Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

AZOXYSTROBIN

methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin -4-yloxy]phenyl}-3-methoxyacrylate

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

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

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

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

INTRODUCTION

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

From 2002, the development of FAO specifications follows the **New Procedure**, described in the 1st edition of the "Manual on 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. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

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

PART ONE
SPECIFICATIONS

AZOXYSTROBIN

AZOXYSTROBIN

INFORMATION

ISO common name:

Azoxystrobin (E-ISO, BSI)

Chemical name(s):

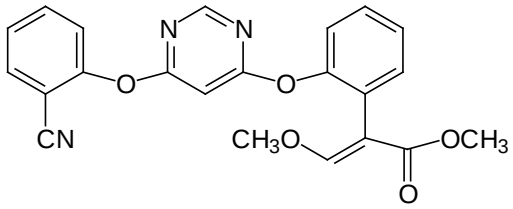
IUPAC, methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate

CA, methyl (*E*)-2-[[6-(2-cyanophenoxy)-4-pyrimidinyl]oxy]-α-(methoxymethylene) benzeneacetate (9CI)

Synonyms:

none

Structural formula:



Molecular formula:

$C_{22}H_{17}N_3O_5$

Relative molecular mass:

403.4

CAS Registry number:

131860-33-8

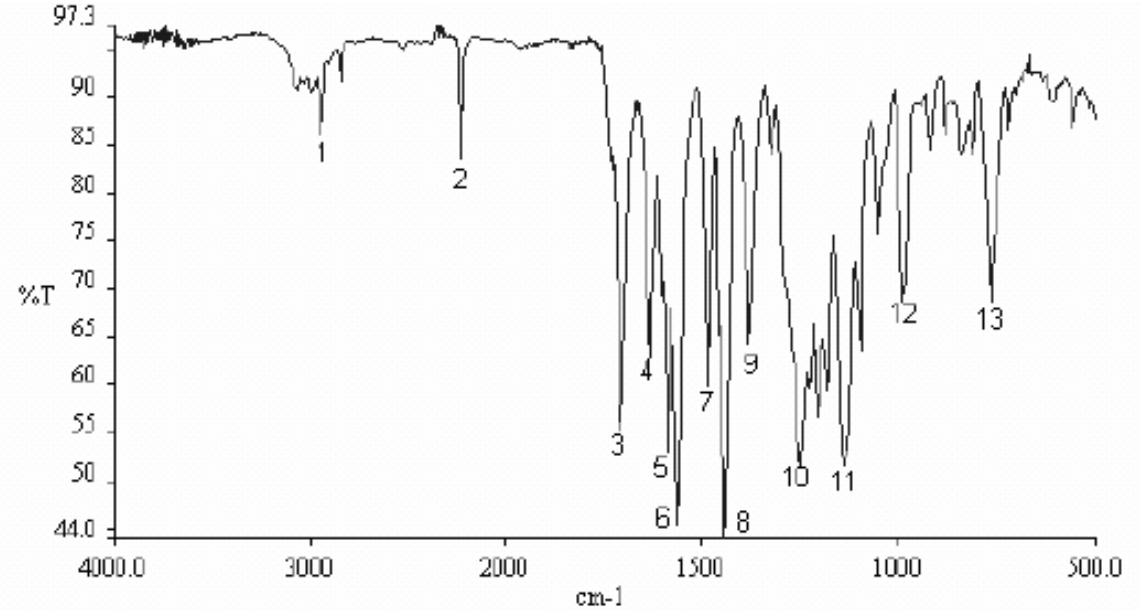
CIPAC number:

571

Identity tests:

GC retention time; IR spectrum

Typical IR spectrum of Azoxystrobin



Peak	Wavelength cm^{-1}		Peak	Wavelength cm^{-1}
1	2949		7	1487
2	2233		8	1436
3	1710		9	1382
4	1635		10	1252
5	1591		11	1144
6	1564		12	991
			13	556

AZOXYSTROBIN TECHNICAL MATERIAL

FAO Specification 571 / TC (May 2017*)

*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 (*571/2007, 571/2009, 571/2013 & 571/2016*). 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 specifications. The specification may not be appropriate for TC produced by other manufacturers. The evaluation reports* 571/2007, 571/2009, 571/2013 & 571/2016*, as PART TWO, form an integral part of this publication.*

1 Description

The material shall consist of azoxystrobin together with related manufacturing impurities, in the form of an off-white to light brown or yellowish powder and shall be free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (CIPAC 571/TC/M/2, Handbook M, p. 11, 2009)

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

2.2 **Azoxystrobin content** (CIPAC 571/TC/M/3, Handbook M, p. 11, 2009)

The azoxystrobin content shall be declared (not less than 965 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

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

AZOXYSTROBIN WATER DISPERSIBLE GRANULES

FAO Specification 571 / WG (May 2017*)

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 (571/2007 and 571/2009). *It should be applicable to relevant products of these manufacturers, and those of any other formulators who use only TC from the evaluated sources. The specification 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 who use TC from other sources. The evaluation reports 5*71/2007 and 571/200*9, as PART TWO, form an integral part of this publication.*

1 Description

The material shall consist of an homogeneous mixture of technical azoxystrobin, complying with the requirements of FAO specification 571/TC (May 2017), together with carriers and any other necessary formulants. It shall be in the form of cylindrical granules (approximate diameter 0.6–1 mm and length 2–8 mm), 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 571/WG/M/2, Handbook M, p. 14, 2009)

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

2.2 **Azoxystrobin content** (CIPAC 571/WG/M/3, Handbook M, p. 14, 2009).

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

Declared content	Permitted tolerance
Above 250 up to 500 g/kg	± 5% of the declared content

3 Physical properties

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

The formulation shall be completely wetted in 30 seconds, with swirling.

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

Maximum: 0.5% retained on a 75 µm test sieve.

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

Dispersibility: minimum 70% after 1 minute of stirring.

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

3.4 **Suspensibility** (MT 168, CIPAC Handbook F, p.417, 1995 or MT 184, CIPAC Handbook K, p.142, 2003) (Notes 1 & 2)

A minimum of 60% shall be in suspension after 30 minutes in CIPAC Standard Water D at 30 ± 2°C.

3.5 **Persistent foam** (MT 47.3, (Notes 3 & 4)

Maximum: 60 ml after 1 minute.

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

Essentially non-dusty.

3.7 **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.

3.8 **Attrition resistance** (MT 178.2, CIPAC Handbook K, p.140, 2003)

Minimum: 90% attrition resistance.

4 Storage stability

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

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

- wet sieve test (3.1)
- degree of dispersion (3.3)
- suspensibility (3.4)
- dustiness (3.6)
- attrition resistance (3.8)

Note 1 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in methods MT 168 and MT 184.

Note 2 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, the simpler gravimetric method, MT 168, may be used on a routine basis provided that it has been shown to give equal results to those of chemical assay. In case of dispute, chemical assay shall be the "referee method".

Note 3 The mass of sample to be used in the test should be specified at the highest rate recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 4 MT 47.3 is a revised version of MT 47.2 using a standard measuring cylinder. This new method was accepted as a full CIPAC method in 2013. Prior to publication of the method in a Handbook, copies of the method may be obtained through the CIPAC website, http://www.cipac.org/prepubme.htm.

Note 5 Measurement of dustiness must be carried out on the sample "as received" and, where practicable, the sample should be taken from a newly opened container, because changes in the water content of samples may influence dustiness significantly. The optical 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 6 MT 171.1 is a revised version of MT 171. This new method was accepted as a provisional CIPAC method in 2015. Prior to publication of the method in a Handbook, copies of the method may be obtained through the CIPAC website, http://www.cipac.org/prepubme.htm.

Note 7 Analysis of the formulation, before and after the storage stability test, may be carried out concurrently (i.e. after storage) to reduce analytical error.

AZOXYSTROBIN AQUEOUS SUSPENSION CONCENTRATE

FAO Specification 571 / SC (May 2017*)

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 (571/2007 and 571/2009). It should be applicable to relevant products of these manufacturers, and those of any other formulators who use only TC from the evaluated sources. The specification 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 who use TC from other sources. The evaluation reports 571/2007 and 571/2009, as PART TWO, form an integral part of this publication.

1 Description

The material shall consist of a suspension of fine particles of technical azoxystrobin complying with the requirements of FAO specification 571/TC (May 2017), 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 571/SC/M/2, CIPAC Handbook M, p. 15, 2009)

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

2.2 **Azoxystrobin content** (CIPAC 571/SC/M/3, CIPAC Handbook M, p. 15, 2009)

The azoxystrobin content shall be declared (g/kg or g/l at 20 ± 2ºC, Note 3) and, when determined, the average content measured shall not differ from that declared by more than the following amounts:

Declared content, g/kg or g/l at 20ºC	Permitted tolerance
Above 100 up to 250	± 6% of the declared content

3 Physical properties

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

pH range: 6 to 8.

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

Maximum residue: 8%.

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

A minimum of 80% of the azoxystrobin content found under 2.2 shall be in suspension after 5 minutes in CIPAC Standard Water D at 30 ± 2°C.

3.4 **Suspensibility** (MT 184, CIPAC Handbook K, p.142, 2003) (Note 3)

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

A minimum of 90% of the azoxystrobin content found under 2.2 shall be in suspension after 30 minutes in CIPAC Standard Water D at 30 ± 2°C.

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

Maximum: 0.1% of the formulation shall be retained on a 75 µm test sieve.

3.6 **Persistent foam** (MT 47.3) (Notes 5 & 6)

Maximum: 20 ml after 1 minute.

4 Storage stability

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

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

- suspensibility (3.4),
- wet sieve test (3.5).

4.2 **Stability at elevated temperature** (MT 46.3, CIPAC Handbook J, p.128, 2000)

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 7) 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).

Amend Notes

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 Unless homogenization is carried out carefully, it is possible for the sample to become aerated. This can lead to errors in the determination of the mass per millilitre and in calculation of the active ingredient content (in g/l) if methods other than MT 3.3 are used. 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 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 the chemical assay method. In case of dispute, the chemical method shall be the referee method.

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

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

Note 6 MT 47.3 is a revised version of MT 47.2 using a standard measuring cylinder. This new method was accepted as a full CIPAC method in 2013. Prior to publication of the method in a Handbook, copies of the method may be obtained through the CIPAC website, http://www.cipac.org/prepubme.htm.

Note 7 Samples of the formulation taken before and after the storage stability test may be analyzed concurrently after the test in order to reduce the analytical error.

PART TWO

EVALUATION REPORTS

AZOXYSTROBIN

AZOXYSTROBIN

FAO/WHO EVALUATION REPORT 571/2013

Recommendations

The Meeting recommended that:

(i) the azoxystrobin TC proposed by Jiangsu Sevencontinent Green Chemical Co., Ltd., be accepted as equivalent to the azoxystrobin reference profile
(ii) the existing FAO specification for azoxystrobin TC should be extended to encompass the material produced by Jiangsu Sevencontinent Green Chemical Co., Ltd.

Appraisal

The Meeting considered data and information submitted by Jiangsu Sevencontinent Green Chemical Co., Ltd., (Jiangsu Sevencontinent) in 2015 in support of extension of the existing FAO specification for azoxystrobin TC. The data submitted by Jiangsu Sevencontinent were broadly in accordance with the requirements of the Manual on development and use of FAO and WHO specifications for pesticides (November 2010 - second revision of the First Edition) (Section 3.2).

The Meeting was provided by the company with commercially confidential data on the manufacturing process, the manufacturing specification and 5-batch analysis data for azoxystrobin and all detectable impurities at or above 1 g/kg. Furthermore, a data package covering the acute toxicity tests as for Tier-2 was submitted. The manufacturing process used by the proposer is similar to the process used to produce the material the reference specification is based upon.

The company stated that their azoxystrobin TC has been registered in China. A written confirmation was received that the confidential data provided on the manufacturing process and specification of azoxystrobin produced by Jinagsu Sevencontinents are the same as those submitted to ICAMA for registration in China [Chen, 2016].

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data, which have been updated in December 2015. Mass balances were 99.0 – 99.1 % in the 5-batch data. The declared minimum active ingredient content (980 g/kg) was higher than that of the published FAO specification. The company confirmed that their product complies with the existing specification.

The manufacturing limits for those impurities occurring both in the reference profile and in the material under consideration did not exceed the limits in the reference profile, however two new impurities were identified.

The Jiangsu Sevencontinent manufacturing process includes four steps while that the reference is based upon is a one step process. The last step of Jiangsu Sevencontinent process is similar to the reference process. The declared minimum active ingredient content in the TC is 980 g/kg and four impurities were identified. The maximum limits for the impurities were supported by the batch data. Three impurities were declared to occur at levels at or above 1 g/kg, whereas the content of one of the new impurities was always below 1 g/kg in the batches and not specified. The new impurities were screened based on structural similarity and SAR analysis (Toxtree v2.6.6, VAGA v 1.0.8, T.E.S.T. and OECD Toolbox v3.3.0.132). The outcome of of the similarity considerations and SAR analysis did

not gave rise to structural alerts and the Meeting concluded, that these impurities should be considered as non-relevant.

The analytical method for the determination of the active ingredient in azoxystrobin technical was GC with FID detection with internal standardisation. The method is the full CIPAC Method 571/TC/M published in Handbook M. The organic impurities were determined by HPLC-UV and GC-FID. The LOQ for impurities ranged from 10 mg/kg to 1 g/kg. Test methods for determination of physico-chemical properties of the technical active ingredient were CIPAC, OECD and EC, where appropriate.

Data on physical-chemical properties like melting point and solubility in organic solvents for technical material (98.05%) were provided. Toxicity data were available for acute toxicity, skin irritation, eye irritation, skin sensitisation and mutagenicity profile (Ames test, micronucleus test) derived from the technical grade active ingredient manufactured by the proposer with a purity of 98.05%. OECD technical guidelines were used. As equivalence could be established on Tier-1, the results of the acute tests were not further considered.

Based on the higher purity and similarity of the impurity profiles of the reference and of the material produced by Jiangsu Sevencontinents and considering the absence of mutagenicity in the OECD 471 and OECD 474 tests, the Meeting concluded that the Jiangsu Sevencontinent azoxystrobin TC was equivalent to the azoxystrobin reference TC based on Tier-1 evidence.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 471/2016

Table 1: Chemical composition and properties of azoxystrobin 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 99.0 – 99.1 %			
Declared minimum azoxystrobin 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 and/or TK	116.7 °C	98.05	OECD 102	B2279
Solubility in organic solvents	48.9 g/l toluene at 25 °C	98.05	OECD 105	B2279
	17.5 g/l methanol at 25 °C	98.5	OECD 105	B2279

FORMULATIONS AND CO-FORMULATED ACTIVE INGREDIENTS

The present submission is for determination of equivalence of azoxystrobin technical grade only.

METHODS OF ANALYSIS AND TESTING

The analytical method for the active ingredient (including identity tests) is based on CIPAC 571/TC/M. The azoxystrobin is determined by GC with FID and internal standardisation.

The method(s) for determination of organic impurities are based on analysis by reverse phase liquid chromatography using UV detection and quantification by external standard. Test methods for determination of physico-chemical properties of the technical active ingredient were OECD.

CONTAINERS AND PACKAGING

Not applicable: The present application is for determination of equivalence of azoxystrobin technical grade only.

EXPRESSION OF THE ACTIVE INGREDIENT

The active ingredient is expressed as azoxystrobin.

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 azoxystrobin 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 the azoxystrobin technical material based on *in vitro* and *in vivo* tests

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium TA1535, TA1537, TA98, TA100 and TA 102	Bacterial mutation assay; *in vitro*	98.05	OECD guidelines 471 (purity 98.05% w/w), doses up to 5000 µg/plate	Negative	JRF-481-1-06-5064
Mouse bone marrow (m,f)	Mouse bone marrow micronucleus assay, *in vivo*	98.05	OECD 474 (purity 98.05% w/w), single dose 2000 mg/kg bw	Negative	JRF-485-1-06-5065

There were no eco-toxicological studies performed with the present source of azoxystrobin technical material.

Annex 2

References

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
FAO, 2009		2015	http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/Azoxystrobin__2015_10.pdf
FAO/WHO Manual, 2010		2010	Manual on development and use of FAO and WHO specifications for pesticides, November 2010 second revision of the first edition http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/PestSpecsManual2010.pdf
Chen, 2016			E-mail from Tiechun Chen, sent on 11 April 2016 11:00 [From: chentiechun@caas.cn to laszlo.bura@efsa.europa.eu]
CIPAC, M	Martijn A and Dobrat W	2009	CIPAC Handbook Volume M, p.11
CIPAC, F	Martijn A and Dobrat W	1995	CIPAC Handbook Volume F. Physico-chemical Methods for Technical and Formulated Pesticides
B2279		2013	Physical and Chemical properties of one batch of Azoxystrobin TC. Study No. B2279. GLP.
JRF-481-1-06-5064	KIRTI E.TENDULKAR	2013	Bacterial reverse mutation test of Azoxystrobin Technical using Salmonella typhimurium. JRF Laboratorios, India. GLP. Report No. JRF-481-1-06-5064. Unpublished.
JRF-485-1-06-5065	SHEKHAR S. GAIKWAD	2013	Micronucleus test of Azoxystrobin Technical in mice. JRF Laboratorios, India. GLP. Report No. JRF-485-1-06-5065. Unpublished.

AZOXYSTROBIN

FAO/WHO EVALUATION REPORT 571/2013

Recommendations

The Meeting recommended:
(i) that the azoxystrobin TC proposed by Helm AG be accepted as equivalent to the azoxystrobin reference profile
(ii) to extend the existing TC specification to the technical material produced by Helm AG

Appraisal

Azoxystrobin is a fungicide belonging to the strobilurin family and is used for the control of a wide variety of fungal diseases in agricultural crops. Azoxystrobin is not under patent.

A data package provided by Helm AG (Helm) for azoxystrobin TC in 2010 was evaluated in support of the determination of equivalence with the existing FAO specification for that compound. Azoxystrobin has been evaluated by the FAO/WHO JMPR and WHO/IPCS in 2008. [JMPR 2008a, JMPR 2008b].

Supporting data on azoxystrobin TC was provided by Helm AG for an equivalence determination with the reference profile FAO specification 571/TC (August 2009). The data package for the TC reference profile and formulated products has been submitted by Syngenta in 2007 and later extended to the technical material produced by Makhteshim (now Adama) in 2009.

The data submitted were in accordance with the requirements of the FAO/WHO Manual, [2010] and supported the existing specifications. The confidential data provided on the manufacturing process of azoxystrobin are the same as those submitted for registration in Mexico, however there were differences in the batch data. [Vidaca, 2013] The explanation was that the batch data submitted to Mexico were dated before the re-analysis of the same batches by HPLC, requested by the JMPS.

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data, which have ben updated in 2012. Only one of the impurities present in batches was above 1 g/kg and as a consequence included in the specification of the TC. Mass balances were 99.5 – 99.9 % in the 5-batch data. The declared minimum active ingredient content (970 g/kg) was higher than that of the FAO specification. Helm confirmed that their product complies with the existing specification, however based on the Helm's data a higher value could have been proposed.

Manufacturing limits for impurities identified in the technical material did not exceed the limits in the reference profile. There were no new impurities identified. Helm's manufacturing process is comprised of several steps while Syngenta's is a one step process which is the same as the last step of Helm AG. The declared minimum active ingredient content in the TC is 970 g/kg. Two impurities were identified and specified at concentrations > 1 g/kg, whereas eight other impurities were detected in the range from

0.036 g/kg to 0.72 g/kg. They were declared as consistently being below 1 g/kg and hence below the generic threshold limit of 1 g/kg for non-relevant impurities. Accordingly, Helm AG confirmed that their product complied with the existing specification. The Meeting noticed that in the first submission the five batch data were generated using GC-FID and GC-MS and as a conclusion some potential impurities which could occur on the basis of the manufacturing process could not have been identified, if present. The company conducted a new five batch study using HPLC-UV and an additional impurity above 1 g/kg was identified, whose limit was below the respective limit in the reference profile.

The azoxystrobin content in TC was determined by GC with FID detection and internal standardisation in the initial submission. The method is CIPAC Method 571/TC/M and published in Handbook M. The methods for the determination of impurities were based on GC/FID and GC/MS.

In the updated submission the analytical method for the active ingredient and impurities was reversed-phase HPLC with UV detection, the amount of certain unidentified impurities were estimated using the response factor of the anlytical standard of the active ingredient azoxystrobin to ensure they were below 1 g/kg.

Data on physical-chemical properties like melting point and solubility in organic solvents for technical material (98.5%) were provided. OECD test methods were used. The same batch with a purity of 98.5% was used for studies of acute toxicity, skin irritation, eye irritation, skin sensitisation and mutagenicity profile (Ames test, Micronucleus test). Results are similar to those provided for the reference profile.

Based on the similarity of the purity and impurity profiles of the reference and of Helm's product and absence of mutagenicity in the OECD 471 test, the Meeting concluded that the Helm AG azoxystrobin TC was equivalent to the azoxystrobin reference TC based on Tier-1.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 471/2013

Table 1: Chemical composition and properties of azoxystrobin 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 99.5 - 99.9 %			
Declared minimum azoxystrobin content	970 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	116–118°C	98.5	OECD 102	48401180
Solubility in organic solvents	14.97 g/l methanol at 20 °C	98.5	OECD 105	48408201
	257.80 g/l acetone at 20 °C	98.5	OECD 105	48408201
	17.16 g/l p-xylene at 20 °C	98.5	OECD 105	48408201
	425.38 g/l dichloromethane at 20 °C	98.5	OECD 105	48408201
	282.48 g/l ethyl acetate at 20 °C	98.5	OECD 105	48408201
	< 0.05 g/l n-heptane at 20 °C	98.5	OECD 105	48408201

FORMULATIONS AND CO-FORMULATED ACTIVE INGREDIENTS

Formulations and co-formulated active ingredients
The present application is for determination of equivalence of azoxystrobin technical grade only.

METHODS OF ANALYSIS AND TESTING

The analytical method for the active ingredient (including identity tests) is based on CIPAC 571/TC/M. The azoxystrobin is determined by GC with FID and internal standardisation. The methods for determination of impurities are based on analysis by reverse phase liquid chromatography using UV detection and quantification by external standard. Test methods for determination of physico-chemical properties of the technical active ingredient were OECD.

EXPRESSION OF THE ACTIVE INGREDIENT

The active ingredient is expressed as azoxystrobin.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from azoxystrobin 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 the azoxystrobin technical material based on *in vitro* and *in vivo* tests

Species	Test	Purity % Note[2]	Guideline	Result	Study number
Salmonella typhimurium	Ames Test – *in vitro*	98.5	OECD 471 Five test concentrations of 31.6, 100, 316, 1000, 2500 and 5000 µg/plate with and without S9 were chosen for mutagenicity evaluation employing five strains of *S. typhimurium* (TA100, TA102, TA1535, TA98 and TA1537), respectively.	Negative	090142

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

ANNEX 2

REFERENCES

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
JMPR 2008a		2008	Azoxystrobin. Pesticide residues in food 2008. Joint FAO/WHO Meeting on Pesticide Residues. Evaluations, 2008. Part I, Residues. FAO Plant Production and Protection Paper. 194:1-202.
JMPR 2008b		2008	Azoxystrobin. Pesticide residues in food 2008. Joint FAO/WHO Meeting on Pesticide Residues. Report, 2008. FAO Plant Production and Protection Paper. 193:55-95.
FAO, 2009		2009	http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/Azoxystrobin09.pdf
FAO/WHO Manual, 2010		2010	Manual on development and use of FAO and WHO specifications for pesticides, November 2010 second revision of the first edition http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/manual/en/
Vidaca, 2013		2013	E-mail from Marco Antonio Arias Vidaca, Executive Director of Authorization of Products and Establishment (Mexico), sent on 27 February 2013 2:26 [From: mvidaca@cofepris.gob.mx to YongZhen.Yang@fao.org]
090142		2009	Reverse Mutation Assay using Bacteria (Salmonella typhimurium) with Azoxystrobin TC. Study 090142. GLP. Unpublished.
090143		2009	Mammalian Micronucleus Test of Murine Peripheral Blood Cells with Azoxystrobin TC. Study 090143. GLP.

AZOXYSTROBIN

FAO/WHO EVALUATION REPORT 571/2009

Recommendation

The Meeting recommended that

(i) the existing FAO specifications for azoxystrobin TC, WG and SC should be extended to encompass the products of Makhteshim Chemical Works

Appraisal

Data provided by Makhteshim Chemical for azoxystrobin in 2008 were evaluated in support of an equivalence determination with the existing FAO specifications. Makhteshim azoxystrobin suspension concentrate is currently registered in the United Kingdom.

The confidential data provided on the manufacturing process and batch analyses of azoxystrobin are identical to those submitted for registration in UK.

As some differences in the proposed specifications for azoxystrobin TC, WG and SC became evident which were not expected to adversely affect hazard, the existing FAO specifications had to be extended to encompass the material of Maktheshim. This holds for the specifications as follows:

TC:.The Makhteshim TC is described as "…..a yellowish powder…" whereas the reference is an off-white powder. The description was modified to include the yellowish powder.as "… an off-white to light brown powder …".

The declared minimum active ingredient content (965 g/kg) agrees with that of the FAO specification.

WG: For the WG, data were available on: flowability, pH, wettability, persistent foam, dispersibility, suspensibility, wet sieve, dustiness, attrition resistance and accelerated storage testing (54 ˚C). The WG formulation generally complied with all specification clauses except the pH range with measured values of 9.7 before and after storage (specification pH range 5 to 7.5).

Azoxystrobin was reported as stable to hydrolysis (<10 % loss) at pH 5, 7 and 9 and 25 ˚C when tested for 31 days. Its half-life (DT_{50}) was estimated at 12 days and 2 hours at pH 9 and 50 ˚C (Germany, 1997). The content of active ingredient in a WG of pH 9.7 complied with the specification in the elevated temperature storage stability test, demonstrating stability in a WG at pH 9.7. Makhteshim provided information that the measured pH of two other WG batches was 8.4. Furthermore, the calcium carbonate filler material was responsible for the alkaline pH.

The 2007 JMPS had questioned the requirement for control of pH. "The manufacturer explained that product stability was known to be acceptable within the proposed pH ranges, whereas certain formulants may be adversely affected at more extreme pH values and the active ingredient is more stable at pH below 9." The 2007 Meeting therefore accepted the proposed limits.

The additional evidence now suggests that a pH specification is not necessary for quality control. The Meeting agreed to delete the pH range specification for azoxystrobin WG formulations and to amend the WG specifications accordingly.

SC: Data were available on the following clauses: pH, spontaneity of dispersion, suspensibility, wet sieve, pourability, persistent foam, accelerated storage testing (54 ˚C) and storage stability at 0 ˚C. The SC formulations generally complied with all specifications except pourability with measured values of 7.5-8.0 % (specification 5 %).

The Meeting agreed that 8 % is an acceptable value for pourability and that the specification could be increased to 8 % to include this product.

Manufacturing limits for impurities identified in the technical material did not exceed the limits in the reference profile. No new impurities were identified. Mass balances were in the range of 99.3-99.8 %.. It should be noted that at the time of data submission this material was not in commercial production and the manufacturing limits had been calculated from the results of the 5-batch analyses.

The analytical method for the active ingredient, azoxystrobin, was reversed-phase HPLC with UV detection. HPLC-UV, and others also determined some impurities by GC-MSD. Validation data were provided for azoxystrobin and the impurities. Methods for the impurities were validated to LOQs of 0.5 g/kg in the TC.

Toxicity data were available for rat acute oral, rat acute dermal, rat acute inhalation, rabbit eye irritation, rabbit skin irritation and guinea-pig skin sensitization. The ratings were equivalent to those of the reference material.

The Meeting concluded that the Makhteshim azoxystrobin TC was equivalent to the azoxystrobin reference TC.

The physical and chemical properties of pure and technical grade active ingredient were essentially the same as those for the reference material for melting point, water solubility and log P_{ow}.

The vapour pressures at 20 ˚C were substantially different: 1.1×10^{-10} Pa for the reference material and 6.3×10^{-9} Pa for the pure material from Makhteshim. For the reference material, measurements were made on the solid at elevated temperatures and for the Makhteshim material, measurements were made on the liquid at elevated temperatures. In both cases the elevated temperature values were extrapolated to 20 ˚C values. Most likely the difference is because the reference material vapour pressure is for solid and the Makhteshim material is for theoretical liquid at 20 ˚C.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 571/2009

Physico-chemical properties of azoxystrobin

Table 1. Physical and chemical properties of pure and technical grade azoxystrobin.

Parameter	Value(s) and conditions	Purity %	Method reference	Study ref
Pure azoxystrobin				
Vapour pressure	6.3×10^{-9} Pa at 20 °C (extrapolated from liquid phase measurements at 116.9 to 151.3 ˚C). Note[1]	99.2 %	OECD 104, effusion. Measurements from 103.1 to 151.3 ˚C	R-24107
Temperature of decomposition	265 °C by differential thermal calorimetric scanning (nitrogen atmosphere)	99.2 %	OECD 113	R-24107
Technical grade material				
Melting point	115.9 °C	97.2 %	OECD 102	PE DEPDA 018/07-BPL
Solubility in water	5.6 ±0.2 mg/l at 20 °C at pH 5.91. No pH dependency can be expected from structural formula	96.9 %	OECD 105	R-21824
Solubility in acetone	94.3±0.79 g/l at 20 °C	96.9 %	based on OECD 105	R-21824
Solubility in methanol	22.7±0.46 g/l at 20 °C	96.9 %	based on OECD 105	R-21824
Octanol-water partition coefficient	log P_{OW} = 2.71 at 20 °C at pH 5.03. No pH dependency can be expected from structural formula	96.9 %	OECD 107	R-21827
Hydrolysis	no data	no data		
Photolysis	no data	no data		
Dissociation characteristics	does not dissociate	no data		

Note[1] Vapour pressure measurements were made over the temperature range 103.1 to 151.3 ˚C with 2 measurements on the solid (103.1 and 109.0 ˚C) and 10 on the liquid (116.9 to 151.3 ˚C). Extrapolation beyond the range of measurement relies on the Clapeyron-Clausius equation.

$$\ln(p) = \frac{\Delta Hv}{RT} + const$$

p: vapour pressure
∠Hv: heat of vaporization
R: gas constant
T: absolute temperature

The extrapolation is valid only over the temperature range where △Hv is constant and it is not constant through a liquid-solid phase change.

If the vapour pressure measurements for the liquid phase are extrapolated to 20 ˚C, the extrapolated value at 20 ˚C represents a theoretical vapour pressure for liquid phase at 20 ˚C.

It should be noted that the vapour pressure recorded for azoxystrobin in the 2007 JMPS Evaluation (1.1×10^{-10} Pa at 20 ˚C) was based on an extrapolation from measurements on azoxystrobin all

below its melting point, i.e. an extrapolation from vapour pressure measurements on solid phase.

Table 2. Chemical composition and properties of azoxystrobin technical materials (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 99.3-99.8 %. Percentages of unknowns were 0.3-0.7 %.
Declared minimum active ingredient content	965 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities < 1 g/kg and maximum limits for them:	None
Stabilisers or other additives and maximum limits for them:	None
Melting temperature range of the TC	115.9 ˚C

Formulations

The main formulation type available for Makhteshim azoxystrobin is the SC. Azoxystrobin may be co-formulated with other active ingredients. Makhteshim formulations are currently registered and sold e.g. in the United Kingdom.

Physical properties of azoxystrobin formulations

The physical properties, the methods for testing them and the limits proposed for the SC and WG formulations, comply with the requirements of the FAO Manual (FAO, 2006).

Methods of analysis and testing

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

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as azoxystrobin.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

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

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

Species	Test	Duration and conditions or guideline adopted	Result	Study ref
Rat (f)	oral	OECD 423, 6 animals. Single dose 2000 mg/kg bw administered in corn oil purity 96.9 % w/w, observed for 14 days.	LD_{50} > 2000 mg/kg bw no adverse effects	RF-0023.305.401.06
Rat, (m,f)	dermal	OECD 402, 10 animals. Single dose 2000 mg/kg bw administered in corn oil, 24-hours skin contact exposure purity 96.9 % w/w, observed for 14 days.	LD_{50} > 2000 mg/kg bw no adverse effects	RF-0023.310.381.06
Rat, (m,f)	inhalation	OECD 403, 10 animals (5M+5F) per dose. powder aerosol 0.18, 0.38, 0.93 mg/l air, 4-hours nose only exposure. Purity 98.4 % w/w. Observed for 14 days after exposure.	LC50 ~ 0.38 mg/l air	R-24802
Rabbit (m)	skin irritation	OECD 404, 3 animals. Single dose 0.5 g/kg bw 4 h dermal exposure, purity 96.9% w/w, observed for 72 hours.	Not irritating	RF-0023.311.401.06
Rabbit (m,f)	eye irritation	OECD 405, 3 animals. Single instillation of 100 mg in one eye purity 96.9% w/w. observed for 7 days.	Not irritating	RF-0023.312.499.06
Guinea pig (m)	skin sensitisation Buehler test	OECD 406, 20 animals applied undiluted 0.5 g/animal for both induction and challenge purity 96.9% w/w.	Not sensitizing	RF-0023.318.358.06

Technical azoxystrobin is of low acute toxicity upon oral or dermal administration and of moderate toxicity by the inhalation route. It is a slight skin and eye irritant. According to EU guidelines, classification and labelling as a skin or eye irritant are not required. The compound is not a skin sensitizer.

Classification of azoxystrobin based on GHS conclusions for toxicity would be (O'Brien, 2009):

Category:	4.
GHS pictogram:	diamond with exclamation mark.
Signal word:	Warning.
Hazard sentences:	H332 Harmful if inhaled.
Precautionary sentences:	P304 + P340, P312.

CHRONIC TOXICITY

No information was available on subacute to chronic toxicity of the azoxystrobin technical material.

MUTAGENICITY

No information was available on the mutagenicity profile of the azoxystrobin technical material.

ECOTOXICITY

No information was available on ecotoxicity of the azoxystrobin technical material.

REFERENCES **(SORTED BY REPORT OR STUDY NUMBER)**

FAO	2006	Manual on development and use of FAO and WHO specifications for pesticides. March 2006 revision of the First Edition. Pesticide Specifications.
FAO	2008	FAO specifications and evaluations for azoxystrobin.
Germany	1997	Monograph, 29 January 1997. Azoxystrobin. Volume 3. Annex B. Rapporteur Member State: Germany.

http://72.14.235.132/search?q=cache:FLZW5yDzYasJ:www.bvl.bund.de/DE/04__Pflanzenschutzmittel/00__doks__downloads/02__eu__berichte/Azoxystrobin-DAR-Part2,templateId%3Draw,property%3DpublicationFile.pdf/Azoxystrobin-DAR-Part2.pdf+Azoxystrobin,+monograph+%2229+January+1997%22&cd=1&hl=en&ct=clnk&gl=au

JMPR	2008a	Azoxystrobin. Pesticide residues in food 2008. Joint FAO/WHO Meeting on Pesticide Residues. Evaluations, 2008. Part I, Residues. FAO Plant Production and Protection Paper. 194:1-202.
JMPR	2008b	Azoxystrobin. Pesticide residues in food 2008. Joint FAO/WHO Meeting on Pesticide Residues. Report, 2008. FAO Plant Production and Protection Paper. 193:55-95.
Martijn A and Dobrat W	1995	CIPAC Handbook Volume F. Physico-chemical Methods for Technical and Formulated Pesticides.
Martijn A and Dobrat W	2000	CIPAC Handbook Volume J. Analysis of Technical and Formulated Pesticides.
O'Brien K	2009	RE: KO090514 JMPS 2009 Azoxystrobin evaluation. Email, 27-May-2009. Unpublished.
20061387/01-PCAS	2006	Physico-chemical properties of the formulation MCW 403 250 SC. before and after accelerated storage at 54 ˚C for 2 weeks. Study code R-20977. Sponsor: Irvita Plant Protection. Test facility: Eurofins-GAB GmbH, Germany. Unpublished.
20061387/01-PCRD	2006	Relative density of MCW 403 250 SC. Study code R-20973. Sponsor: Irvita Plant Protection. Test facility: Eurofins-GAB GmbH, Germany. Unpublished.
20071255/01-PCAS	2007	Physico-chemical properties of the formulation MCW 403 500 WDG (Azoxystrobin 500 WDG) after accelerated storage at 54 ˚C for 2 weeks. Study code R-21768. Sponsor: Irvita Plant Protection. Test facility: Eurofins-GAB GmbH, Germany. Unpublished.
20071255/01-PCF0	2007	Physico-chemical properties of the formulation MCW 403 500 WDG (Azoxystrobin 500 WDG). Study code R-21767. Sponsor: Irvita Plant Protection. Test facility: Eurofins-GAB GmbH, Germany. Unpublished.
20071255/01-PCFL	2007	Flowability of the formulation MCW 403 500 WDG. Study code R-21766. Sponsor: Irvita Plant Protection. Test facility: Eurofins-GAB GmbH, Germany. Unpublished.
20071255/01-PCTD	2007	Pour and tap density of MCW 403 500 WDG. Study code R-21765. Sponsor: Irvita Plant Protection. Test facility: Eurofins-GAB GmbH, Germany. Unpublished.
PE DEPDA 018/07-BPL	2007	Determination of melting point of MIL S 130/05 azoxystrobin. Testing facility: Milenia Agrociências S/A, Londrina-Paraná, Brasil. GLP. Study PE DEPDA 018/07-BPL. Unpublished.
R-21072	2007	Determination of active ingredient and impurities in five batches of MCW 403 Technical. Testing facility: eurofins-GAB GmbH, Niefern-Öschelbronn, Germany. GLP. Report R-21072. Unpublished.
R-21824	2007	Solubility of MIL S 130/05 in water and organic solvents. Testing facility: BIOAGRI Laboratorios Ltda., Piracicaba-SP, Brazil. GLP. Study 0023.008.447.06. Report R-21824. Unpublished.

R-21827	2007	Partition coefficient (*n*-octanol/water) of MIL S 130/05. Testing facility: BIOAGRI Laboratorios Ltda., Piracicaba-SP, Brazil. GLP. Study 0023.014.159.06.Report No. R-21827. Unpublished.
R-24107	2008	Azoxystrobin. Vapour pressure A.4. (OECD 104). Testing facility: Siemens AG, Prozess-Sicherheit, Frankfurt am Main, Germany. GLP. Report R-24107. Unpublished.
R-24802	2009	Acute inhalation toxicity of MCW 403-technical in rats (*Rattus norvegicus).* Irvita Plant Protection, a Branch of Celsius Property B.V., Netherlands Antilles. Study by Microquim S.A., Argentina. GLP. Report R-24802. Unpublished.
RF-0023.305.401.06	2007	Acute oral toxicity study with MIL S 130/05 in rats. BIOAGRI Laboratorios, Brazil. GLP. Report RF-0023.305.401.06. Unpublished.
RF-0023.310.381.06	2006	Acute dermal toxicity study with MIL S 130/05 in rats. BIOAGRI Laboratorios, Brazil. GLP. Report RF-0023.310.381.06. Unpublished.
RF-0023.311.401.06	2006	Acute dermal irritation/corrosion study in rabbits with MIL S 130/05. BIOAGRI Laboratorios, Brazil. GLP. Report RF-0023.311.401.06. Unpublished.
RF-0023.312.499.06	2006	Acute eye irritation/corrosion study in rabbits with MIL S 130/05. BIOAGRI Laboratorios, Brazil. GLP. Report RF-0023.312.499.06. Unpublished.
RF-0023.318.358.06	2006	Skin sensitisation test of MIL S 130/05 in guinea pigs (*Cavia porcellus*). (Buehler test method). BIOAGRI Laboratorios, Brazil. GLP. Report RF-0023.318.358.06. Unpublished.
S08-00992	2008	Storage stability of the formulation MCW 403 250 SC at 0 ˚C for 7 days. Study code R-23541. Sponsor: Irvita Plant Protection. Test facility: Eurofins-GAB GmbH, Germany. Unpublished.

AZOXYSTROBIN

FAO/WHO EVALUATION REPORT 571/2007

Recommendation

The Meeting recommended that the specifications for azoxystrobin TC, WG and SC, proposed by Syngenta Crop Protection AG, should be adopted by FAO.

Appraisal

Data provided by Syngenta Crop Protection AG for azoxystrobin in 2006 were evaluated in support of proposed new FAO specifications for TC, SC and WG.

Azoxystrobin has not been evaluated by the FAO/WHO JMPR or IPCS, but has been reviewed by the US EPA and the EU.

Azoxystrobin is under patent in most countries until 2010.

Azoxystrobin is a solid, melting at 116ºC. Its water solubility is about 6 mg/l and is not pH dependent. It is very soluble in certain organic solvents but its octanol-water partition coefficient (log P_{OW} = 2.5) does not indicate fat solubility. It has a low vapour pressure and Henry's constant, therefore significant volatilization is not expected. Azoxystrobin is stable at pH 4-9 and it is degraded only slowly by photolysis.

The Meeting was provided with details of the manufacturing process, 5 batch analysis data (production from March to December 2005), and manufacturing limits for azoxystrobin content and impurities present at or above 1 g/kg. Mass balances were high (98.7-99.6%), no unknowns (≥1 g/kg) were detected and the minimum active ingredient in technical material was 965 g/kg. The current manufacturing process produces a higher purity than previously and no new impurities have been found. The data were confirmed as being essentially similar to those submitted for registration in the UK, with the exception of an increase in the minimum azoxystrobin content from 930 g/kg to 965 g/kg in the current manufacturing specification.

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

Analytical methods for the determination of azoxystrobin and impurities were based on gas chromatography. The method for determination of azoxystrobin in TC, WG and SC and was adopted by CIPAC in 2007, with provisional status.

The proposed specifications were broadly in accordance with the requirements of the manual (FAO/WHO 2006) but the following issues were addressed by the Meeting.

WG and SC. The Meeting questioned the requirement for control of pH. The manufacturer explained that product stability was known to be acceptable within the proposed pH ranges, whereas certain formulants may be adversely affected at more extreme pH values and the active ingredient is more stable at pH <9. The Meeting therefore accepted the proposed limits.

WG. The Meeting questioned the proposed limits of 60% for suspensibility and 60 ml of persistent foam, as both represented the maximum normally accepted. The manufacturer explained that the dispersed particles are relatively large and the

surfactants required for the product mean that neither limit can be changed Based on experience of selling the product over a number of years, the manufacturer stated that these properties have not caused any problems in use. The Meeting therefore accepted the proposed limits. The Meeting considered a proposed limit of 80% attrition resistance to be low for an extruded WG. After reconsideration of the supporting data, the manufacturer stated that it would be possible to comply with a limit of 90% and this was agreed by the Meeting.

SC. The manufacturer proposed a non-standard pourability sub-clause for “rinsed residue” but agreed with the Meeting that this characteristic should not be specified. The manufacturer also proposed non-standard clauses for viscosity and particle size distribution but agreed with the Meeting that, although these characteristics may be important for manufacturing purposes, they should not form part of the FAO specification.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 571/2007

Uses

Azoxystrobin is a systemic fungicide, its activity resulting from inhibition of electron transfer between cytochrome b and cytochrome c in fungal mitochondria.

It is used for the control of a wide variety of fungal diseases in agriculture/horticulture and viticulture.

Identity of the active ingredient

ISO common name:

Azoxystrobin (E-ISO, BSI)

Chemical name(s):

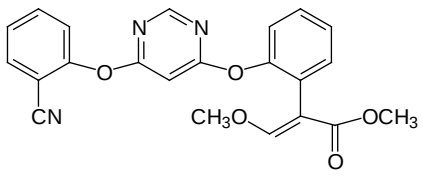
IUPAC, methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate

CA, methyl (*E*)-2-[[6-(2-cyanophenoxy)-4-pyrimidinyl]oxy]-α-(methoxymethylene) benzeneacetate (9CI)

Synonyms:

none

Structural formula:



Molecular formula:

$C_{22}H_{17}N_3O_5$

Relative molecular mass:

403.4

CAS Registry number:

131860-33-8

CIPAC number:

571

Identity tests:

GC retention time; IR spectrum

Physico-chemical properties of azoxystrobin

Table 1. Physico-chemical properties of pure azoxystrobin

Parameter	Value(s) and conditions	Purity %	Method	Reference
Vapour pressure	1.1 x 10^{-10} Pa at 20°C	99.0	OECD 104, by extrapolation	ICI5504/0028
Melting point	116°C	99.0	OECD 102	ICI5504/0028
Boiling point, temperature of decomposition	Boiling point: cannot be determined at atmospheric pressure Decomposition temperature: ~345°C	99.0	OECD 113	ICI5504/0039
Solubility in water at 20°C	6.0 mg/l at 20°C in purified water, approximately neutral pH	99.0	EPA Guideline CG-1510	ICI5504/0028
Partition coefficient	log P_{OW} = 2.5 at 20°C at pH 7	99.0	OECD 107	ICI5504/0028
Hydrolysis characteristics	Half-life = 12 days at 50°C at pH 9 No significant hydrolysis (<10%) after 31 days at 25°C nor after a further 12 days at 50°C at pH 5 and 7.	>98	EPA Guideline 161-1	ICI5504/0824
Photolysis characteristics	Continuous irradiation at 25°C and pH 7 gave an estimated reaction half-life of 8.7 to 13.9 days Florida summer sunlight. At least 15 photo-degradation products were observed but only one, azoxystrobin *Z*-isomer, was present at >10%.	>98	EPA Guideline 161-2	ICI5504/0823
Dissociation characteristics	Does not dissociate	99.0	OECD 112	ICI5504/0028

Table 2. Chemical composition and properties of technical azoxystrobin (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 98.7-99.6%, with no unknowns ≥1 g/kg.
Declared minimum azoxystrobin content	965 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 temperature range of the TC	114-116°C

Hazard summary

Azoxystrobin has not been evaluated by the FAO/WHO JMPR or IPCS, but has been reviewed by the US EPA and the EU.

EU hazard classifications are: (i) R 23 toxic by inhalation (T, toxic); (ii) R 50/53 very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (N, dangerous for the environment).

The US EPA Signal Word for technical azoxystrobin is: Caution. US EPA has concluded that azoxystrobin in not likely to cause cancer and is not a developmental or reproduction toxicant. However, azoxystrobin can persist for several months or longer and some of its degradation products have properties similar to chemicals which are known to leach through soil to ground water under certain conditions as a result of agricultural use. Thus US EPA concluded that use of azoxystrobin in areas where soils are permeable, particularly where the water table is shallow, may result in ground water contamination. US EPA noted that azoxystrobin is toxic to freshwater and estuarine/marine fish and aquatic invertebrates and issued instructions that it should be kept out of lakes, streams, ponds, tidal marshes, or estuaries.

The WHO hazard classification of azoxystrobin is “U, unlikely to present acute hazard in normal use” (WHO 2002).

Formulations

The main formulation types available are SC and WG and azoxystrobin may be co-formulated with other fungicides. These formulations are registered and sold in many countries worldwide.

Methods of analysis and testing

Azoxystrobin is determined by capillary GC with FID and internal standardization with 3-(2-pyridyl)-5,6-diphenyl-1,2,4-triazine. An additional identity test is based on the IR spectrum. The method was adopted by CIPAC, with provisional status, in 2007, following a successful collaborative study. The GC method gives a good resolution between azoxystrobin (*E*-isomer) and the *Z*-isomer.

Impurities were determined by GC.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD and EPA, 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 SC and WG formulations, comply with the requirements of the manual (FAO/WHO 2006).

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as azoxystrobin.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

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

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

Species	Test	Duration and conditions	Result	Reference
Rat (m,f)	Oral	Administered in corn oil, observed up to 15 days, OECD 401 (purity 95.2% w/w), single dose 5000 mg/kg bw	MLD >5000 mg/kg bw	ICI5504/0081
Mouse (m,f)	Oral	Administered in corn oil, observed up to 15 days, OECD 401 (purity 95.2% w/w), single dose 5000 mg/kg bw	MLD >5000 mg/kg bw	ICI5504/0084
Rat (m,f)	Dermal	Dermal application for 24 h, observed up to 15 days, OECD 402 (purity 95.2% w/w), single dose 2000 mg/kg bw	LD_{50} >2000 mg/kg bw	ICI5504/0085
Rat (m,f)	Inhalation	4 h exposure nose-only, OECD 403 (purity 96.2% w/w), doses up to 968 µg/l (atmospheric concentration)	LC_{50} = 698 mg/m^3 (f) = 962 mg/m^3 (m)	ICI5504/0087
Rabbit (f)	Skin irritation	4 h dermal exposure, observed up to 7 d, OECD 404 (purity 95.2% w/w), single dose 500 mg/kg bw	Non-irritant (based on EU legislation)	ICI5504/0082
Rabbit (f)	Eye irritation	Single instillation of 100 mg, OECD 405 (purity 95.2% w/w)	Non-irritant (based on EU legislation)	ICI5504/0083
Guinea pig	Skin sensitization	Magnusson & Kligman OECD 406 (purity 95.2% w/w), doses of 30 and 67% w/v.	Non-sensitizer	ICI5504/1259
Rat	Acute neurotoxicity	Draft OECD 424 (purity 96.2% w/w), single dose 2000 mg/kg bw	No neurotoxicity	ICI5504/0161

Azoxystrobin is very poorly absorbed through the skin. Moderate inhalation toxicity was observed with particulates having a highly inhalable size distribution. Azoxystrobin is a slight irritant to rabbit skin and a slight irritant to rabbit eyes but, for both end-points, the observations were insufficient to trigger EU hazard classification.

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

Species	Test	Duration and conditions	Result	Reference
Rat (m,f)	Oral	90 d, OECD 408 (purity 95.2% w/w), doses up to 6000 ppm	NOAEL = 20 mg/kg bw/d LOEL = 20 mg/kg bw/d	ICI5504/0099
Dog (m,f)	Oral	90 d, OECD 409 (purity 96.2% w/w), doses up to 250 mg/kg bw/d	NOAEL = 10 mg/kg bw/d	ICI5504/0101
Rat (m,f)	Dermal	21 d, OECD 410 (purity 96.2% w/w), doses up to 1000 mg/kg bw	NOEL = 1000 mg/kg bw/d (limit dose)	ICI5504/0089
Rat (m,f)	feeding, carcinogenicity	2 years, OECD 453 (purity 96.2% w/w), doses up to 1500 ppm	No carcinogenicity NOAEL = 18 mg/kg bw/d LOEL = 18 mg/kg bw/d	ICI5504/0110

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

Species	Test	Duration and conditions	Result	Reference
Dog (m,f)	feeding, carcinogenicity	1 year, OECD 452 (purity 96.2% w/w) doses up to 200 mg/kg bw/d	No carcinogenicity NOEL = 3 mg/kg bw/d NOAEL = 200 mg/kg bw/d	ICI5504/0106
Mouse (m,f)	carcinogenicity	2 years, OECD 451 (purity 96.2% w/w), doses up to 2000 ppm	No carcinogenicity	ICI5504/0108
Rat (m,f)	Generation reproduction	2-generation, OECD 416 (purity 96.2% w/w), doses up to 1500 ppm (170 mg/kg bw/d)	NOAEL = 32 mg/kg bw/d (general toxicity) NOAEL = 170 mg/kg bw/d (reproductive toxicity)	ICI5504/0117
Rat (m,f)	sub-chronic neurotoxicity	Draft OECD 424 (purity 96.2% w/w), doses up to 2000 ppm	No neurotoxicity up to highest dose of ~100 mg/kg/d	ICI5504/0163
Rabbit	Developmental toxicity	OECD 414 (purity 96.2% w/w), doses up to 50 mg/kg bw/d	NOEL/NOAEL = 20 mg/kg bw (developmental) NOEL/NOAEL = 7.5 mg/kg bw (maternal toxicity)	ICI5504/0122
Rabbit	Developmental toxicity	OECD 414 (purity 96.2% w/w), doses up to 500 mg/kg bw/d	NOEL >500 mg/kg bw/d (developmental) NOAEL = 50 mg/kg bw/d (maternal) Not teratogenic	ICI5504/0122
Rat	Developmental toxicity	OECD 414 (purity 95.2% w/w), doses up to 300 mg/kg bw/d	NOAEL = 25 mg/kg (maternal and developmental) Not teratogenic	ICI5504/0112

Azoxystrobin at doses up to the maximum tolerated in rat and mouse provided no evidence for carcinogenicity.

In the first rabbit developmental toxicity study, azoxystrobin appeared to cause developmental toxicity at a dose level of 50 mg/kg/day in presence of maternal toxicity. However, a series of investigative studies (reported in ICI5504/0122) conclusively demonstrated that the effects seen in the first study were caused by the dose vehicle. In the second definitive rabbit developmental toxicity study, maternal toxicity occurred at ≥150 mg/kg bw/d but there was no effect on foetal development up to the highest dose. In the rat developmental toxicity study, development effects were seen only at maternally toxic doses (100 mg/kg bw/d). A two-generation reproduction study in the rat showed no evidence of reproductive toxicity, even at doses where maternal toxicity was evident. No evidence for neurotoxicity was observed in any study.

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

Species	Test	Duration and conditions	Result	Reference
Salmonella typhimurium TA1535, TA1537, TA98, TA100; *Escherichia coli* WP2P, WP2P *uvrA*	Bacterial mutation assay; *in vitro*	OECD guidelines 471 and 472 (purity 97.2% w/w), doses up to 5000 µg/plate	Negative	ICI5504/0140
L5178Y TK+/- mouse lymphoma cells	Mammalian cell gene mutation assay, *in vitro*	OECD 476 (purity 96.2% w/w), doses up to 80 µg/ml	Positive	ICI5504/0143
Human lymphocytes (chromosomal aberrations)	Mammalian cell cytogenetic assay, *in vitro*	OECD guidelines 473 (purity 95.2% w/w), doses up to 1500 µg/ml	Positive	ICI5504/0131
Mouse bone marrow (m,f)	Mouse bone marrow micronucleus assay, *in vivo*	OECD 474 (purity 97.2% w/w), single dose 5000 mg/kg bw	Negative	ICI5504/0133
Rat hepatocytes (m)	Rat liver unscheduled DNA synthesis assay, *in vivo*	Draft OECD 486 (purity 97.2% w/w), doses up to 2000 mg/kg bw	Negative	ICI5504/0136

Azoxystrobin was negative in most genotoxicity tests but induced TK mutations in mouse lymphoma cells *in vitro* and there was evidence of a concentration-dependent clastogenic activity in human lymphocytes *in vitro* in the presence of moderate to severe cytotoxicity.

Table D. Ecotoxicology profile of azoxystrobin technical material

Species	Test	Duration and conditions	Result	Reference
Mallard duck (*Anas platyrhynchos*)	Acute oral toxicity	5 m 5 f, single dose of 0, 250, 400, 1000 or 2000 mg/kg bw (purity 96.2% w/w)	LD_{50} >2000 mg/kg	ICI5504/0851
Bobwhite quail (*Colinus virginianus*)	Acute oral toxicity	5 m 5 f, single dose of 0, 250, 400, 1000 or 2000 mg/kg bw (purity 96.2% w/w)	LD_{50} >2000 mg/kg	ICI5504/0852
Mallard duck	Short-term dietary toxicity	10 ducks, diet with 163, 325, 650, 1300, 2600 or 5200 ppm for 5 days (purity 96.2% w/w)	LC_{50} >5200 mg/kg diet	ICI5504/0853
Bobwhite quail	Short-term dietary toxicity	10 ducks, diet with 163, 325, 650, 1300, 2600 or 5200 ppm for 5 days (purity 96.2% w/w)	LC_{50} >5200 mg/kg diet	ICI5504/1272
Mallard duck	Sub-chronic toxicity and reproduction	6 replicates, 2 m 5 f, diet with 0, 500, 1200 or 3000 ppm, 23 weeks (purity 96.2% w/w)	NOEC = 1200 mg/kg diet	ICI5504/0856
Colinus virginianus northern bobwhite quail	Sub-chronic toxicity and reproduction	20 replicates, 1 m 1 f adults, diet with 0, 500, 1200 or 3000 ppm, 22 weeks (purity 96.2% w/w)	NOEC = 1200 mg/kg diet	ICI5504/0857
Onchorhynchus mykiss rainbow trout	Acute toxicity	96 h exposure to 32, 56, 100, 180, 320 or 560 µg/l, flow-through system (purity 96.2% w/w)	LC_{50} = 0.47 mg/l	ICI5504/0909

Table D. Ecotoxicology profile of azoxystrobin technical material

Species	Test	Duration and conditions	Result	Reference
Fathead minnow *Pimephales promelas*	Extended life stage	33 d exposure to 45, 90, 140, 180, 360 or 720 µg/l (purity 96.2% w/w)	NOEC = 0.147 mg/l	ICI5504/0924
Daphnia magna (water flea)	Acute toxicity	48 h exposure up to 1000 at 20°C (purity 96.2% w/w)	EC_{50} = 0.28 mg/l	ICI5504/0928
Daphnia magna (water flea)	Chronic toxicity	21 d exposure to 0, 6.25, 12.5, 25, 50, 100, 200 or 400 µg/l, static system at 20°C (purity 96.2% w/w)	NOEC = 0.044 mg/l	ICI5504/0957
Scenedesmus subspicatus (green alga)	Effect on growth	96 h exposure to 0, 3.2, 10, 32, 100, 320, 1000 or 3200 µg/l (purity 96.2% w/w), static water	E_bC_{50} = 0.36 mg/l	ICI5504/0961
Apis mellifera (Bee)	Acute oral	24 h EPPO Guideline No. 170 ref. 2, (purity 51.6% w/w)	LD_{50} >200 µg ai/bee	ICI5504/0862
Apis mellifera (Bee)	Acute Contact	24 h EPPO Guideline No. 170 ref. 2 (purity 51.6% w/w)	LD_{50} >25 µg ai/bee	ICI5504/0862
Parasitic wasp, *Aphidius rhopalosiphi*	Dose-response on glass plate	48 h IOBC (Mead-Briggs *et al*. 2000), formulation 250 g/l SC (content 23.3% w/w)	LR_{50} >625 ml/ha	ICI5504/2627
Predatory mite *Typhlodromus pyri*	Dose-response on glass plate	7 d C.E.B. No. 167 (Jan 1993), formulation 250 g/l SC (content 23.0% w/w)	LR_{50} >5000 ml/ha	ICI5504/0006
Earthworm *Eisenia andrei*	Reproduction toxicity	Artificial soil, 14 d exposure to 10, 100, 180, 320, 560 or 1000 mg formulation/kg, 250 g/l SC (content 23.0% w/w)	LC_{50} = 881 mg/kg dry soil NOEC = 20 mg/kg	ICI5504/0903
Folsomia candida (Collembola)	Reproduction toxicity	28 d, ISO 11267, formulation 250 g/l SC, (content 25.1% w/v)	NOEC = 50 mg/kg	ICI5504/1319
Non-target terrestrial plant seedlings	Effect on seedling emergence	18 d, OECD 208 (purity 98.6% w/w)	NOEC = 20 mg ai/kg soil	ICI5504/1376
Soil micro-organisms	Tier 1	28 d OECD 216 & 217 with formulation 250 g ai/l SC (content 22.8% w/w)	No effects up to 2.5 kg ai/ha	ICI5504/0960
Soil macro- and micro-organisms	Litterbag study	Field conditions, 188 d, formulation 250 g/l SC (content 24.8% w/v)	No negative impact on decomposition of soil organic matter	ICI5504/2319

ANNEX 2. REFERENCES

Syngenta document number or other reference	Year and title of report or publication details
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