



Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS
FOR AGRICULTURAL
PESTICIDES

IPRODIONE

**3-(3,5-dichlorophenyl)-*N*-isopropyl-2,4-dioxo-
imidazolidine- 1- carboxamide**

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DISCLAIMER¹

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

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

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

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

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

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

¹ This disclaimer applies to all specifications published by FAO.

INTRODUCTION

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

From 1999, the development of FAO specifications follows the **New Procedure**, described in the 1st edition of “Manual for Development and Use of FAO and WHO Specifications for Pesticides” (2002) - currently available as 3rd revision of the 1st edition (2016) - , which is available only on the internet through the FAO and WHO web sites.

This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPM, rather than the JMPS.]

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently from the year 2000 onwards the publication of FAO specifications under the **New Procedure** has changed. Every specification consists now of two parts namely the specifications and the evaluation report(s):

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

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

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

Specifications bear the date (month and year) of publication of the current version.

* NOTE: PUBLICATIONS ARE AVAILABLE ON THE INTERNET AT

<http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/ps-new/en/>

PART ONE

SPECIFICATIONS

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IPRODIONE

INFORMATION

ISO common name Iprodione (E-ISO, (m) F-ISO, BSI, ANSI)

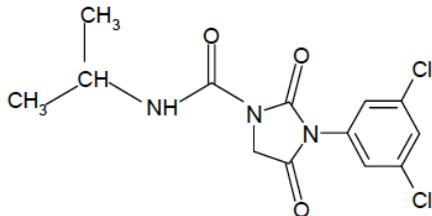
Synonym Glycophene (rejected common name proposal)

Chemical names

IUPAC 3-(3,5-dichlorophenyl)-*N*-isopropyl-2,4-dioxo-imidazolidine-1- carboxamide

CA 3-(3,5-dichlorophenyl)-*N*-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide

Structural formula



Empirical formula C₁₃H₁₃Cl₂N₃O₃

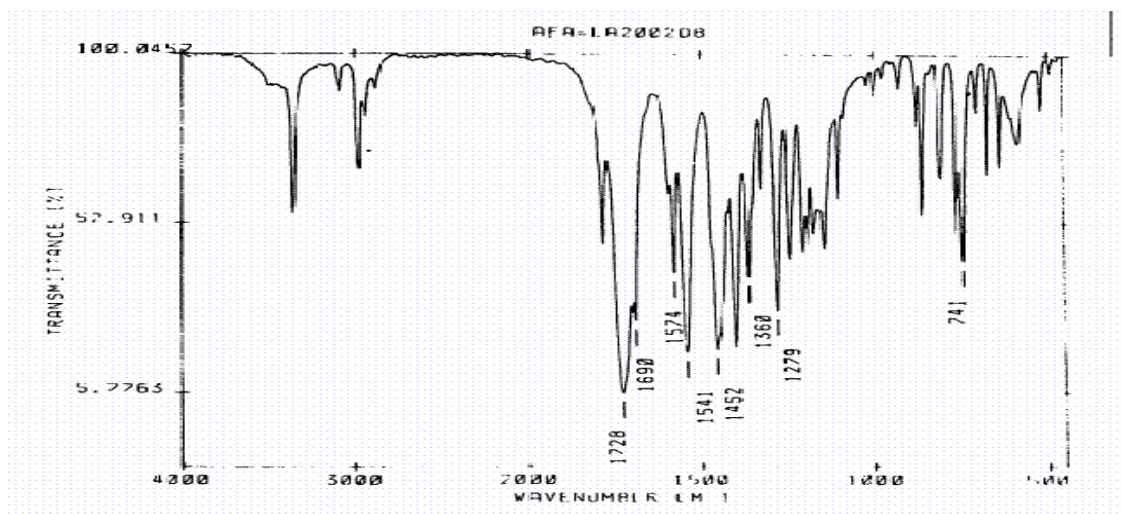
Relative molecular mass 330.2

CAS Registry number 36734-19-7

CIPAC number 278

Identity tests HPLC retention time; IR spectrum

IR spectrum of iprodione



IPRODIONE TECHNICAL MATERIAL

FAO Specification 278 / TC (November 2019*)

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 (278/2004, 278/2018 & 278/2019). It should be applicable to technical materials 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 TC of other manufacturers. The evaluation reports (278/2004, 278/2018 & 278/2019) as PART TWO form an integral part of this publication.

1 Description

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

2 Active ingredient

2.1 Identity tests (CIPAC 278/TC/M/2, CIPAC Handbook G, p.99, 1995)

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 Iprodione content (CIPAC 278/TC/M/3, CIPAC Handbook G, p.99, 1995)

The iprodione content shall be declared (not less than 960 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

3 Relevant impurities

3.1 Loss on drying (MT 17.2, CIPAC Handbook F, p.56, 1995)

Maximum: 10 g/kg.

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

IPRODIONE WETTABLE POWDER

FAO Specification 278 / WP (November 2019*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose name are listed in the evaluation reports (278/2004 & 278/2019). It should be applicable to wettable powders 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 report (278/2004 & 278/2019) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of an homogeneous mixture of technical iprodione complying with the requirements of FAO specification 278/TC (November 2019). It shall be in the form of a fine powder free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 Identity tests (CIPAC 278/WP/M/2, CIPAC Handbook G, p.102, 1995)

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 Iprodione content (CIPAC 278/WP/M/3, CIPAC Handbook G, p.102, 1995)

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

Declared content, g/kg	Tolerance
above 100 up to 250	± 6% of the declared content
above 250 up to 500	± 5% of the declared content
above 500	± 25 g/kg
Note: in each range the upper limit is included.	

3 Relevant impurities

3.1 Water (MT 30.6) (Note 1)

Maximum: 20 g/kg.

4 Physical properties

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

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

pH range: 4 to 6.

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

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

4.3 **Suspensibility** (MT 184.1) (Notes 2 & 3)

A minimum of 70% of the iprodione content found under 2.2 shall be in suspension after 30 min in CIPAC standard water D at 25 ± 5°C (Note 4).

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

Maximum: 50 ml after 1 min.

4.5 **Wettability** (MT 53.3.1, CIPAC Handbook F, p.165, 1995)

The formulation shall be completely wetted in 1 min without swirling.

5 Storage stability

5.1 **Stability elevated temperature** (MT 46.4) (Note 6)

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

- pH range (4.1),
- wet sieve test (4.2),
- suspensibility (4.3),
- wettability (4.5).

Note 1 The revised and amended CIPAC MT 30.6 Karl Fischer Water determination was presented and provisionally adopted at the 2019 CIPAC Meeting in Braunschweig. Briefly, it consists of two sub-methods: MT 36 A for volumetric determination and B for coulometric determination covering different concentration ranges. Prior to its publication in a next Handbook, copies of the method can be obtained through <https://www.cipac.org/index.php/methods-publications/pre-published-methods>

Note 2 MT 184.1 is the revised and updated version of MT 184 and was adopted at the CIPAC Meeting in Panama in 2018. Prior to its publication in a next Handbook, copies of the method can be obtained through <https://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.

Note 4 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 results which are in agreement to those of the chemical assay method. In case of dispute, the chemical method shall be the referee method.

Note 5 The mass of sample to be used in the test should be at the highest rate of use recommended by the supplier.

Note 6 MT 46.4 is the harmonized and updated accelerated storage method. It was presented and provisionally adopted at the 2019 CIPAC Meeting in Braunschweig. Prior to its publication in a next Handbook, copies of the method can be obtained through <https://www.cipac.org/index.php/methods-publications/pre-published-methods>

Note 7 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.

IPRODIONE WATER DISPERSIBLE GRANULES

FAO Specification 278 / WG (November 2019*)

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 (278/2004 & 278/2019). It should be applicable to water dispersible granules 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 (278/2004 & 278/2019) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of an homogeneous mixture of technical iprodione, complying with the requirements of the FAO specification 278/TC (November 2019), together with carriers and any other necessary formulants. It shall be in the form of granules for application after disintegration and dispersion in water. The formulation shall be dry, free-flowing, essentially non-dusty, and free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 Identity tests (CIPAC 278/WP/M/2, CIPAC Handbook G, p.102, 1995, Note 1)

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 Iprodione content (CIPAC 278/WP/M/3, CIPAC Handbook G, p.102, 1995, Note 1)

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

Declared content, g/kg	Tolerance
above 250 up to 500	± 5% of the declared content
above 500	± 25 g/kg
Note: the upper limit is included in the range	

3 Relevant impurities

3.1 Water (MT 30.6 A) Note 2)

Maximum: 8 g/kg.

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

4 Physical properties

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

pH range: 8.9 to 9.9.

4.2 Wettability (MT 53.3.1, CIPAC Handbook F, p.165, 1995)

The formulation shall be completely wetted in 1 min without swirling.

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

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

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

Dispersibility: minimum 90% after 2 min stirring.

4.5 Suspensibility (MT 184.1), (Notes 3 & 4)

A minimum of 70% shall be in suspension after 30 min in CIPAC standard water D at $25 \pm 5^\circ\text{C}$ (Note 5).

4.6 Persistent foam (MT 47.3, CIPAC Handbook F, p.152, 1995) (Note 6)

Maximum: 50 ml after 1 min.

4.7 Dustiness (MT 171.1) (Notes 7 & 8) Essentially non-dusty.

4.8 Flowability (MT 172, CIPAC Handbook F, p.430, 1995)

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

5 Storage stability

5.1 Stability at elevated temperature (MT 46.4,) (Note 6)

After storage at $54 \pm 2^\circ\text{C}$ for 14 days, the determined average active ingredient content must not be lower than 97% relative to the determined average content found before storage (Note 7) and the formulation shall continue to comply with the clauses for:

- pH range (4.1),
- wet sieve test (4.3),
- degree of dispersion (4.4),
- suspensibility (4.5),
- dustiness (4.7),
- flowability (4.8).

Note 1 The CIPAC method for determination of iprodione in wettable powders (WP) is also applicable to water dispersible granules (WG). However, prior to analysis, samples of the granules should be ground to a powder.

Note 2 The revised and amended CIPAC MT 30.6 Karl Fischer Water determination was presented and provisionally adopted at the 2019 CIPAC Meeting in Braunschweig. Briefly, it consists of two sub-methods: MT 36 A for volumetric determination and B for coulometric determination covering different residual water concentration ranges. Prior to its publication in a next Handbook, copies of the method can be obtained through <https://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.
- Note 4** 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 results which are in agreement to those of the chemical assay method. In case of dispute, the chemical method shall be the referee method.
- Note 3** The mass of sample to be used in the test should be at the highest application rate of use recommended by the supplier.
- Note 4** Measurement of dustiness must be carried out on the sample "as received" and, where practicable, the sample should be taken from a newly opened container, because changes in the water content of samples may influence dustiness significantly. The optical method, MT 171.2, usually shows good correlation with the gravimetric method, MT 171.1, and can, therefore, be used as an alternative where the equipment is available. Where the correlation is in doubt, it must be checked with the formulation to be tested. In case of dispute the gravimetric method shall be used.
- Note 5** The mass of sample to be used in the test should be at the highest rate of use recommended by the supplier.
- Note 5** The mass of sample to be used in the test should be at the highest rate of use recommended by the supplier.
- Note 6** Measurement of dustiness must be carried out on the sample "as received" and, where practicable, the sample should be taken from a newly opened container, because changes in the water content of samples may influence dustiness significantly. The optical submethod of MT 171.1, usually shows good correlation with the gravimetric submethod, MT 171, and can, therefore, be used as an alternative where the equipment is available. Where the correlation is in doubt, it must be checked with the formulation to be tested. In case of dispute the gravimetric method shall be used.
- Note 7** MT 171.1 is the corrected and amended version of MT 171. Prior to its publication in a next Handbook, copies of the method may be downloaded from the CIPAC website <https://www.cipac.org/index.php/methods-publications/errata>
- Note 8** MT 46.4 is the harmonized and updated accelerated storage method. It was presented and provisionally adopted at the 2019 CIPAC Meeting in Braunschweig. Prior to its publication in a next Handbook, copies of the method can be obtained through <https://www.cipac.org/index.php/methods-publications/pre-published-methods>
- Note 9** Analysis of the formulation, before and after the storage stability test, may be carried out concurrently (i.e. after storage) to reduce analytical error.

IPRODIONE SUSPENSION CONCENTRATE

FAO Specification 278 / SC (November 2019*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose name are listed in the evaluation reports (278/2004, 278/2018 & 278/2019). It should be applicable to suspension concentrates 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 (278/2004, 278/2018 & 278/2019) as PART TWO form an integral part of this publication.

1 Description

The material shall consist of a suspension of fine particles of technical iprodione, complying with the requirements of FAO specification 278/TC (November 2019), in an aqueous phase together with suitable formulants. After gentle agitation the material shall be homogeneous (Note 1) and suitable for further dilution in water.

2 Active ingredient

2.1 Identity tests (CIPAC 278/SC/M/2, CIPAC Handbook G, p.104, 1995)

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 Iprodione content (CIPAC 278/SC/M/3, CIPAC Handbook G, p.104, 1995)

The iprodione content shall be declared in (g/kg or g/l at $20 \pm 2^\circ\text{C}$, Note 2) and, when determined, the average content measured shall not differ from that declared by more than the following tolerances:

Declared content, g/kg or g/l at $20 \pm 2^\circ\text{C}$	Tolerance
above 100 up to 250	$\pm 6\%$ of the declared content
above 250 up to 500	$\pm 5\%$ of the declared content
Note: in each range the upper limit is included.	

3 Physical properties

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

range: 4.0 to 6.0.

3.2 Pourability (MT 148, CIPAC Handbook F, p.348, 1995)

Maximum residue: 5%.

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

3.3 Spontaneity of dispersion (MT 160, CIPAC Handbook F, p.391, 1995) (Note 3)

A minimum of 90% of the iprodione content found under 2.2 shall be in suspension after 5 min in CIPAC standard water D at $30 \pm 2^\circ\text{C}$.

3.4 Suspensibility (MT 184.1) (Notes 4, 5 & 6)

A minimum of 70% of the iprodione content found under 2.2 shall be in suspension after 30 min in CIPAC standard water D at $25 \pm 5^\circ\text{C}$.

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

Maximum: 1% of the formulation shall be retained on a 75 μm test sieve.

3.6 Persistent foam (MT 47.3, CIPAC Handbook O, p.177, 2017) (Note 7)

Maximum: 25 ml after 1 min.

4 Storage stability

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

After storage at $0 \pm 2^\circ\text{C}$ for 7 days, the formulation shall continue to comply with the clauses for:

- spontaneity of dispersion (3.3),
- suspensibility (3.4),
- wet sieve test (3.5).

4.2 Stability at elevated temperature (MT 46.4) (Note 7)

After storage at $54 \pm 2^\circ\text{C}$ for 14 days, the determined average active ingredient content must not be lower than 97%, relative to the determined average content found before storage (Note 9), and the formulation shall continue to comply with the clauses for:

- pH range (3.1),
- pourability (3.2),
- spontaneity of dispersion (3.3),
- suspensibility (3.4),
- wet sieve test (3.5).

Note 1 Before sampling to verify the formulation quality, inspect the commercial container carefully. On standing, suspension concentrates usually develop a concentration gradient from the top to the bottom of the container. This may even result in the appearance of a clear liquid on the top and/or of sediment on the bottom. Therefore, before sampling, homogenize the formulation according to the instructions given by the manufacturer or, in the absence of such instructions, by gentle shaking of the commercial container (for example by inverting the closed container several times). Large containers must be opened and stirred adequately.

After this procedure, the container should not contain a sticky layer of non-dispersed matter at the bottom. A suitable and simple method of checking for a non-dispersed sticky layer "cake" is by probing with a glass rod or similar device adapted to the size and shape of the container. All the physical and chemical tests must be carried out on a laboratory sample taken after the recommended homogenization procedure.

Note 2 If the buyer requires both g/kg and g/l at 20°C , then in case of dispute the analytical results shall be calculated as g/kg.

Note 3 This test will normally only be carried out after the heat stability test: 4.2.

Note 4 The revised MT 184.1 was adopted at the CIPAC Meeting in Panama in 2018. Prior to its publication in a next Handbook, copies of the method may be obtained through <https://www.cipac.org/index.php/methods-publications/pre-published-methods>

Note 5 The formulation should be tested at the highest and lowest rates of use recommended by the sup-

plier.

Note 6 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 results which are in agreement to those of the chemical assay method. In case of dispute, the chemical method shall be the referee method.

Note 7 The mass of sample to be used in the test should be at the highest application rate of use recommended by the supplier.

Note 8 MT 46.4 is the harmonized and updated accelerated storage method. It was presented and provisionally adopted at the 2019 CIPAC Meeting in Braunschweig. Prior to its publication in a next Handbook, copies of the method can be obtained through <https://www.cipac.org/index.php/methods-publications/pre-published-methods>

Note 9 Analysis of the formulation, before and after the storage stability test, should be carried out concurrently to reduce analytical error.

PART TWO

EVALUATION REPORTS

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IPRODIONE

FAO/WHO EVALUATION REPORT 278/2019

Recommendations

The Meeting recommended the following:

- i) the change of the manufacturer consortium for the reference specifications for iprodione TC, WP, WG and SC from Bayer Crop Science and BASF SE to BASF SE and FMC Corporation, respectively, should be noted by FAO.

Appraisal

The reference FAO specifications for iprodione TC, WP, WG and SC formulations had been jointly proposed by Bayer Crop Science (BCS) and BASF and published in 2006 (FAO/WHO Evaluation report 278/2006).

Bayer Crop Science recently contacted FAO and informed, that since 2011 the intellectual property rights for iprodione outside the European Union had been sold to FMC Corporation² (FMC) and requested that the new shared responsibility for iprodione including the reference FAO specifications for this compound and its formulations should be reflected in a notification report.

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

FMC later provided confirmation in writing (FMC, 2019)³ to FAO confirming the continued support for the FAO reference specifications for iprodione and its formulated products. FMC explained that both the manufacturing site and processes for iprodione were not affected by the transition from BCS to their company and confirmed the continued validity of the published specifications and stewardship for them.

For this reason, the Meeting recommended that the transition of the consortium BCS and BASF as the holder of the reference specifications for iprodione and its formulations to BASF and FMC should be noted by FAO.

² see also <https://agrow.agribusinessintelligence.informa.com/AG005527/FMC-gains-two-Bayer-fungicides>

³ E-mail from Mrs. R. McKenna, FMC, to FAO dated 29 November 2019

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IPRODIONE

FAO/WHO EVALUATION REPORT 278/2018

Recommendations

The Meeting recommended that:

- (i) The iprodione TC produced by Rotam Agrochemical Co., Ltd should be accepted as equivalent to the iprodione reference profile by FAO;
- (ii) The existing FAO specifications for iprodione TC should be extended to the corresponding products of Rotam Agrochemical Co., Ltd.
- (iii) The existing FAO specifications for iprodione SC should be extended to the corresponding products of Jiangsu Rotam Chemistry Co., Ltd.

Appraisal

The Meeting considered data and supporting information submitted in October 2017 by Rotam Agrochemical Co., Ltd for the determination of the equivalence for iprodione TC and by Jiangsu Rotam Chemistry Co., Ltd for extension of the existing FAO specifications for SC (FAO specifications 278/TC and SC). The data submitted were broadly in accordance with the requirements of the Manual on Development and Use of FAO and WHO specifications for Pesticides (March 2016 - 3rd revision of the 1st edition) and supported the draft specifications. The reference specifications and supporting data for iprodione were provided by Bayer Crop Science and BASF, and the FAO specifications had been published in 2006.

Iprodione is the ISO common name for 3-(3,5-dichlorophenyl)-*N*-isopropyl-2,4-dioxoimidazolidine-1-carboxamide (IUPAC). Iprodione is a non-systemic fungicide, widely used in agriculture.

Iprodione was evaluated several times by JMPR (JMPR 1992, 19954). It is not under patent, and the main formulation types for agricultural use are WP, WG and SC. These formulations are registered and sold in about 90 countries, in all continents. Iprodione may be co-formulated with other fungicides, such as carbendazim, thiophanate-methyl, diniconazole or bromuconazole.

The confidential information (manufacturing process, purity and impurity profile) submitted to FAO was compared by the UK Chemicals Regulation Directorate as being the same as that submitted for registration in UK⁴.

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on all impurities present at or above 1 g/kg, as well as any potentially relevant impurities below 1 g/kg, and their manufacturing limits in the TC. Mass balances ranged from 99.63% to 99.84% in the 5-batch data. The maximum limits for

⁴ E-mail from CRD, May 2018

the impurities were supported by the 5-batch data and statistically justified. The proposer declared the minimum purity of the iprodione TC as 980 g/kg which is statistically justified (mean value-3 standard deviation = 982 g/kg) and it is thus compliant with the existing specifications (not less than 960 g/kg).

The manufacturing process, impurity profile and five batch analyses were compared with the data submitted in the reference profile. The manufacturing process utilized by Rotam is similar to that of the reference TC.

However, iprodione TC produced by Rotam contains one additional impurity not present in the reference profile. The Meeting noted that, in a recent EU evaluation of iprodione⁵, two relevant impurities were identified by EFSA. One of these two impurities is not considered as relevant by the JMPs as it is - also a mammalian metabolite of iprodione. The other impurity - 3,5-dichloroaniline - is a starting material used in the manufacturing process and was considered as potentially relevant at a concentration ≥ 0.325 g/kg. The Meeting questioned the company on the possible presence of this impurity in their iprodione TC. Rotam provided a 5-batch analysis study to demonstrate the absence of this impurity at a detection limit of 5 μ g/kg which is well below the cut of limit for relevance and the Meeting therefore concluded that this impurity was not relevant (Chen, L. and Zhao D., 2019).

A mutagenicity study (Ames test) for iprodione has been conducted as Tier-1 data. Iprodione TC from Rotam does not show mutagenicity in *in vitro* bacterial assays (OECD 471).

The proposer used the CIPAC method 278/TC/M/3 (HPLC-UV at 220 nm with external standardization) for the determination of the active ingredient content in iprodione TC. The validation data (specificity, linearity of response, linearity range, precision and accuracy in one laboratory) were provided. The method was validated according to the EU SANCO/3030/99 rev.4 guideline.

The determination of impurities was achieved using an HPLC-DAD method with detection at 200 nm. The method was validated with respect to specificity, linearity of response, precision, accuracy and limit of quantification for impurities according to EU SANCO/3030/99 rev.4 guideline.

The confirmation of structural identity of iprodione and the impurities was achieved using GC-MS based on mass and functional group by FT-IR and NMR (¹H- and ¹³C-NMR spectrometry).

The water content of the technical material was determined using the CIPAC method MT 30.1 (Karl Fischer titration).

Though not required, the Meeting was also provided with data on melting point, vapour pressure, density, pH range, surface tension, octanol/water partition coefficient, dissociation characteristic and solubility in water and organic solvents.

The melting point range is in good agreement with the reference material (133.4 °C for

⁵ Peer review of the pesticide risk assessment of the active substance iprodione, EFSA Journal 2016;14(11):4609

Bayer CropScience versus 133.1-133.9 °C for Rotam).

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

The Meeting concluded that Rotam iprodione TC was equivalent to the iprodione reference TC based on Tier-1 evaluation and recommended the extension the existing FAO TC specification to the technical material produced by Rotam.

A data package with physical-chemical properties was provided in support of a claim for an equivalent suspension concentrate (SC) containing 500 g/l of iprodione for comparison with reference SC specification. Rotam's SC formulation complied with all specification clauses including before and after cold temperature and accelerated storage where appropriate.

The Meeting also recommended an editorial update of formulation specifications including the SC taking into account the revised CIPAC methods for pourability (MT 148.1 instead of MT 148), suspensibility (MT 184.1 instead of MT 184) and persistent foam (MT 47.3 instead of MT 47.2) to bring them in line with the current CIPAC methods and the latest version of the FAO/WHO Manual on pesticide specifications and its amendments.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 278/2018

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

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 99.63 – 99.84 % and percentages of unknowns were 0.16 – 0.37%.			
Declared minimum iprodione content	980 g/kg			
Relevant impurities ≥ 1 g/kg and maximum limits for them	None			
Relevant impurities < 1 g/kg and maximum limits for them	None			
Stabilisers or other additives and maximum limits for them	None			
Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature of the TC	-133.1-133.9°C	97.65%	OECD 102	Study No: 0517

FORMULATIONS AND CO-FORMULATED ACTIVE INGREDIENTS

The main formulation types available are SC, WG and WP. Iprodione may be co-formulated with other fungicides like thiophanate-methyl, carbendazim, fosetyl-aluminium. These formulations are registered and sold in countries in Central American and Caribbean countries, Latin America, and North Africa.

METHODS OF ANALYSIS AND TESTING

Rotam used the CIPAC method 278/TC/M/3 (HPLC-UV method with external standardization) for the determination of the active ingredient content in iprodione TC. The determination of impurities was achieved using a HPLC-UV method. The method is validated with respect to specificity, linearity of response, precision, accuracy and limit of quantification for impurities according to the EU SANCO/3030/99 rev.4 guideline. A Karl Fischer titration method (CIPAC method MT 30.1) is used for the determination of water.

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

PHYSICAL PROPERTIES

The physical properties, the methods for testing them, and the limits proposed for the SC formulation comply with the requirement described in the existing FAO specifications for iprodione SC (278/SC, 2006)

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified

EXPRESSION OF THE ACTIVE INGREDIENT

The the content of the active ingredient iprodione is expressed as iprodione.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

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

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

Species	Test	Purity % Note ⁶	Guideline, duration, doses and conditions	Result	Study number
<i>Salmonella typhimurium</i>	<i>In vitro</i> Reverse Mutation Assay (Ames Test)	97.65	OECD 471 (1997), OPPTS 870.5100, EC B.13/14 Technical Iprodione was tested in concentrations ranging from 39.07 to 625 µg/plate in the absence and presence of S-9 in the five strains of <i>Salmonella typhimurium</i> .	Non-mutagenic	08333
<i>Mus musculus</i> (Mouse), Swiss albino	<i>In vivo</i> Micronucleus Assay	97.65	OECD 474 (1997), OPPTS 870.5395, EC B.12, Dose: 2000 mg/kg b.w. No mortality and apparent induction of chromosomal or any other genetic damage leading to micronuclei formation in polychromatic erythrocytes was observed in 2000 mg/kg b.w. at different time points of sacrifice.	Non-mutagenic	08334

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

ANNEX 2 REFERENCES

(sorted by study number)

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
0537	Rachel Joseph	2009	ACTIVE INGREDIENT CONTENT DETERMINATION AND IMPURITY PROFILING OF FIVE DIFFERENT BATCHES OF IPRODIONE TECHNICAL. Study No. 0537. GLP. Rotam Research Laboratory (R.R.L.). Unpublished.
1191/2009–2.0PV	Lilian Polakiewicz	2010	Iprodione TG - Determination of vapour pressure. Study No. 1191/2009–2.0PV. Report Number: RL1191/2009–2.0PV-B GLP. TECAM Tecnologia Ambiental Ltda.. Unpublished.
0517	Rachel Joseph	2009	STUDY ON THE PHYSICO-CHEMICAL PROPERTIES OF IPRODIONE TECHNICAL. Study No. 0517. GLP. Rotam Research Laboratory. Unpublished.
0595	Rachel Joseph	2010	DISSOCIATION CONSTANT IN WATER FOR IPRODIONE TECHNICAL. Study No. 0595. GLP. Rotam Research Laboratory (R.R.L.). Unpublished.
08327		2009	Acute Oral Toxicity Study with Iprodione Technical in Wistar Rats. Study No. 08327. GLP. Unpublished.
08328		2009	Acute Dermal Toxicity Study with Iprodione Technical in Wistar Rats. Study No. 08328. GLP. Unpublished.
08331		2009	Acute inhalation toxicity study with Iprodione Technical in Wistar rats. Study No. 08331. GLP. Unpublished.
08329		2009	Acute Dermal irritation/corrosion of Iprodione Technical in New Zealand White Rabbits. Study No. 08329. GLP. International Institute of Biotechnology and Toxicology (IIBAT). Unpublished.
08330		2009	Acute Eye Irritation/Corrosion of Iprodione Technical in New Zealand White Rabbits. Study No. 08330. GLP. International Institute of Biotechnology and Toxicology (IIBAT). Unpublished.
08332		2009	Skin Sensitization potential of Iprodione Technical in Guinea Pigs. Study No. 08332. GLP. Unpublished.
08333		2009	Mutagenicity evaluation of Iprodione Technical by Ames <i>Salmonella typhimurium</i> - Reverse Mutation Assay. Study No. 08333. GLP. Unpublished.
08334		2009	Genotoxicity Evaluation of Iprodione Technical by <i>In vivo</i> mouse micronucleus assay. Study No. 08334. GLP. International Institute of Biotechnology and Toxicology (IIBAT). Unpublished.
PCD0800	Linda Chen Damily Zhao	2019	3,5-Dichloroaniline Content Determination In Five Batches Of Iprodione Technical. Report No. PCD0800. Non GLP. TEST FACILITY: ACD (Analytical Chemistry Department), Jiangsu Rotam Chemistry Co., Ltd. P.R.China, 215301. Unpublished. SUBMITTED BY Rotam Agrochemical Co., Ltd.

IPRODIONE

FAO/WHO EVALUATION REPORT 278/2004

Recommendations

The Meeting recommended that:

- (i) the existing FAO specifications for iprodione TC, WP and SC should be withdrawn;
- (ii) the specifications for iprodione TC, WP, WG and SC proposed by Bayer CropScience and BASF, as amended, should be adopted by FAO.

Appraisal

The Meeting considered data on iprodione, submitted by Bayer CropScience and BASF, for review of existing (1999) FAO specifications for TC, WP and SC and a proposed new specification for WG.

Iprodione is a non-systemic fungicide, widely used in agriculture. It is not under patent.

Iprodione is a solid (m.p. 133°C) of low vapour pressure (5×10^{-7} at Pa 250C), with log P Kow of 3.0. It is slowly hydrolyzed at pH 5 and progressively more rapidly at higher pH values. It is degraded only slowly by photolysis. Its water solubility is not pH dependent and iprodione has no acidic or basic properties.

Iprodione has been evaluated for toxicology and residues by the JMPR on a number of occasions and has been reviewed by the US EPA and the EU. The Meeting asked the manufacturer to provide evidence to whether or not cataracts may be induced by iprodione (certain other dicarboximides present this hazard). The manufacturer stated (M-267118-01-1) that iprodione does not induce cataracts and referred to 7 unpublished studies which addressed this issue (M-211475-01-1, M-211414-01-1, M-213190-01-2, M-213364-01-1, M-160902-01-1, M-210816-01-1 and M-210652-01-1).

The Meeting was provided with confidential information on the manufacturing process and the manufacturing specifications for all impurities ≥ 1 g/kg, which were supported by 5 batch analyses. Mass balances were high, in the range 997 to 1001 g/kg. These data were confirmed as identical to those submitted in support of registration of iprodione in The Netherlands. Information was provided on the methods of analysis used for determination of all impurities.

The Meeting questioned whether one of the impurities, 3,5-dichloroaniline (which is also a metabolite of iprodione), should be considered relevant for specifications purposes. Information relating to the toxicity of 3,5-dichloroaniline (M-213979-01-1, 1997/1002678, Rashid *et al.* 1987, Yoshimi 1988, Valentovic *et al.* 1997, Rankin *et al.* 1986 and Lo *et al.* 1990) was provided by the manufacturer (M-267118-01-1) to WHO/PCS. After reviewing the data, the PCS secretariat concluded (PCS 2005) that (i) 3,5-dichloroaniline does not show toxicity that is qualitatively different from iprodione; (ii) the irritation characteristics of the impurity are not reflected in iprodione TC; and (iii), in the improbable worst-case scenario of 3,5-dichloroaniline occurring at 40 g/kg in iprodione TC (minimum purity 960 g/kg), it would not contribute significantly to the acute toxicity of the TC. WHO/PCS therefore concluded that 3,5-dichloroaniline does not constitute a relevant impurity and the Meeting agreed. No other impurities were considered to be relevant.

Analytical methods for the TC, WP and SC are full CIPAC methods. The manufacturer stated that, after grinding, the WG is effectively in the form of a WP and provided an in-house validation study showing that the CIPAC method for WP was appropriate for analysis of the WG. The Meeting accepted the evidence presented.

Test methods for physical properties of the formulations, referenced in the specifications, are all full CIPAC methods.

The Meeting considered the proposed specifications for TC, WP, WG and SC.

TC. The Meeting welcomed the proposed lower limit for iprodione content of 960 g/kg, which was higher than the 940 g/kg in the existing specification.

The Meeting questioned the requirement for a clause for "loss on drying", which also appeared in the existing specification (though with a new limit of 20 g/kg instead of 10 g/kg). The manufacturer explained that the clause was primarily intended to control the water content (and hence to limit potential hydrolysis of active ingredient) but provided a faster and cheaper method than direct measurement of water. The Meeting agreed to the proposed clause.

WP. The Meeting noted that the proposed specification was broadly similar to the existing specification, with some limits having been changed slightly. The manufacturer stated that the clauses to restrict water content and pH are essential to maintain quality of the formulation and avoid loss of active ingredient.

WG. The Meeting noted that the clauses in this proposed new specification were in accordance with the WG guideline in the manual (FAO/WHO 2002) but questioned the limits (8.9-9.9) given for pH range, because the hydrolysis half-life of iprodione is only 27 min at pH 9. Although the water content of the WG is limited to 8 g/kg, it appeared possible that degradation could occur during storage or use (the corresponding limits proposed for WP and SC were pH 4 to 6). The manufacturer provided a report (M-210100-01-1) to show that storage stability of the WG is satisfactory. The pH of diluted WG suspensions (at concentrations corresponding to normal use) decreased very rapidly after initial dispersion. Over a 3 h period, the pH declined from 8.9 to 7 in CIPAC water A and from 8.0 to 7.8 in CIPAC water D. During the following 3 days, the pH in CIPAC water A remained unchanged but there was a small decrease to pH 7.4 in CIPAC water D. Over the 3-day period, the iprodione content had declined by only 3% in both waters. Thus the initial pH of the dispersed WG is not indicative of potential hydrolysis.

The manufacturer stated that while it was known that formulation quality is maintained in the proposed pH range, no information was available to show whether or not adverse effects occur at higher or lower pH. In the absence of such information, the Meeting agreed that the proposed clause and limits should be adopted on a precautionary basis.

SC. The Meeting accepted that the clause to restrict pH is essential to avoid loss of active ingredient but questioned whether the rearrangement of iprodione (to an isomer with low fungicidal activity), known to occur in alcoholic solution (Cooke *et al.* 1979), could occur in the SC. The manufacturer indicated that compliance with the clause for stability at elevated temperature showed that the rearrangement did not occur.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 278/2004

Uses

Iprodione is non-systemic dicarboxamide fungicide, with both protectant and eradicant properties. It is active against both spores and mycelium of a number of parasitic fungi. It is used in as a selective contact fungicide to control diseases in a wide range of fruit, vines, vegetable crops, cereals, oilseed rape, sunflower, ornamental plants and turf.

Identity of the active ingredient

ISO common name

Iprodione (E-ISO, (m) F-ISO, BSI, ANSI)

Synonyms

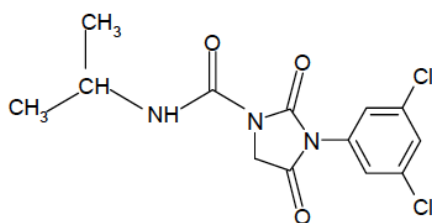
Glycophene (rejected common name proposal)

Chemical names

IUPAC 3-(3,5-dichlorophenyl)-*N*-isopropyl-2,4-dioxo-imidazolidine-1-carboxamide

CA 3-(3,5-dichlorophenyl)-*N*-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide

Structural formula



Empirical formula

C₁₃H₁₃Cl₂N₃O₃

Relative molecular mass

330.2

CAS Registry number

36734-19-7

CIPAC number

278

Identity tests

HPLC retention time; IR spectrum

Physico-chemical properties of iprodione

Table 1. Physico-chemical properties of pure iprodione

Parameter	Value(s) and conditions	Purity %	Method	Reference
Vapour pressure	5 x 10 ⁻⁷ Pa at 25°C 2 x 10 ⁻⁸ Pa at 35°C 4 x 10 ⁻⁵ Pa at 51°C	99.7	OECD104	M-189561-01-1
Melting point, boiling point and/or temperature of decomposition	Melting point: 133.4°C Boil- ing point: undetermined Decomposition point: 164.5°C	99.7	OECD 102, ECA1 OECD 103, ECA2 OECD 103, ECA2	M-189622-01-1
Solubility in water	12.2 mg/l at 20°C at pH 7 No dissociation in water, so no other pH measurement	96.1	EPA series 63-8, EEC A6	M-209773-01-1
Solubility in organic solvents (g/l at 20°C)	acetone: 342 hexane: 0.59 acetonitrile: 168 dichloromethane: 450 ethyl acetate: 225 toluene: 147 octanol: 10.0	96.1	EPA 63-8, EEC A6	M-209773-01-1
Octanol/water partition coefficient (at 25°C)	log P K _{OW} = 2.99 at pH 3 log P K _{OW} = 3.00 at pH 5 log P K _{OW} is independent of pH	99.7	EPA series 63-11, EEC A8	M-209810-01-1
Hydrolysis characteristics	Half-life = 130.7 d at pH 5 Half-life = 6.4 d at pH 7 Half-life = 27.2 min. at pH 9 At 20-25°C in the dark, iprodione is stable at pH ≤ 5. It is increas- ingly unstable at pH ≥ 6.	98.0	EPA series 161-1	M-189558-01-1
Photolysis characteristics	In pH 5 buffer, the half live was about 67 d of the equivalent of summer sunlight in Florida. No reaction products accounted for >10%.	99.3	EPA series 161-2	M-189545-01-1
Dissociation characteristics	Iprodione does not dissociate.	-	OECD 112 Assessment	M-189579-01-1

Table 2 Chemical composition and properties of technical iprodione (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 99.6-100.1% and no unknowns were reported
Declared minimum iprodione content	960 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities < 1 g/kg and maximum limits for them:	None
Stabilisers or other additives and maximum limits for them:	None
Melting or boiling temperature range of the TC	128-130°C decomposition occurs at 153°C

Hazard summary

Iprodione has been evaluated by the FAO/WHO JMPR (JMPR 1977, 1980, 1992a, 1992b, 1994a, 1994b, 1995a, 1995b, 2001). The JMPR (JMPR 1995a, 1995b) allocated an ADI of 0-0.06 mg/kg bw/d, based on an NOAEL of 6 mg/kg bw per day derived from a 2-year study of carcinogenicity in rats and a safety factor of 100. It was also concluded that the intake of residues of Iprodione, resulting from its uses considered by the JMPR, is unlikely to present a public health concern (JMPR 1995a, 1995b). In the EU, it is listed in the Annex I of directive 91/414/EC (EU 2003). With respect to wildlife, the EU concluded that use of iprodione is unlikely to pose a significant risk to birds but that it should be classified as very toxic to aquatic organisms (Commission Directive 2001/59/EC, 6 July 2001). The U.S. EPA considered that registered uses of iprodione will not cause unreasonable risk to humans (EPA 1991). The WHO classification of iprodione is U: unlikely to cause acute hazard in normal use (WHO 2002).

Formulations

The main formulation types are WP, WG and SC. These formulations are registered and sold in about 90 countries, in all continents. Iprodione may be co-formulated with other fungicides, such as carbendazim, thiophanate-methyl, diniconazole or bromuconazole.

Methods of analysis and testing

The analytical method for determination of the active ingredient (including identity tests) is a full CIPAC method. Iprodione is determined by reversed-phase HPLC, utilising internal standardization with propiophenone and UV detection at 220 nm. Although the method was validated by CIPAC for analysis of WP and SC, not WG, grinding the WG produces (for analytical purposes) material similar to WP and the CIPAC method for WP may then be used to analyze the powdered material (M- 203801-02-1). Identification is by HPLC retention time and IR spectrum.

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

Physical properties

The physical properties, the methods for testing them and the limits proposed for the WP, SC and WG formulations, comply with the requirements of the FAO/WHO manual, 1st edition (FAO/WHO 2002).

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as iprodione (g/kg in WP and WG; g/kg or g/l in SC).

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

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

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

Species	Test	Duration and conditions or guideline adopted	Purity %	Result	Reference
Rat, Sprague Dawley	Oral	Gavage, guideline not stated. Observed 14 d.	97.9	LD ₅₀ >2000 mg/kg bw	M-210407-01-1
Dog, beagle	Oral	Gavage, guideline not stated. 1000 and 2000 mg/kg. Observed 14 d.	Not known	LD ₅₀ >2000 mg/kg bw	M-210404-01-1
Rabbit	Dermal	24-h exposure. Observed 14 d post-treatment, guideline not stated.	95.8	LD ₅₀ >2000 mg/kg bw	M-210415-01-2
Rat, Sprague Dawley	Inhalation	4-h whole body exposure, guideline not stated.	96.0	LC ₅₀ >5.16 mg/l	M-189593-01-2
Rabbit, New Zealand white	Skin irritation	4-h exposure (abraded and intact skin). Skin evaluated at 72 h post-treatment, guideline not stated.	96.2	Non irritating	M-189547-01-2
Rabbit, New Zealand white	Eye irritation	Eyes evaluated at 1, 24, 72 h and day 7, guideline not stated.	96.2	Non irritating*	M-189546-01-1
Guinea pig, Hartley albino	Skin sensitization	9 topical induction applications, 2 weeks later a challenge treatment, followed 1 week later by a 2 nd challenge treatment (Buehler)	95.8	Non sensitizer	M-210418-01-1

* Technical iprodione caused mild and transient eye irritation without eye washing, whereas it is not irritant to the rabbit eye when instillation is followed by eye washing.

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

Species	Test	Duration and conditions or guideline adopted	Purity %	Result	Reference
Rabbit, New Zealand White (m,f)	Dermal study	21-d, guideline not stated. 0, 100, 500 and 1000 mg/kg/day	96.2	NOEL = 1000 mg/kg bw/d. No critical effects	M-213195-01-1
Rat, CrI/CD (m,f)	Sub-chronic dietary study	90-d, guideline not stated. 0, 250, 500, 800, 3000 ppm	97.1	NOEL = 500 ppm or 33.3 mg/kg bw/d. No critical effects. Effects at 800 ppm: decreased body weight gain and increased incidence and severity of corticocellular vacuolation of the adrenals	M-189655-01-1
Dog, beagle (m,f)	90-d dietary study	90-d, guideline not stated. 0, 800, 2400, and 7200 ppm	100	NOEL = 2400 ppm or 60-76 mg/kg bw/d. No critical effects. Effects at 7200 ppm: slight hepatomegaly and increase in alkaline phosphatase activity	M-247665-01-2
Dog, beagle (m,f)	1-year dietary studies	1 st study: 0, 100, 600 and 3,600 ppm, guideline not stated.	96.5	NOEL = 100 ppm or 4.2 mg/kg bw/d. No critical effects. Effects at 600 ppm: transient increase in Heinz bodies, lower prostate weight, slight adrenals and kidney microscopic changes	M-211475-01-1
		2 nd study: 0, 200, 300, 400 and 600 ppm., guideline not stated	96.1	NOEL = 400 ppm or 18 mg/kg bw/d. No critical effects. Effects at 600 ppm (NOAEL): slight and occasional significant reduction in RBC, Hb and Ht	M-211465-02-1
Rat, Sprague Dawley (m,f)	Oncogenicity, chronic toxicity study	0, 150, 300 and 1600 ppm, guideline not stated	Not stated	NOEL = 150 ppm or 6.1 and 8.4 mg/kg/day (m & f respectively), mean = 7.25 mg/kg/day No critical effects*	M-189567-02-1

* Effects observed at 300 ppm: Increased liver weight, slight centrilobular hepatocyte enlargement, atrophy or reduced activity of male accessory sexual glands, vacuolation of the “*zona reticularis*” (male) in adrenals and interstitial cell hyperplasia in testes. Effects observed at 1600 ppm: similar lesions plus generalized vacuolation of the “*zona fasciculata*” and “*zona reticularis*” in adrenals (males) and significantly increased testes weight related to increased incidence of interstitial cell tumours in testes with cell hyperplasia and atrophy of seminiferous tubules. Leydig cell tumours arose only at a high dose level (\geq MTD, 1600 ppm). A clear NOEL (150 ppm) and a clear threshold for oncogenic effects (300 ppm) were determined. Iprodione was shown to act via a disruption of testosterone biosynthesis from interstitial cells which in turn causes perturbation in the hypothalamic-pituitary gonadal axis. The overproduction of LH results in the overstimulation of leydig cells and tumours may then further develop in sensitive species, such as the rat, due to persistent hyperplasia. Mechanistic studies have demonstrated the existence of a clear threshold for these effects on testosterone and LH biosynthesis. Iprodione was shown to be non genotoxic. Hence the tumours observed in Leydig cells of rats receiving high doses of iprodione (10-fold higher than the NOEL of the 2-year rat carcinogenicity study) are considered to be of limited concern.

Species	Test	Duration and conditions or guideline adopted	Purity %	Result	Reference
Mouse, CD-1 (m,f)	Oncogenicity study	0, 160, 800 and 4000 ppm, guideline not stated	97.5	NOEL = 160 ppm or 23 and 27 mg/kg bw/d (m & f respectively), mean value of 25 mg/kg/day. No critical effects**	M-211435-04-1
Rat, Sprague-Dawley (m,f)	2-generation reproduction	Dietary administration, 0, 300, 1,000 and 3,000 ppm, guideline not stated.	96.2	NOEL = 300 ppm or 20 mg/kg bw/d. No critical effects observed. Effects at 1000 and 3000 ppm: depression of body weight gain in F0 and F1, lower food consumption in F0 and F, lower number of live pups/litter and lower pup weight, poor health of pups	M-211460-01-1
Rat, Sprague-Dawley (f)	Developmental toxicity study	Gavage, 0, 40, 90 and 200 mg/kg bw/d, guideline not stated	94.2	NOEL = 90 mg/kg bw/d. No teratogenic effects	M-214215-02-1
Rabbit, New Zealand White (f)	Developmental toxicity study	Gavage 0, 20, 60 and 200 mg/kg bw/d, guideline not stated	95	NOEL = 20 mg/kg bw/d No teratogenic effects	M-231159-01-1

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

Species	Test	Conditions	Purity %	Result	Reference
<i>Salmonella typhimurium</i> , strains TA98, TA100, TA1535, TA1537 and TA1538.	Bacterial reverse mutation assay (Ames), <i>in vitro</i>	10-5000 µg/plate with activation, 1-250µg/plate without activation	95 to 99.3	Negative	M-214044-01-1, M-214045-01-1, M-214052-01-2, M-208976-01-1, M-242402-01-2

** Centrilobular hypertrophy enlargement (female), vacuolation and hypertrophy of interstitial cells in testes, hyperkeratosis of non-glandular stomach. Effects observed at 4000 ppm: increased liver weight, decreased uterus weight, increased incidence of benign and malignant liver cell tumors and slight increase of luteomas in females ovaries, vacuolation and hypertrophy of interstitial cells in testes, hyperkeratosis of non-glandular stomach, heamosiderosis in spleen, amyloidosis and cortical scarring in kidneys (female). Liver tumours arose only at a high dose level which were at or exceeded the MTD (4000 ppm). A clear NOEL (160 ppm) and threshold for oncogenic effects (800 ppm) were determined. Iprodione was shown to act via a phenobarbital-like mechanism, which is widely considered to be non relevant to humans. Iprodione was shown to be non genotoxic. Hence the tumours observed in the liver of mice receiving high dose of iprodione (25- fold higher than the NOEL of the mice oncogenicity study) are considered to be of limited concern.

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

Species	Test	Conditions	Purity %	Result	Reference
<i>E. coli</i> , po/A [±]	DNA repair assay, <i>in vitro</i>	12.5-200 µg/plate, with and without S9 activation	95.1 & 99.3	Negative	M-214044-01-1, M-214045-01-1
CHO/HGPRT	Mammalian cell gene mutation	5-100 µg/ml (without activation), 100-1500 µg/ml with activation	Not known	Negative	M-214055-01-1
Mouse (CD-1), (m,f)	Micronucleus formation assay, <i>in vivo</i>	1 dose by gavage at equivalent to 0-3000 mg/kg iprodione	96.1	Negative	M-189578-01-1
Chinese hamster ovary cells	sister chromatid exchange, <i>in vitro</i>	5-100 µg/ml without activation, 5-400 µg/ml with activation	Not known	Negative	M-209011-01-1
Chinese hamster ovary cells	Chromosome aberrations in CHO cells <i>in vitro</i>	15-150 µg/ml without activation, 40-400 µg/ml with activation	Not known	Negative	M-214057-01-1
<i>Bacillus subtilis</i> , 19-strains M45(rec-) and H17(rec+) strains	Recombination assay, <i>in vitro</i>	20.6, 61.9, 185.6, 556.7 and 1670 µg/disc	96.8	Positive response at 20.6, 61.9 and 1670 µg/disc but not at 185.6 and 556.7*	M-214041-01-1

* These results were considered by the manufacturer to be of doubtful significance, due to several deficiencies in the testing method.

Table D. Ecotoxicology profile of iprodione technical material

Species	Test	Duration and conditions	Purity %	Result	Reference
<i>Daphnia magna</i> (water flea)	Acute toxicity	48-h flow-through, observed at 24 and 48 h.	96.2	EC ₅₀ = 0.25 mg/l	M-189543-01-1 M-211781-01-1
		48-h static	97.3	EC ₅₀ = 0.66 mg/l	
<i>Lepomis macrochirus</i> (bluegill sunfish)	Acute toxicity	96-h, flow-through, 20°C	96.2	LC ₅₀ = 3.7 mg/l	M-189541-01-1
<i>Oncorhynchus mykiss</i> (rainbow trout)	Acute toxicity	96-h, static, 12°C	96.2	LC ₅₀ = 4.1 mg/l	M-211742-01-1
<i>Selenastrum capricornutum</i> (green algae)	Effect on growth	FIFRA guidelines 122-2 and 123-2, 120 h	96.2	EC ₅₀ = 1.9 mg/l	M-189542-01-1
<i>Eisenia foetida</i> (earthworm)	Acute toxicity	14 d, artificial soil	96.1	LC ₅₀ >1000 mg/kg soil (dry weight)	M-189556-01-1
<i>Apis mellifera</i> (honey bee)	Acute contact toxicity	Topical application, observed at 24 and 48h, 24°C	97.1	LD ₅₀ >200 µg/bee	M-189653-01-1
<i>Apis mellifera</i> (honey bee)	Oral toxicity (normal feeding)	Dosed and observed for 24 and 48 h, 24°C	97.1	LD ₅₀ >25 µg/bee	M-189654-01-1

Table D. Ecotoxicology profile of iprodione technical material.

Species	Test	Duration and conditions	Purity %	Result	Reference
<i>Anas platyrhynchos</i> (Mallard duck)	Acute oral toxicity	Administered orally, as 2% cellulose gum (CMC) suspension, or in gelatine capsules, up to 10400 mg/kg bw	Not known	LD ₅₀ >10400 mg/kg bw	M-210594-01-1
<i>Colinus virginianus</i> (Bobwhite quail)	Acute oral toxicity	Single dose administered in corn oil. Observed 14 d post-treatment	96.2	LD ₅₀ >2000 mg/kg bw	M-211328-01-1
<i>Anas platyrhynchos</i> (Mallard duck)	Dietary sub-acute toxicity	8-day (5-day exposure, 3-day observation), up to 5620 ppm	96.2	LC ₅₀ >5620 ppm	M-211322-01-1

ANNEX 2: REFERENCES

Bayer CropScience Doc. Nr. or other Ref.	Year and title of report, publication details
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M-189541-01-1	1990. Iprodione technical - acute toxicity to bluegill sunfish (<i>Lepomis macrochirus</i>) under flow-through conditions.
M-189542-01-1	1990. Iprodione technical - toxicity to the freshwater green alga <i>Selenastrum capricornutum</i> .
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