FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

AZOXYSTROBIN

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

FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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INTRODUCTION

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

From 2002, the development of WHO specifications follows the **New Procedure**, described in the 1st edition of "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (2002) and amended with the supplement of this manual (2006), 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 JMPS, 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. Dates of publication of the earlier versions, if any, are identified in a footnote. 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/ag/agp/agpp/pesticid/) OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.

PART ONE

SPECIFICATIONS

AZOXYSTROBIN

PART ONE

AZOXYSTROBIN

INFORMATION

ISO common name:

Azoxystrobin (E-ISO, BSI)

Chemical name(s):

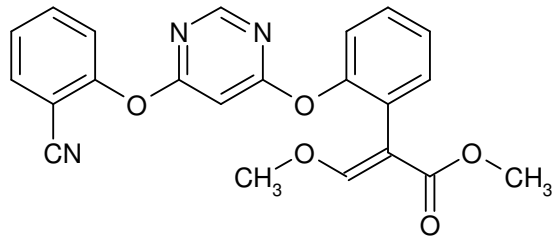
IUPAC, methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate

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

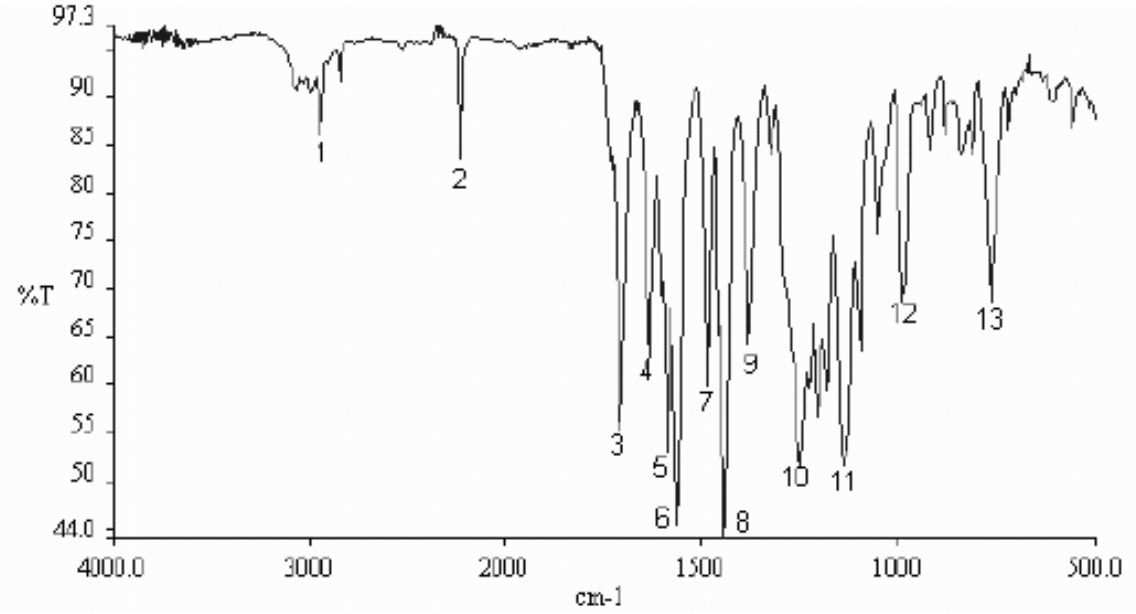
CIPAC number:

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 (July 2008*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (*571/2007*). It should be applicable to TC produced by this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for TC produced by other manufacturers. The evaluation report (*571/2007*), as PART TWO, forms 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 powder and shall be free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (CIPAC/TC/M/- 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 **Azoxystrobin content** (CIPAC/TC/M/- Note 1)

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.

Note 1 Methods for the identification and determination of azoxystrobin content were adopted by CIPAC in 2007 but are not yet published in a Handbook. Prior to publication of the Handbook, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/ag/agp/agpp/pesticid/.

AZOXYSTROBIN WATER DISPERSIBLE GRANULES

FAO specification 571/WG (July 2008*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose names is listed in the evaluation report (*571/2007*). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated source. 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 report (*571/2007*), as PART TWO, forms 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 (July 2008), 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/WG/M/- 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 **Azoxystrobin content** (CIPAC/WG/M/- Note 1).

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

pH range: 5 to 7.5.

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

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

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/ag/agp/agpp/pesticid/.

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

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

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

Dispersibility: minimum 70% after 1 minute of stirring.

3.5 **Suspensibility** (MT 168, CIPAC Handbook F, p.417, 1995 or MT 184, CIPAC Handbook K, p.142, 2003) (Notes 2 & 3)

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

3.6 **Persistent foam** (MT 47.2, CIPAC Handbook F, p.152, 1995) (Note 4)

Maximum: 60 ml after 1 minute.

3.7 **Dustiness** (MT 171, CIPAC Handbook F, p.425, 1995) (Note 5)

Essentially non-dusty.

3.8 **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.

3.9 **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 6) and the formulation shall continue to comply with the clauses for:

- pH range (3.1)
- wet sieve test (3.2)
- degree of dispersion (3.4)
- suspensibility (3.5)
- dustiness (3.7)
- attrition resistance (3.9)

Note 1 Methods for the identification and determination of azoxystrobin content were adopted by CIPAC in 2007 but are not yet published in a Handbook. Prior to publication of the Handbook, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org.

Note 2 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 3 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 4 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 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 Analysis of the formulation, before and after the storage stability test, should be carried out concurrently (i.e. after storage) to reduce analytical error.

AZOXYSTROBIN AQUEOUS SUSPENSION CONCENTRATE

FAO specification 571/SC (July 2008*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose names is listed in the evaluation report (*571/2007*). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated source. 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 report (*571/2007*), as PART TWO, forms 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 (July 2008), 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/-, Note 2)

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/-, Note 2)

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: 5%.

3.3 Spontaneity of dispersion (MT 160, CIPAC Handbook F, p.391, 1995) (Note 4)

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.

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* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/ag/agp/agpp/pesticid/.

3.4 **Suspensibility** (MT 184, CIPAC Handbook K, p.142, 2003) (Note 4)

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 5)

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

3.6 **Persistent foam** (MT 47.2, CIPAC Handbook F, p.152, 1995) (Note 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).

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 Methods for the identification and determination of azoxystrobin content were adopted by CIPAC in 2007 but are not yet published in a Handbook. Prior to publication of the Handbook, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org.

Note 3 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 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 equal results to those of the chemical assay method. In case of dispute, the chemical method shall be the referee method.

Note 5 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 6 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 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.

PART TWO

EVALUATION REPORTS

AZOXYSTROBIN

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):

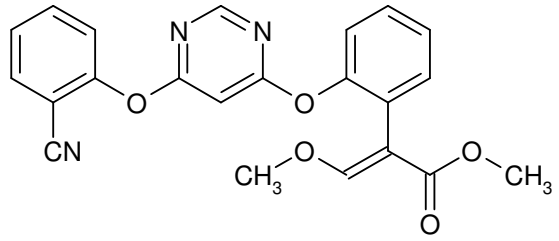
IUPAC, methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate

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℃	99.0	OECD 104, by extrapolation	ICI5504/0028
Melting point	116℃	99.0	OECD 102	ICI5504/0028
Boiling point, temperature of decomposition	Boiling point: cannot be determined at atmospheric pressure Decomposition temperature: ~345℃	99.0	OECD 113	ICI5504/0039
Solubility in water at 20℃	6.0 mg/l at 20℃ in purified water, approximately neutral pH	99.0	EPA Guideline CG-1510	ICI5504/0028
Partition coefficient	log P_{OW} = 2.5 at 20℃ at pH 7	99.0	OECD 107	ICI5504/0028
Hydrolysis characteristics	Half-life = 12 days at 50℃ at pH 9 No significant hydrolysis (<10%) after 31 days at 25℃ nor after a further 12 days at 50℃ at pH 5 and 7.	>98	EPA Guideline 161-1	ICI5504/0824
Photolysis characteristics	Continuous irradiation at 25℃ 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℃

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 µg/l 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

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