14 days. Gharda Report No.: C.DF2.038. GLP. International Institute of Biotechnology and Toxicology. Unpublished.
17037	S. Pandiselvi	2017	Diflubenzuron 2% GR: Attrition resistance. Gharda Report No.: C.DF2.039. GLP. International Institute of Biotechnology and Toxicology. Unpublished.
17038	S. Pandiselvi	2017	Diflubenzuron 2% GR: Dustiness. Gharda Report No.: C.DF2.040. GLP. International Institute of Biotechnology and Toxicology. Unpublished.
17039	S. Pandiselvi	2017	Diflubenzuron 2% GR: Nominal Size Range. Gharda Report No.: C.DF2.041. GLP. International Institute of Biotechnology and Toxicology. Unpublished.
17040	S. Pandiselvi	2017	Diflubenzuron 2% GR: Water content. Gharda Report No.: C.DF2.042. GLP. International Institute of Biotechnology and Toxicology. Unpublished.

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
17041	S. Pandiselvi	2017	Diflubenzuron 2% GR: Determination of Active Ingredient Content. Gharda Report No.: C.DF2.043. GLP. International Institute of Biotechnology and Toxicology. Unpublished.
17042	S. Pandiselvi	2017	Diflubenzuron 2% GR: Acidity. Gharda Report No.: C.DF2.044. GLP. International Institute of Biotechnology and Toxicology. Unpublished.
17043	S. Pandiselvi	2017	Diflubenzuron 2% GR: Bulk density. Gharda Report No.: C.DF2.045. GLP. International Institute of Biotechnology and Toxicology. Unpublished.
17022	S. Pandiselvi	2017	Diflubenzuron 2% Tablets: Determination of Water content. Gharda Report No.: C.DF2.031. GLP. International Institute of Biotechnology and Toxicology. Unpublished.
17023	S. Pandiselvi	2017	Diflubenzuron 2% GR: Acidity. Gharda Report No.: C.DF2.032. GLP. International Institute of Biotechnology and Toxicology. Unpublished.
17024	S. Pandiselvi	2017	Diflubenzuron 2% GR: Tablet integrity. Gharda Report No.: C.DF2.033. GLP. International Institute of Biotechnology and Toxicology. Unpublished.
17021	S. Pandiselvi	2017	Diflubenzuron 2% GR: AI content. Gharda Report No.: C.DF2.035. GLP. International Institute of Biotechnology and Toxicology. Unpublished.
17025	S. Pandiselvi	2017	Diflubenzuron 2% GR: Degree of attrition. Gharda Report No.: C.DF2.036. GLP. International Institute of Biotechnology and Toxicology. Unpublished.
17026	S. Pandiselvi	2017	Diflubenzuron 2% GR: Accelerated Storage Stability at 54±2°C for 14 days. Gharda Report No.: C.DF2.037. GLP. International Institute of
17081	S. Pandiselvi	2017	Biotechnology and Toxicology.. Unpublished.
17084	S. Pandiselvi	2017	Diflubenzuron 25% WP, active content
17083	S. Pandiselvi	2017	Diflubenzuron 25% WP, Persistent Foam
17082	S. Pandiselvi	2017	Diflubenzuron 25% WP, Suspensibility
17085	S. Pandiselv	2017	Diflubenzuron 25% WP, Wet Sieve test Diflubenzuron 25% WP, Wettability
17086	S. Pandiselvi	2017	Diflubenzuron 25% WP, Accelerated storage stability
SN 1803	MR.S.R.NAYAK	2018	Analysis of the content of a highly reactive intermediate in Diflubenzuron Technical.

DIFLUBENZURON

FAO/WHO EVALUATION REPORT 339/2016.2

Recommendations

The Meeting recommended the following.

(i) The diflubenzuron TC as proposed by Helm AG should be accepted as equivalent to the diflubenzuron reference profile.

(ii) The FAO diflubenzuron TC specification should be extended to encompass the material produced by Helm AG.

(iii) The WHO diflubenzuron TC specification should be extended to encompass the material produced by Helm AG.

Appraisal

The data for diflubenzuron provided by Helm AG were evaluated in support of an equivalence determination with the existing FAO and WHO specifications for TC.

Diflubenzuron is no longer under patent.

The supporting data were provided in 2011, updated in 2012, 2016 and 2017.

The analytical method for the active ingredient (including identity tests) is derived from a CIPAC method published in Handbook N. Diflubenzuron is determined by reverse phase HPLC on a C_{18} column using UV detection at 260 nm. The in-house method offered better resolution. A bridging study between the in-house and CIPAC methods was submitted by the proposer and showed that the results of both methods are in good agreement for all batches.

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on all impurities present at or above 1 g/kg and their manufacturing limits in the TC. The manufacturing process provided by Helm AG is similar to those supporting the existing FAO and WHO specification for a TC. Mass balances in the 5-batch data ranged from 993 to 1002 g/kg. The percentage of unknowns was no higher than 0.7%. The minimum purity of diflubenzuron in the TC is 960 g/kg and complies with the existing specification. Based on available information and the criteria as defined in the Manual, the Meeting concluded that none of the impurities in the TC had to be considered as relevant.

The analytical methods used in the 5-batch analysis study were validated for their specificity, linearity of response, accuracy, repeatability and limits of detection and quantification and were found satisfactory for the determination of the active substance and specified impurities.

The minimum purity of the TC specification registered in Argentina is 950 g/kg. The impurities and their maximum limits in the manufacturing specification were considered to be equivalent to the diflubenzuron impurity profile provided to Argentina authority for registration. The company provided additional data beginning

of 2017 with regard to the levels of 4-chloroanilin, demonstrating that in all batches the concentrations of that potentially relevant compound were below 0.1 g/kg.

A closer comparison of the manufacturing specifications of the reference product and the product under evaluation with their associated 5-batch data revealed some new impurities not present in the reference profile at or above 1 g/kg. However, these impurities did not give rise to structural alerts other than those present in the active ingredient as judged by the OECD QSAR Toolbox [1]. The Cramer hazard classification was the same for the impurities and the active ingredient itself (Cramer Class III). Furthermore, in the Tier-2 equivalence determination, the Helm product was not genotoxic *in vitro*, not irritating to the eye or skin nor sensitizing to the skin, nor more hazardous than the reference product in acute toxicity assays. The JMPS therefore concluded that the Helm product is equivalent to the reference product based on Tier-1 and Tier-2 considerations.

The batches used in toxicity and genotoxicity studies were different from those used in 5 batch study. The proposer stated that the batches were from the same commercial manufacturing process as the 5 batches, however the analytical details were not available to establish the links between the hazard and purity/impurity profile data submitted.

The Meeting also recommended, in the WHO WP and DT specifications, to refer to the CIPAC methods MT 47.3 for persistent foam and MT 193 for attrition of tablets respectively, as published in Handbook O.

[1] http://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 339/2016.2

Physico-chemical properties of diflubenzuron

Table 1. Chemical composition of diflubenzuron 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 and WHO. Mass balances were 99.3 - 100.2% and percentages of unknowns were ≤0.7 %.
Declared minimum diflubenzuron content	960 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities < 1 g/kg and maximum limits for them	None
Stabilisers or other additives and maximum limits for them	None

Formulations and co-formulated active ingredients

The proposer did not propose any specifications of formulations.

Methods of analysis and testing

The analytical method for the active ingredient (including identity tests) was based on the CIPAC methods 339/TC/M/2 & 3. Diflubenzuron is determined by reverse phase HPLC on a C_{18} column using UV detection at 260 nm. Diflubenzuron elutes with a retention time of approximately 34 min.

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

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient diflubenzuron is expressed as g/kg.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

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

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

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

Species	Test	Purity %	Guideline	Result	Study number
Rat, female	oral	97.5	OECD 423	LD_{50} > 5000 mg/kg bw	3790/03
Rat, female and male	dermal	97.5	OECD 402	LD_{50} > 2000 mg/kg bw	3791/03
Rat, female and male	inhalation	97.5	OECD 403	LC_{50} > 1550 mg/m^3	3792/03
Rabbit, female	skin irritation	97.5	OECD 404	No irritant	3793/03
Rabbit, female	eye irritation	97.5	OECD 405	Mild irritant	3794/03
Guinea Pig, female and male	skin sensitisation	97.5	OECD 406	No sensitizer (Magnusson and Kligman Test)	3795/03

Table B. Mutagenicity profile of diflubenzuron technical material based on *in vitro* tests

Species	Test	Purity %	Guideline	Result	Study number
Salmonella typhimurium	Ames Test – *in vitro*	98.77	OECD 471	No genotoxic potential	12282-06AM

ANNEX 2: REFERENCES

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
	FAO/WHO	2016	Manual on development and use of FAO and WHO specifications for pesticides. Third Revision of First Edition. FAO Plant Production and Protection Paper 228. www.fao.org/ag/AGP/AGPP/Pesticid/Default.htm and http://whqlibdoc.who.int/publications/2006/9251048576_eng_update2.pdf
3790/03		2004	Acute oral toxicity study (acute toxic class method) with Diflubenzuron 97 TC in wistar rats. Report 3790/03. GLP. Unpublished confidential report of HELM AG.
3791/03		2004	Acute dermal toxicity study with Diflubenzuron 97 TC in wistar rats. Report 3791/03. GLP. Unpublished confidential report of HELM AG.
3792/03		2004	Acute inhalation toxicity study with Diflubenzuron 97 TC in wistar rats. Report 3792/03. GLP. Unpublished confidential report of HELM AG.
3793/03		2004	Acute dermal irritation/corrosion study with Diflubenzuron 97 TC in New Zealand white rabbits. Report 3793/03. GLP. Unpublished confidential report of HELM AG.
3794/03		2004	Acute eye irritation/corrosion study with Diflubenzuron 97 TC in New Zealand white rabbits. Report 3794/03. GLP. Unpublished confidential report of HELM AG.
3795/03		2004	Skin Sensitisation study (Magnusson and Kligman test) with Diflubenzuron 97 TC in guinea pigs. Report 3795/03. GLP. Unpublished confidential report of HELM AG.
12282-06AM	Ribeiro do Val R	2007	Bacterial reverse mutation test (Ames Test) for Diflubenzuron 96 Technical Grade Helm. Report 12282-06AM. GLP. TECAM. Brazil. Unpublished confidential report of HELM AG.
PR04/003	K. Bockholt	2005	Analytical Profile of Five Batches of Diflubenzuron TC. Unpublished confidential report of HELM AG.

DIFLUBENZURON

FAO/WHO EVALUATION REPORT 339/2016.1

Recommendations

The Meeting recommended the following.

(i) The new specification for diflubenzuron TC, proposed by Arysta LifeScience, and as amended, should be adopted by FAO and WHO.

(ii) The existing FAO and WHO specifications for diflubenzuron TK should be revised taking the newly submitted data into account.

(iii) The WHO specifications for diflubenzuron formulated products (WP, GR, DT) should be editorially revised to refer to the latest physical-chemical test methods.

Appraisal

The first specifications for diflubenzuron TK under the "New procedure" have been published by WHO and FAO in 2005. The data were proposed by Crompton Europe B.V. in 2003. In the meantime diflubenzuron has been reviewed by EU in 2010 based on data submitted by Chemtura, a successor company of Crompton (DG SANCO, 2010) and clear differences in minimum purity and other parameters between the published TK specifications and those of the EU review became apparent. The Meeting therefore requested the successor of Chemtura, Arysta LifeScience (Arysta), to submit an updated data package for this compound based on Section 2.7 of the FAO/WHO Pesticide Specification Manual (Review of specifications). Subsequently a new data package with confidential and non-confidential data was provided by Arysta.

A comparison of the manufacturing processes shows that they have remained essentially the same. The difference is that a TC is isolated that later may be converted to a TK with the addition of some inert material.

The TC has the aspect of an off-white fine powder. The declared minimum content of the active ingredient is 950 g/kg. Mass balances in the new 8-batch analysis data were high (> 98%) and no unidentified impurities were detected. The purity and impurity profiles were equivalent to those submitted in 2004, and the reference profile is renewed based on new batch analysis results and QC data.

A limit of 0.03 g/kg for impurity 4-chloroaniline was specified after the EU evaluation. However, in the context of FAO/WHO pesticide specification evaluation, the impurity at this level was not considered relevant. However a note was added to specify that if 4-chloroaniline occurs at $\geqslant$ 0.1 g/kg (of diflubenzuron) in the products of other manufacturers, it may be designated as relevant impurity and requires a clause to limit its concentration.

The methods for the identification and determination of diflubenzuron in the TC are the CIPAC methods.

The clause of diflubenzuron content in the TK specification was revised to 900 g/kg with a tolerance of ± 25 g/kg to reflect the requirement of the FAO/WHO Pesticide Specification Manual.

The TK is used to formulate some solid formulations like the WP, GR and DT. These specifications, therefore, refer to the TK material rather than the TC.

The Meeting also recommended to update the CIPAC physical-chemical methods for WP and GR formulations where necessary (e.g. wet sieve test: MT 185 instead of MT 59.3, persistent foam: MT 47.3 instead of MT 47.2, nominal size range: MT 170 instead of MT 58, dustiness: MT 171.1 instead of MT 171) and to refer to the renamed “attrition of tablets” MT 193 method for DT formulation.

ANNEX 1: REFERENCES

Study number	Author(s)	Year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
FR-12508	Riggs, A.S	2007	Preliminary Analysis of Diflubenzuron Technical. Study Number GRL-12508, report number FR-12508. Test facility: Chemtura Canada Co. Cie Guelph Technology Centre. Ontario. Canada.
SANCO/831/08 - final1	DG SANCO	2010	Review report for the active substance diflubenzuron.

DIFLUBENZURON

FAO/WHO EVALUATION REPORT 339/2004

Explanation

The data for diflubenzuron were evaluated in support of review of existing WHO specifications, WHO/SIT/25.R1 for diflubenzuron technical concentrate (TK) and WHO/SIF/47.R1 for diflubenzuron wettable powder (WP), as developed by WHOPES following the old procedure and revised on 10 December 1999. New specifications were proposed for diflubenzuron granules (GR) and tablets for direct application (DT) in public health and for suspension concentrates (SC) for use in agriculture.

Diflubenzuron is not under patent.

Diflubenzuron was evaluated by the FAO/WHO JMPR and WHO/IPCS in 1981, 1984, 1988 and 2002. The US EPA published a Re-registration Eligibility Decision for diflubenzuron in August 1997. Diflubenzuron is currently under review by the European Commission under Directive 91/414/EC. Crompton Europe B.V. has notified diflubenzuron as an existing biocidal active ingredient under the Biocidal Products Directive 98/8/EC.

The draft specification and the supporting data were provided by Crompton Europe B.V. in October 2003 and February 2004.

Uses

Diflubenzuron is an insect growth regulator, used in agriculture, horticulture and forestry against larvae of Lepidoptera, Coleoptera, Diptera, Hymenoptera and in public health against larvae of mosquitoes and other noxious insects.

Identity

ISO common name

Diflubenzuron (E-ISO, (m) F-ISO, ANSI, ESA)

Chemical names

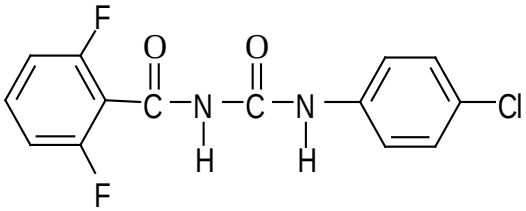
IUPAC: 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea

CAS: *N*-[[(4-chlorophenyl)amino]carbonyl]-2,6-difluorobenzamide

Synonyms

Dimilin, Micromite, Adept, Du-Dim, Device, DU 112307, PH 60-40, TH 6040, ENT-29054, OMS 1804 (Crompton trade names and/or past development codes).

Structural formula



Molecular formula

$C_{14}H_9ClF_2N_2O_2$

Relative molecular mass

310.7

CAS Registry number

35367-38-5

CIPAC number

339

Identity tests

HPLC retention time; IR spectrum.

Physical and chemical properties

Table 1. Physicochemical properties of pure diflubenzuron

Characteristic	Value	Purity, %	Method	Reference
Vapour pressure	≤1.2 x 10^{-7} Pa at 25°C	>99.5	OECD guideline 104	DI 7081
Melting point, boiling point and/or temperature of decomposition	Melting point: 228°C Boiling point: Not required, because diflubenzuron is neither a liquid, nor a low melting substance Decomposition temperature: no decomposition at melting point	99.9	OECD guideline 102	DI 9321 DI 11496 DI 9321
Solubility in water	0.08 mg/l at 25°C at pH 7 0.10 mg/l at pH 4 0.32 mg/l at pH 10	>99.5	EEC guideline A6	DI 7233 DI 9167
Octanol/water partition coefficient	Log P_{OW} = 3.89 at 22°C at pH 3	99.9	EEC guideline A8	DI 7016
Hydrolysis characteristics	Half-life > 180 days at 25°C at pH 5 and 7 Half-life = 32.5 days at 25°C at pH 9	97.1	EPA guideline CG5000	DI 6799
Photolysis characteristics	The estimated half-life of diflubenzuron in natural sunlight at latitude 40° N is 80 days at 25°C (from 40 days continuous irradiation with a 450 W Xenon arc lamp)	97.1	EPA guideline CG6000	DI 6799 DI 6689
Dissociation characteristics	Does not dissociate	99.9	OECD guideline 112	DI 11387

Table 2. Chemical composition and properties of diflubenzuron technical concentrate (TK)

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 99.0-100.3%.
Declared minimum diflubenzuron content:	875 g/kg
Relevant impurities ≥1 g/kg and maximum limits for them:	None *
Relevant impurities <1 g/kg and maximum limits for them:	None
Stabilizers or other additives and maximum limits for them:	None
Melting or boiling temperature range	228°C, no decomposition at melting point.
Particle size	Particles smaller than 5 µm: not less than 70% w/w. Average particle size: not more than 3.75 µm.

* Water is a relevant impurity in GR (20 g/kg) and DT (40 g/kg), because these formulations contain effervescent systems.

Hazard summary

Notes.

(i) The proposers provided written confirmation that the toxicological and ecotoxicological data included in the summary below were derived from diflubenzuron having impurity profiles similar to those referred to in the table above.

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

(iii) The acute toxicity data relate to studies with diflubenzuron TC and/or with diflubenzuron VC-90, a TK containing 90% diflubenzuron, which has the same toxicological profile as the active ingredient itself.

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

Species	Test	Duration and conditions	Result	Reference
Rat (male and female)	Oral	OECD guideline 401, purity 90%	LD_{50} >5000 mg/kg bw	DI 4959
Rat; mouse (male and female)	Oral (gavage)	Guideline not stated, purity 99.6%	LD_{50} >4640 mg/kg bw	DI 2207
Mouse (male and female)	Oral (gavage)	Guideline not stated, purity 99.6%	LD_{50} >4640 mg/kg bw	DI 2203
Rat (male and female)	Dermal	OECD guideline 402, purity 90%	LD_{50} >2000 mg/kg bw	DI 4958
Rat	Dermal	24 hours. PSD, UK (1971) purity 99.6%	LD_{50} >10000 mg/kg bw	DI 2227
Rat (male and female)	Inhalation	OECD guideline 403 purity 90%	LC_{50} >2490 mg/m^3	DI 5710
Rat	Inhalation	Guideline not stated, purity 99.6%	LC_{50} >2900 mg/m^3	DI 3513
Rabbit (male and female)	Skin irritation	OECD guideline 404, purity 90%	Non-irritant	DI 4961

Species	Test	Duration and conditions	Result	Reference
Rabbit (male and female)	Eye irritation	OECD guideline 405, purity 90%	Slightly irritating (Note 1)	DI 4960
Guinea pig	Skin sensitization	OECD guideline 406, purity 95.6%	Non-sensitizer	DI 8423

Note 1: Although a slight reaction was observed during the eye irritation tests, the findings did not trigger classification of diflubenzuron as an eye irritant.

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

Species	Test	Duration and conditions	Result	Reference
Mouse	Oral 6-week	No guideline specified, Dose range tested: 0; 16 & 50 ppm; purity 99.6%	NOAEL = 2.0 mg/kg bw/day (16 ppm)	DI 3523
Mouse	Oral 90-day	No guideline specified, Dose range tested: 0; 16; 50; 400; 2,000; 10,000 & 50,000 ppm; purity 97.2%	NOAEL = 7.1 mg/kg bw/day (50 ppm)	DI 2212 DI 3522
Mouse	Oral 14-week	No guideline specified, Dose range tested: 0; 80; 400; 2000; 10,000 & 50,000 ppm; purity 97.2%	NOAEL = 10.4 mg/kg bw/day (80 ppm)	DI 4155
Rat	Oral 28-day	No guideline specified, dose range tested: 0; 800; 4,000; 20,000 & 100,000 ppm; purity 98.5%.	LOEL = 84 mg/kg bw/day (800 ppm)	DI 4161
Rat	Oral 90-day	No guideline specified, dose range tested: 0; 3.125; 12.5; 50 & 200 ppm; purity 96.0%.	NOAEL = 21.6 mg/kg bw/day (200 ppm)	DI 2376 DI 3528
Rat	Oral 90-day	No guideline specified, Dose range tested: 0; 160; 400; 2,000; 10,000 & 50,000 ppm; purity 96.0%	NOAEL = 12.6 mg/kg bw/day (160 ppm)	DI 2168 DI 4279
Rat	Oral 9-week	No guideline specified; Dose range tested: 0; 10,000 & 100,000 ppm; purity 98.5%	LOEL = 1000 mg/kg bw/day (10.000 ppm)	DI 3517
Dog	Oral 90-day	No guideline specified, Dose range tested: 0; 10; 20; 40 & 160 ppm; purity 99.6%	NOAEL = 0.84 mg/kg bw/day (20 ppm)	DI 2375
Dog	Oral 90-day	No guideline specified, Dose range tested: 0; 2; 4; 50 &; 250 mg/kg bw/day; purity 97.6%	NOAEL = 4 mg/kg b.w./day	DI 987
Dog	Oral 1-year	No guideline specified, Dose range tested: 0; 2; 10; 50 & 500 mg/kg b.w./day; purity 97.6%	NOAEL = 2 mg/kg b.w./day	DI 4852

Species	Test	Duration and conditions	Result	Reference
Rat	Inhalation 28-day (1 hr/day)	No guideline specified, Dose range tested: 0; 0.5/0.12; 5.0/0.87 & 50/1.85 mg/L (nominal/actual); purity: 99.6%	NOAEL = 0.12 mg/L (actual)	DI 2359
Rabbit	Inhalation 21-day (1 hr/day)	No guideline specified, Dose range tested: 0; 0.5/0.15; 5.0/0.75; 25/1.79 mg/L (nominal/actual); purity 99.6%	NOAEL = 0.15 mg/L (actual)	DI 2360
Rat	Inhalation 28-day (6 hr/day)	OECD Guideline 412; Dose range tested: 0; 10/12; 30/34 & 100/109 mg/m^3 (nominal/actual); purity 96.5%	NOAEL = 34 mg/m^3 (actual)	DI 11497
Rabbit	Percutaneous 21-day	No guideline specified, Dose range tested: 0; 69.6; 150 & 322.5 mg/kg/day; purity 99.6%	NOAEL = 150 mg/kg/day	DI 2216
Rabbit	Percutaneous 21-day	No guideline specified, Dose range tested: 0; 113 & 345 mg/kg/day; purity 99.6%	Not established	DI 2217
Rat	Percutaneous 21-day	Guideline US EPA FIFRA vol 43, no 163, Dose range tested: 0; 20; 500 & 1,000 mg/kg/day; purity 96.7%	NOAEL = 20 mg/kg/day	DI 9429
Rat	104 weeks dietary carcinogenicity	No guideline specified; Dose range tested: 0; 10; 20; 40; and 160 ppm; purity 99.6%	NOAEL = 1.43 mg/kg bw (males) and 1.73 mg/kg bw (females) (40 ppm) Not carcinogenic	DI 4037
Rat	104 weeks dietary carcinogenicity	Guideline US EPA FIFRA vol. 43 no. 163; Dose range tested: 0; 156; 625; 2,500 and 10,000 ppm; purity 97.6%	LOAEL = 7.8 mg/kg bw/day (156 ppm) Not carcinogenic	DI 8147
Mouse	80 weeks dietary carcinogenicity	No guideline specified; Dose range tested: 0; 4; 8; 16 and 50 ppm; purity: 99.6%	> 7.4 mg/kg bw/day (> 50 ppm) Not carcinogenic	DI 3525
Mouse	91 weeks dietary carcinogenicity	No guideline specified; Dose range tested: 0; 16; 80; 400; 2,000 and 10,000 ppm; purity 97.6%.	NOAEL = 2.4 mg/kg bw/day (16 ppm) Not carcinogenic	DI 8146
Rat	3-generation parental and reproduction toxicity	No guideline specified; Dose range tested: 0, 10, 20, 40 and 160 ppm; purity 99.6%	NOAEL = 8 mg/kg bw/day (160 ppm)	DI 3516

Species	Test	Duration and conditions	Result	Reference
Rat	1-generation reproduction toxicity	No guideline specified; Dose range tested: 0, 1000 and 100000 ppm; purity 98.5%	NOAEL = 50 mg/kg bw/day (1000 ppm)	DI 3462
Rat	2-generation reproduction toxicity	OECD guideline 416; Dose range tested: 0, 500, 5000 and 50000 ppm; purity 97.1%	NOAEL for reproductive function = 2500 mg/kg bw/day (50000 ppm)	DI 9182
Rat	Teratogenicity (gavage)	No guideline specified; Dose range tested: 0, 1,2 and 4 mg/kg bw during days 6-15 of gestation; purity 98.5%	Pregnancy rates were unaffected	DI 2349
Rat	Teratogenicity (gavage)	US EPA guideline 83-3 subdivision F; Dose range tested: 0 and 1000 mg/kg bw during days 6-15 of gestation; purity 98.5%	No maternal or embryotoxicity at 1000 mg/kg bw/day	DI 6552
Rabbit	Teratogenicity (gavage)	No guideline specified; Dose range tested: 0, 1,2 and 4 mg/kg bw during days 6-19 of gestation; purity 98.5%	Pregnancy rates were unaffected	DI 2350
Rabbit	Teratogenicity (gavage)	US EPA guideline 83-3 subdivision F; Dose range tested: 0 and 1000 mg/kg bw during days 7-19 of pregnancy; purity 98.5%	NOAEL for maternal and embryotoxicity = 1000 mg/kg bw/day	DI 6553

a Highest dose tested.
b Lowest dose tested.

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

Species	Test	Conditions	Result	Reference
Salmonella typhimurium	*In vitro* genotoxicity test	OECD guideline 471, purity 96.9%	Negative	DI 7988
Saccharomyces cerevisiae	*In vitro* genotoxicity test	OECD guideline 471, purity 98.5%	Negative	DI 2261
BALB/3T3 cells	*In vitro* genotoxicity test	OECD guideline 471, purity 98.5%	Negative	DI 2263
CHO cells	*In vitro* genotoxicity test	OECD guideline 473, purity 97.6%	Negative	DI 5707
Rat hepatocytes	*In vivo* genotoxicity test	OECD guideline 482, purity 96.9%	Negative	DI 7987
WI-38	*In vivo* genotoxicity test	OECD guideline 486, purity 98.5%	Negative	DI 2264
Mouse germ cells	Dominant lethal study in mice. *In vivo* genotoxicity test	Guideline not stated, purity not stated	Negative	DI 2348

Table 6. Ecotoxicology profile of diflubenzuron technical concentrate

Species	Test	Duration and conditions	Result	Reference
Daphnia magna	Acute toxicity	48 hr, 20°C, Guideline ASTM E729-80, purity 97.6%	EC_{50} = 2.6-7.1 µg/l NOEC 0.45 µg/l	DI 6773
Daphnia magna	Acute toxicity	48 hr, 20°C OECD Guideline 202, purity 79.4% (WG, Note 1)	EC_{50} = 3.2 µg WG-80/l NOEC = 0.38 µg WG-80/l	DI 9180
Zebra fish (*Brachydanio rerio*)	Acute toxicity	96 hr, 22°C OECD Guideline 203, purity 95.6%	LC_{50} >0.2 mg/l	DI 8925
Minnow (*Cyprinodon variegates*)	Acute toxicity	96 hr, 22°C Guideline US EPA 40 CFR 158.145 72-3, purity 100% (Note 1)	LC_{50} >130 µg/l	DI 6152
Zebra fish (*Brachydanio rerio*)	Acute toxicity	96 hr, 22°C OECD Guideline 203, purity 79.4% (WG, Note 1)	LC_{50} >106 mg a.i/l	DI 8929
Minnow (*Cyprinodon variegates*)	Acute toxicity	96 hr, 22°C Guideline US EPA FIFRA Subdivision E 72-3 and OECD 203, purity 95.6%	LC_{50} >130 µg a.i./l	DI 8668
Rainbow trout (*Oncorhynchus mykiss*)	Acute toxicity	96 hr, 15°C Guideline OECD 203, purity 95.6% but WG 80 formulation used purity 79.4% (Note 1)	LC_{50} >65 mg/l	DI 8926
Rainbow trout (*Oncorhynchus mykiss*)	Acute toxicity	96 hr, 15°C Guideline OECD 203, purity 79.4% (Note 1)	LC_{50} >106 mg a.i/l	DI 8927
Selenastrum capricornutum (green alga)	Growth rate test	5 days, 22°C Guideline US EPA FIFRA Subdivision J, Series 123-2, purity 95.6%d but WG formulation used (Note 1)	EC_{50} >80 mg a.i./l NOEC = 80 mg a.i./l	DI 8667
Selenastrum capricornutum (green alga)	Acute toxicity	OECD guideline 201, purity 79.4%	EC_{50} >80 mg a.i./l NOEC = 80 mg a.i./l	DI 9104
Earthworm (*Eisenia fetida)*	Acute toxicity	14 days exposure, 22°C according to OECD guideline 207, purity 95.6%	LC_{50} >780 mg/kg dry soil	DI 8580
Apis mellifera (honey bee)	Acute oral toxicity and field test	Various laboratory, semi-field and field tests under varying conditions. BBA Guideline, purity 79.4% (Note 1).	LD_{50} >100 µg/bee (adults) Dimilin can be applied in the field without affecting honeybee colonies	DI 7234 DI 9386

Species	Test	Duration and conditions	Result	Reference
Bobwhite quail	Acute oral toxicity	Diflubenzuron administered as a single oral exposure by gavage, birds observed for 14 days. No guideline specified, purity 99.4%	LD_{50} >5000 mg/kg bw	DI 3598
Mallard duck	Acute oral toxicity	Diflubenzuron administered as a single oral exposure by gavage, birds observed for 14 days. No guideline specified, purity 99.4%	LC_{50} >5000 mg/kg bw	DI 3597
Mallard duck	8-day dietary exposure	Birds housed in thermostatically controlled brooders. No guideline specified, purity 100%	LC_{50} >4640 ppm diet (Note 2)	DI 3603
Bobwhite quail	8-day exposure	Birds housed in thermostatically controlled brooders. No guideline specified, purity 100%	LC_{50} >4640 ppm diet (Note 2)	DI 3604

Note 1: Due to the low solubility of diflubenzuron in water (0.08 mg/l), the acute toxicity was established using Dimilin WG-80 to suspend the active ingredient in water during the test.

Note 2: Highest dose tested.

Diflubenzuron was evaluated by IPCS in 1994 (IPCS 1994) and by the FAO/WHO JMPR for toxicology in 2001 (JMPR 2001) and for residues in 2002 under the periodic review programme of the Codex Committee on Pesticide Residues (JMPR 2002). The 2002 JMPR concluded that the long-term intake of residues of diflubenzuron in food resulting from its uses that have been considered by JMPR is unlikely to present a public health concern. The WHO panel of the 2001 JMPR 2001 that an acute RfD is unnecessary and therefore the 2002 JMPR concluded that the short-term intake of diflubenzuron residues is unlikely to present a public health concern. The 2001 JMPR re-confirmed the previously established ADI of 0-0.02 mg/kg bw.

The WHO hazard classification of diflubenzuron is: unlikely to present acute hazard in normal use (WHO 2002).

Formulations

The main formulation types available are WP (25%), SC (48%, 24%, 22%, 15%), WG (80%), GR (4%), OF (45% and 6%, the latter a ready-to-use formulation) for both agricultural and public hygiene use. Effervescent GR (2%) and DT (2%) formulations are under development and testing for use in public hygiene and submissions have been made for registration of this use.

These formulations are registered and sold in many countries throughout the world. Europe: Austria, Belarus, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Macedonia, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Russia, Slovakia, Spain, Sweden, Switzerland, U.K. Uzbekistan, Yugoslavia. Middle East: Egypt, Iran, Israel, Jordan, Saudi Arabia, Syria, Turkey, United Arab Emirates. Africa: Algeria, Burkina Faso, Cape Verde, Chad, Gambia, Guinea Bissau, Kenya, Madagascar, Mali, Mauritania, Morocco, Niger, Senegal, South Africa, Zimbabwe. Australasia and Asia: Australia, P. R. China, India, Indonesia, Japan, Kazakhstan, Korea South, Kyrgyzstan, Malaysia, Nepal, New Zealand, Pakistan, Taiwan, Thailand. Americas: Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Paraguay, Peru, USA, Uruguay.

Methods of analysis and testing

The analytical method for determination of the active ingredient (including identity tests) in the TK and WP is a full CIPAC method (CIPAC H). Diflubenzuron is determined by reversed-phase HPLC, using a C-18 column and acetonitrile/water mobile phase, with UV detection at 254 nm and linuron as the internal standard. The method has not been validated for GR, WG, OF, SC or DT formulations[1].

The methods for determination of impurities were based on HPLC-UV, using external standardization.

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

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of active ingredient

The active ingredient is expressed as diflubenzuron, in g/kg in solid formulations, and in g/kg or g/l at 20 ± 2ºC in liquid formulations.

Appraisal

The Meeting considered data on diflubenzuron, submitted by Crompton Europe B.V. for the review of existing WHO specifications for the TK and WP. New specifications were considered for diflubenzuron granules (GR) and tablets for direct application (DT) in public health and for suspension concentrates (SC) for use in agriculture. The data submitted were in accordance with the requirements of the manual (FAO/WHO 2002).

Diflubenzuron is a benzoylurea insect growth regulator, used in agriculture, horticulture, forestry and public health applications. It is not under patent.

[1] Extension of the analytical method to GR, DT and SC was validated and adopted by CIPAC in 2005.

Diflubenzuron has low solubility in water and is stable in aqueous solution, although its half-life is significantly shorter at higher pH, and it is reasonably stable to photolysis.

The Meeting was provided with confidential information on the manufacturing process and manufacturing specifications for purity and impurities, which were supported by 5-batch analysis data, and a comparison of these data with those submitted for registration in the USA and EU. Mass balances in the 5-batch analyses were high (99.3-100.3%) and no unidentified impurities were detected. A statement was provided by the Australian Pesticides and Veterinary Medicines Authority, confirming that the confidential data on the manufacturing process and declaration of composition (specification limits for the active and impurities) for diflubenzuron provided to the APVMA by Crompton were identical to those provided to the FAO/WHO.

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

Diflubenzuron toxicity was assessed using the relatively pure TC, the TK (VC-90, 90% diflubenzuron), or, for wildlife studies in water, an 80% WG. Diflubenzuron is generally of low acute toxicity and, although a slight reaction was observed in eye irritation tests, this did not warrant its classification as an eye irritant according to EU Directive 67/548/EEC. Diflubenzuron was not observed to cause any carcinogenic, mutagenic, teratogenic or neurotoxic effects. Diflubenzuron is generally of low toxicity to other wildlife, other than insects, with *Daphnia magna* being the most sensitive species reported.

Diflubenzuron was last reviewed by IPCS in 1994 and by the FAO/WHO JMPR in 2001 and 2002. The WHO hazard classification is: unlikely to present acute hazard in normal use.

A full CIPAC analytical method is available for determination and identification of diflubenzuron in the TK and WP. It has not been validated according to CIPAC guidelines for the analysis of GR, DT or SC formulations but it was validated and compared with another method by the manufacturer in a GLP study, in accordance with U.K. PSD guidelines[1]. The two methods are compared in the following table.

[1] U.K. Pesticides Safety Directorate. Guidelines for the Validation of Analytical Methods for Pesticides (PRD 2400), Commission Directive 96/46/EC and SANCO/3030/99 rev 4 'Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex III (part A, Section 5) of Directive 91/414'.

	CIPAC Method 339/TK/M/-	GC Laboratories Ltd Method M569
Column	250 x 4.6 mm Zorbax TM_{BP}-C_8 Spherisorb ODS 5 µm	250 x 4.6 mm 4 µm Synergi Polar-RP
Mobile phase	Acetonitrile-water-dioxane (450+450+100 v/v)	Dioxane-water (55+45 v/v)
Flow rate	1.3 ml/min	1.0 ml/min
Column temperature	Ambient	30°C
Detector wavelength	254 nm	254 nm
Injection volume	20 µl	5 µl
Internal standard	Linuron	Diphenyl phthalate
Retention times	Diflubenzuron about 7 min Linuron about 4 min	Diflubenzuron 8.9 min Diphenyl phthalate 12.5 min
Sample solute	Dioxane	Dimethylformamide

Test methods for the determination of physical properties of the TK and formulations are full CIPAC methods.

The proposed specifications were in accordance with the guidelines given in the manual (FAO/WHO 2002), with the following exceptions.

TK. The Meeting considered whether the specification related to a TC or TK but the manufacturer explained that the TK is a minimally diluted TC, intended for the manufacture of formulations. The nominal content of diflubenzuron in the TK was confirmed to be 900 g/kg, with a tolerance of ±25 g/kg, giving a minimum of 875 g/kg. Additional clauses were proposed for wet sieving, bulk density and particle size distribution. The manufacturer explained that control of particle size is important for good efficacy of the formulations prepared from the TK and the Meeting agreed that a clause for particle size should be included in the specification.

WP. The Meeting questioned the limit of 2 minutes for wettability. The manufacturer explained that this reflected the low affinity of diflubenzuron for water and the Meeting accepted the limit. The manufacturer specified a maximum retention of 1% in the wet sieve test, based on the use of a 44 µm test sieve. The Meeting agreed that the clause should be based on the usual 75 µm test sieve, the manufacturer stated that a limit of 1% would be required and this was accepted by the Meeting.

GR. The Meeting and manufacturer agreed that the term “bulk density” should be replaced by “pour density” and that a clause for pH range was unnecessary. The Meeting agreed that water should be specified as a relevant impurity and that a high limit is required for acidity, after the manufacturer explained that the granules contain an effervescent system, for disintegration of the granules after application to water for insect control. The granules are not intended for dispersion in water prior to application to water in the field and the Meeting agreed that it was not necessary to include a clause for granule disintegration.

DT. The Meeting and manufacturer agreed that a clause for pH range was unnecessary. The Meeting agreed that water should be specified as a relevant impurity and that a high limit is required for acidity, after the manufacturer explained that the tablets contain an effervescent system. The manufacturer explained that the majority of the acid present is not consumed in the effervescent reaction (which aids dispersion of the active ingredient) but, following application of the tablets to water for insect control, also aids dispersal of the active ingredient by simple dissolution. The tablets are not intended for dispersal in water prior to application in the field. Diflubenzuron is a slow-acting insecticide and effects on larvae are generally seen

after 24-48 hours. The manufacturer stated that, at water temperatures where mosquito larvae can survive, the tablets fully disintegrate within 10-30 minutes. The Meeting accepted that the high content of water-soluble acid should be sufficient to ensure dispersion, even in the absence of the effervescence reaction, and that therefore it was not necessary to include a clause for tablet disintegration.

SC. The Meeting and manufacturer agreed that a clause for acidity/alkalinity or pH is not required, because diflubenzuron has a very low solubility in water and does not dissociate. The manufacturer proposed a specification for wet sieve testing, based on a maximum retention of 0.1% of the formulation on a 150 µm test sieve. The Meeting agreed that the usual 75 µm test sieve should be specified. The manufacturer stated that tests indicated that maximum residue retention on a 75 µm sieve is less than 1% and the Meeting accepted this as an appropriate limit.

Recommendations

The Meeting recommended that:

(i) existing WHO specifications for diflubenzuron TK and WP should be withdrawn;

(ii) the proposed specification for diflubenzuron TK, as amended, should be adopted by FAO and WHO;

(iii) the proposed specification for diflubenzuron SC, as amended, should be adopted by FAO, subject to CIPAC adoption of the analytical method extension to SC[1];

(iv) the proposed specification for diflubenzuron WP, as amended, should be adopted by WHO;

(v) the proposed specifications for diflubenzuron GR and DT should be adopted by WHO, subject to CIPAC adoption of the analytical method extensions to these formulations[1] and successful WHOPES testing/evaluation of the GR and DT for public health use[2].

References

Crompton document No.	Year and title or published reference
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DI 11496	1999. The boiling point of diflubenzuron technical.
DI 11497	1999. A 4-week inhalation toxicity study of Dimilin technical in rats.
DI 2168	1980. Subchronic dietary toxicity study in rats-diflubenzuron.
DI 2203	1977. Acute oral toxicity study with DU 112307 Technical in mice.
DI 2207	1973. Acute toxicity studies with DU 112307 in mice and rats.
DI 2212	1980. Ninety-day subchronic toxicity study in mice - diflubenzuron technical.

[1] Extension of the analytical method to GR, DT and SC was validated and adopted by CIPAC in 2005.

[2] WHOPES evaluation was successfully completed in 2005 (WHOPES 2005).

Crompton document No.	Year and title or published reference
DI 2216	1975. Effect of repeated applications of DU 112307 to the skin of rabbits for three weeks.
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DI 2261	1977. Mutagenic evaluation of diflubenzuron technical batch FL 44/605201.
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DI 2349	1975. Effect of DU 112307 on Pregnancy of the Rat.
DI 2350	1975, Effect Of DU 112307 on Pregnancy of the New Zealand white rabbit.
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DI 2375	1974. DU 112307 toxicity in repeated dietary administration to beagle dogs (repeated administration for 13 weeks).
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DI 3604	1973. Eight-day dietary LC50-Bobwhite Quail Technical TH-6040 Final report.
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