FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

FLUMIOXAZIN

N-(7-fluoro-3,4-dihydro-3-oxo-4-prop-2-ynyl-2*H*-1,4-benzoxazin-6-yl)cyclohex-1-ene-1,2-dicarboximide

FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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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 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) - currently available as 3rd revision of the 1st edition (2016) - , which is available only on the internet through the FAO and WHO web sites.

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

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

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

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

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

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

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

PART ONE

SPECIFICATIONS

FLUMIOXAZIN

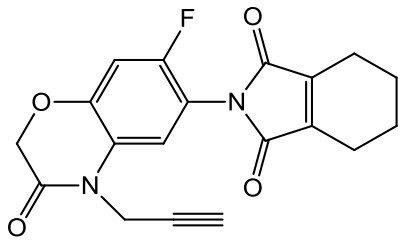
INFORMATION

ISO common name
Flumioxazin (ISO 1750, published)

Chemical names
IUPAC *N*-(7-fluoro-3,4-dihydro-3-oxo-4-prop-2-ynyl-2*H*-1,4-benzoxazin-6-yl) cyclohex-1-ene-1,2-dicarboximide
CA 2-[7-fluoro-3,4-dihydro-3-oxo-4-(2-propynyl)-2*H*-1,4-benzoxazin-6-yl]-4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

Synonym
S-53482, Sumisoya

Structural formula



Molecular formula
$C_{19}H_{15}FN_2O_4$

Relative molecular mass
354.3 g/mole

CAS Registry number
103361-09-7

CIPAC number
578

Identity tests
HPLC retention time, IR spectrum

FLUMIOXAZIN TECHNICAL MATERIAL

FAO Specification 578 / TC (June 2017*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation reports (578/2014 & 578/2017). 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 specification. The specification may not be appropriate for TC produced by other manufacturers. The evaluation reports (578/2014 & 578/2017), as PART TWO, form an integral part of this publication.

1. Description

The material shall consist of flumioxazin together with related manufacturing impurities, in the form of yellowish brown powder, free from visible extraneous matter and added modifying agents.

2. Active Ingredient

2.1 Identity tests (578/TC/M/2, CIPAC Handbook O, p. 78, 2017)

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 Flumioxazin content (578/TC/M/3, CIPAC Handbook O, p. 78, 2017)

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

* 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/

FLUMIOXAZIN WETTABLE POWDER IN SEALED WATER SOLUBLE BAG

FAO Specification 578 / WP-SB (June 2017*)

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 (578/2017). 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 (578/2017) as PART TWO forms an integral part of this publication

1 Description

The material shall consist of a defined quantity of a homogeneous mixture of technical flumioxazin, complying with the requirements of the FAO specification 578/TC (June 2017), together with filler(s) and any other necessary formulants. It shall be in the form of a fine powder, free from visible extraneous matter and hard lumps, contained in a sealed water soluble bag.

2 Active ingredient

2.1 Identity tests (578/WP/M/2, CIPAC Handbook O, p. 80, 2017) (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 Flumioxazin content (578/WP/M/3, CIPAC Handbook O, p. 80, 2017) (Note 1)

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

Declared content in g/kg	Tolerance
above 500	± 25 g/kg of the declared content

3 Physical properties (Note 1)

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

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

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

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

* 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/

3.3 **Suspensibility** (MT 184, CIPAC Handbook K, p.142, 2003) (Notes 2 & 3)

The suspensibility shall be tested on a suspension containing the WP and the bag material in the actual ratio of application, prepared according to the procedure described in Note 4.

A minimum of 60 % of the flumioxazin content found under 2.2 shall be in suspension after 30 min in CIPAC Standard Water D at 30 ± 2°C.

3.4 **Persistent foam** (MT 47.1, CIPAC Handbook O, p.177, 2017) (Note 5)

The persistent foam shall be tested on a suspension containing the WP and the bag material in the actual ratio of application in CIPAC Standard Water C at 30 ± 2 °C, prepared according to the procedure described in Note 4.

Maximum: 60 ml after 1 min.

3.5 **Dissolution of the bag** (MT 176, CIPAC Handbook F, p.440, 1995) (Note 6)

The dissolution of the bag shall be tested on a sample of the emptied and cleaned bag together with appropriate proportion of the WP in CIPAC Standard Water C taken according to the procedure described in Note 4.

Flow time of the suspension: maximum 30 sec.

4 Storage stability

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

The package should be enclosed in a watertight sachet, box or any other container 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:

- wettability (3.1),
- wet sieve test (3.2),
- suspensibility (3.3),
- persistent foam (3.4)
- dissolution of the bag (3.5)

None of the bags tested should show signs of leakage or rupture during normal handling, before and after storage.

Note 1 Sub-sampling.

Lay the bag on a bench and carefully open one side of the bag with a cutter, taking care not to damage the seals. Transfer the contents of the bag into a suitable flask. This material shall be used to carry out the tests for:

- active ingredient identity (2.1),
- active ingredient content (2.2),
- wettability (3.1),
- wet sieve test (3.2),
- suspensibility (3.3),
- persistent foam (3.4),
- dissolution of the bag (3.5).

The bag is then opened on three sides, completely cleaned from adhering powder by brushing or suction and weighed to the nearest 0.01 g. It shall be used to carry out the dissolution test (3.5). Al-

iquots of an aqueous solution of the bag material shall be used in the suspensibility (3.3) and persistent foam (3.4) tests.

In the case of delay of the above tests, the bag shall be stored in a watertight container (glass bottle or equivalent) to avoid any change in its properties.

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 method MT 184.

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 chemical assay. In case of dispute, chemical assay shall be the "referee method".

Note 4 The procedure for adding the bag material to the solution for the suspensibility and persistent foam tests should be as follows:

Prepare a stock solution of the bag material (1 mg/ml) by weighing approximately a sample (n mg) of the bag (excluding sealed parts) to the nearest mg. Dissolve this sample by stirring in the standard water used for the tests to give a final volume of n ml. Store the stock solution in a stoppered bottle before use.

Calculate the volume (V ml) of the stock solution of the bag to be added to the test suspension of the wettable powder according to the following equation:

$$V(ml) = X \times \frac{1000B}{W}$$

Where: B (g) = weight of the emptied and cleaned bag
W (g) = nominal weight of the WP contained in the bag
X (g) = weight of the WP sample used in the test

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

Note 6 The sampling of the bag for the dissolution test should be as follows:

Lay the empty cleaned bag in its original configuration (double layer). Delineate and then cut up a test sample including part of the upper seal (5 cm) and symmetrically including the vertical seal (10 cm). If the size of the bag is less than this dimension, use the whole bag.

Carry out the dissolution test immediately to avoid any modification of the sample.

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

FLUMIOXAZIN

FLUMIOXAZIN

FAO/WHO EVALUATION REPORT 578/2017

Recommendation

The Meeting recommended that the new FAO specification for flumioxazin WP-SB, proposed by Sumitomo Chemical Co. and as amended, should be adopted by FAO.

Appraisal

A draft specification for flumioxazin WP-SB, provided by Sumitomo Chemical Co., was received in 2015 and considered by the JMPS for development of a new FAO specification. A data package on physical-chemical properties of the formulation in the water soluble bag was also received [Kozuki, 2015] and supported the clauses and the proposed limits.

The proposed specification for flumioxazin WP-SB was broadly in agreement with the guidelines given in the Manual (FAO/WHO 2010).

Formulation type, description, content of active ingredient and analytical method

The active ingredient, in the form of a wettable powder, is packed in a water soluble bag. The bag allows a convenient dosage of the formulation according to national registration and minimizes the exposure of the spray personnel to the wettable powder, as one or more whole sachets are directly dissolved in the spray tank and diluted with an appropriate amount of water.

The analytical method for confirmation of the identity of flumioxazin and determination of its content in wettable powders is a full CIPAC method (CIPAC/4763), based on a reversed phase HPLC with UV detection. The method had been available until recently through the CIPAC prepublishment scheme and its publication in Handbook O coincides with the publication of the WP-specification and evaluation. For that reason, the TC specification was editorially revised to refer to the CIPAC analytical methods for the TC and WP (and WP-SB) in Handbook O.

Physical-chemical properties

In certain tests to be carried out to assess the physical-chemical parameters of the WB-SB the neat formulation is used (e.g. in the wet sieve test and wettability). Whereas in wet sieving, the maximum residue is 1 %, the limits of the suspensibilty (minimum 60 %) and of the persistent foam based on the new MT 47.1 in Handbook O (maximum 60 mL) indicate, that the combination of formulation and bag material is more challenging. The results of the studies show that the formulation complies with all generic limits as set in the Manual (November 2010 - second revision of the First Edition at time of preparation and submission of the data package).

Storage stability

Whereas flumioxazin in the formulation is expected to be fairly stable at 54°C for two weeks, the water soluble polymer material used for the bag may deterioriate to a certain extent and have an impact on the limits of certain clauses like dissolution of the bag and suspensibility. The test results of samples before and after storage at 54°C for two weeks showed that the physical-chemical parameters were not adversely affected after storage at 54 °C.

After accelerated storage at 54 °C for 2 weeks, the products still complies with the clauses for wet sieve test, suspensibility, persistent foam, wettability and dissolution of the bag.

ANNEX 1

REFERENCES

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study
FAO/WHO Manual		2010	Manual on development and use of FAO and WHO specifications for pesticides, November 2010 - second revision of the First Edition
CIPAC, F	Martijn A and Dobrat W	1995	CIPAC Handbook Volume L. Analysis of Technical and Formulated Pesticides, p.118
CIPAC, J	Martijn A and Dobrat W	2000	CIPAC Handbook Volume J. Analysis of Technical and Formulated Pesticides
CIPAC, K	Martijn A and Dobrat W	2003	CIPAC Handbook Volume K. Analysis of Technical and Formulated Pesticides
CIPAC, O	de Oliveira, M C C and Garvey J	2017	CIPAC Handbook Volume O. Analysis of Technical and Formulated Pesticides
	Kozuki, Y.	2015	Physico-chemical properties of Flumioxazin wettable powder in sealed water soluble bag - Study report

FLUMIOXAZIN

FAO/WHO EVALUATION REPORT 578/2014

Recommendations

The Meeting recommended that the new specifications for flumioxazin TC proposed by Sumitomo Chemical Co., Ltd. as amended, should be adopted by FAO

Appraisal

Flumioxazin is not under patent.

Flumioxazin has not been evaluated by the FAO/WHO JMPR and WHO/IPCS. The US EPA has completed a review of the toxicological data submitted for this compound. [EPA 2001] It was evaluated by the European Commission and included in Annex I of the Council Directive 91/414/EEC. [CD, 2002] Flumioxazin is currently under evaluation by European Commission as part of the procedure for the renewal of the inclusion in Annex I to Council Directive 91/414/EEC. [CR, 2010] A proposal for harmonised classification and labelling of flumioxazin was submitted to the European Chemicals Agency (ECHA) in 2013. [ECHA, 2013]

The data for flumioxazin were evaluated in support of a new FAO specification based on the draft specification (TC) and the supporting data provided by Sumitomo Chemical Co. in October 2013.

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

Flumioxazin is currently registered in Europe, the United States of America, Latin America, Australia, as well as some Asian countries.

The confidential data submitted by the proposer on the manufacturing process of flumioxazin, the data summary in support of the physical-chemical, toxicological and ecotoxicological properties were in accordance with the information supplied to France for registration purposes. The impurities and QC limits for flumioxazin TC produced by Sumitomo agree between the information submitted to FAO and to France. [Six, 2014]

Flumioxazin is a yellow blown odourless powder with a melting range between 203.5 and 209.7 °C. The compound has a low vapour pressure and water solubility (≈0.8 mg/L) that is not pH dependent. It is soluble in medium polarity organic solvents like dichloromethane, acetone or ethyl acetate, but only slightly soluble in hexane. The octanol/water partition coefficient is not pH dependent and indicates limited potential to bioaccumulation. Flumioxazin is hydrolysed in aqueous media with DT_{50} of 3 to 5 days, 19 to 26 hours, and 14 to 23 minutes at pH 5, 7 and 9, respectively. Flumioxazin absorbs UV light in the 215 to 220 nm range. Photolytic DT_{50} was determined to be 21 – 26 hours in aqueous media at 25°C. No dissociation constant was observed or possible to determine due to rapid hydrolytic decomposition under alkaline conditions.

The main formulation type available is wettable powder (WP).

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on all impurities present below or above 1 g/kg and their manufacturing limits in the TC. Mass balances were 99.89 – 100.55 % in the 5-batch data. The maximum limits for the impurities were supported by the batch data.

In the submission the company proposed that there are no relevant impurities. Nevertheless, a noble metal used as a catalyst in the manufacturing process was considered by the Meeting but it concluded that it is very unlikely that low levels of that metal remaining in the flumioxazin technical material would reach 10% of the GHS limit, leading to classification as a sensitizer. Therefore residues of that noble metal were not considered relevant.

The identity of flumioxazin is confirmed by comparing the retention time of the sample with an authentic standard using reversed phase HPLC, and by comparing IR spectrum. The analytical method for the determination of the active ingredient in flumioxazin technical is reversed-phase HPLC with UV detection (CIPAC/4763) (ISBN 902951629). Impurities were determined by HPLC-UV. The LOQ for all impurities was 0.1 %. Test methods for determination of physical-chemical properties of the technical active ingredient were OECD, EPA, EC and CIPAC, respectively.

Toxicity data were available for acute and sub-acute to chronic toxicity, including carcinogenicity and teratogenicity, genotoxicity and ecotoxicology, derived from the technical grade active ingredient manufactured by the proposer. The Meeting requested further explanations regarding the findings on the two developmental toxicity studies in rat [Aitio, 2014]. Several dose-related effects were observed: cardiac ventricular septum defects, wavy ribs, curvature of the scapular and reduced ossification the cerebral spine. However, a series of mode of action studies showed that the effects were rat specific and could not be extrapolated to humans. The view of the proposer was that the rat is an inappropriate model for assessing the developmental toxicity of flumioxazin in humans. The Meeting accepted this explanation.

The Meeting recommended the adoption of the new FAO specification for the technical material.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 578/2014

USES

Flumioxazin is a contact herbicide, not systemic and hence not translocated in plants. It is used in agriculture in arable and permanent crops, in industrial weed control, amenities (non agricultural uses) to control broad leaved weeds and grasses.

Flumioxazin acts by inhibiting the protoporphyrinogen oxidase, leading to the accumulation of porphyrines in sensitive plants. In presence of light and oxygen, the porphyrines cause the peroxidation of the lipidic membranes, leading to irreversible damages to the cell membranes, causing the death of the cell. Applied in pre-emergence, flumioxazin acts by contact with the radicles and young shoots of the emerging seed, causing the necrosis of the shoots and radicles. Applied in early post emergence, flumioxazin acts by contact with the leaf tissue causing the bleaching, withering and desiccation of the damaged plant organs, followed by the necrosis of the plant.

Identity of the active ingredient

ISO common name

Flumioxazin (ISO 1750, published)

Chemical name(s)

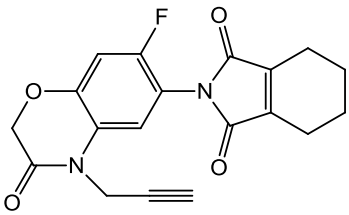
IUPAC *N*-(7-fluoro-3,4-dihydro-3-oxo-4-prop-2-ynyl-2*H*-1,4-benzoxazin-6-yl)cyclohex-1-ene-1,2-dicarboximide

CA 2-[7-fluoro-3,4-dihydro-3-oxo-4-(2-propynyl)-2*H*-1,4-benzoxazin-6-yl]-4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

Synonyms

S-53482, Sumisoya

Structural formula



Molecular formula

$C_{19}H_{15}FN_2O_4$

Relative molecular mass

354.3

CAS Registry number

103361-09-7

CIPAC number

578

Identity tests

HPLC retention time, IR spectrum

Table 1: Physical-chemical properties of pure flumioxazin

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number
Vapour pressure	3.2 x 10^{-4} Pa at 22 °C	99.5	OECD 104 (gas saturation method)	[201] SBP-01-0010
Melting point.	203.51 – 209.74 °C	99.6	OECD 102, EEC Method A.1	[202] SBP-0056
Temperature of decomposition	273.33 °C at an atmospheric pressure of 101.79 kPa	99.6	OECD 103, EEC Method A.2	[202] SBP-0056
Solubility in water	0.786±0.1081 mg/l at 20 °C (doubly-distilled water) Due to neutral properties of flumioxazin, effect of pH was not investigated.	99.6	EEC Method A.6, OECD 105 (column elution)	[203] SBP-0057
Octanol/water partition coefficient	log P_{OW} = 2.55 at 20 °C (pH 5.92 – 5.98)	99.9	OECD 107 (Equivalent to EEC Method A.8)	[204] SBP-00-0001
Hydrolysis characteristics	Half-life = 3.43 days at 25 °C at pH 5 Half-life = 18.9 – 23.9 hours at 25 °C at pH 7 Half-life = 14.0 – 15.1 minutes at 25 °C at pH 9	radiochemical purity > 99	EPA-FIFRA 161-1 (Equivalent to EEC Method C.7 or OECD 111)	[205] SBM-00-0006
	Half-life = 4.91 – 5.20 days at 25 °C at pH 5 Half-life = 23.2 – 25.9 hours at 25 °C at pH 7 Half-life = 21.3 – 22.7 minutes at 25 °C at pH 9	radiochemical purity > 99	EPA-FIFRA 161-1 (Equivalent to EEC Method C.7 or OECD 111)	[206] SBM-00-0005
Photolysis characteristics	Half-life = 20.94 hours at 25 °C at pH 5 under artificial sunlight conditions (imido-label)	radiochemical purity > 99	EPA-FIFRA 161-2	[207] SBM-51-0051
	Half-life = 26.31 hours at 25 °C at pH 5 under artificial sunlight conditions (phenyl-label)	radiochemical purity > 99	EPA-FIFRA 161-2	[208] SBM-51-0052
	Quantum yield = 0.065 at 25±2 °C at pH 4	99.6	OECD 316	[209] SBP-0058
	Calculated half-life = 0.139 – 0.161 days (3.3 – 3.9 hours) for latitude 30, 40 and 50 °N and summer	not applicable	OECD 316, GCSOLAR programme	[210] SBP-0060
Dissociation characteristics	Not determined as the substance decomposed at pH >9 and no spectral changes were observed at pH ≤7	99.5	OECD 112 (spectrophotometric method)	[211] SBP-00-0021

Solubility in organic solvents	Temperature: 25°C g/l acetone 17.0 methanol 1.56 ethyl acetate 17.8 acetonitrile 32.3 dichloromethane 191 hexane 0.0247 n-octanol 0.163 tetrahydrofuran 53.8	97.6 technical	OECD 105 (flask method)	[212] SBP-01-0011

Table 2: Chemical composition and properties of flumioxazin technical material

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 99.89 – 100.55 % and percentages of unknowns were <0.1 %.
Declared minimum flumioxazin content	960 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities **<** 1 g/kg and maximum limits for them:	None
Stabilisers or other additives and maximum limits for them:	None
Melting temperature range of the TC	Not available

The agreed health-based reference values during the first EU peer review were [EC, 2002]:

	Value	Study	Safety factor
ADI	0.009 mg/kg bw per day	Rat, 2-y study	200
AOEL systemic	0.018 mg/kg bw per day	Rat, 90-d study, corrected for 83% oral absorption	100
ARfD	0.05 mg/kg bw	Rat, developmental toxicity Study (10 mg/kg bw/d)	200

The IPCS hazard classification of flumioxazin is: Unlikely to present acute hazard, class U.

EU classification of flumioxazin according to Regulation No 1272/2008/EC (Annex VI Table 3.2): [CLP, 2008]

Hazard class and category codes (Annex VI Table 3.1):

Classification		Labelling	
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)
Repr. 1B Aquatic Acute 1 Aquatic Chronic 1	H360D H400 H410	GHS08 GHS09 Dgr	H360D H410

Hazard statement: H360D (May damage the unborn child),
H400 (Very toxic to aquatic life),
H410 (Very toxic to aquatic life with long lasting effects)

The company proposed the change of classification in the dossier for EU Annex I renewal submitted to the rapporteur member state (Czech Republic) in February 2012. Though the classification “Repr. Cat. 2; R61” was based on developmental effects in the rat and presumed relevance to humans, an extensive program of research with flumioxazin has provided evidence that the rat is particularly sensitive to the toxic effects of flumioxazin whereas this is unlikely to be the case in humans. Therefore, a proposal to remove Repro. Cat 2; R61 and H360D has been made, which is currently under evaluation by ECHA.

FORMULATIONS AND CO-FORMULATED ACTIVE INGREDIENTS

The main formulation types available are wettable powders (WP). These formulations are registered and sold in many countries throughout the world in Europe, USA, Latin American Countries, Australia and some Asian countries.

Flumioxazin may be co-formulated with other pesticides.

METHODS OF ANALYSIS AND TESTING

The flumioxazin content can be determined by HPLC, using UV detection at 292 nm and internal standardisation with naphthalene [101]. The identity of the active ingredient is confirmed by HPLC, IR and MS. [102] and [103].

The analytical method for the active ingredient in TC and WP is a full CIPAC method (ISBN 902951629), adopted at the 2012 CIPAC meeting. The method is not yet published in a Handbook, but is available as a pre-published method. Flumioxazin is determined by reverse phase HPLC chromatography using a 250 mm x 4.6 mm C18 (5 µm) column and UV detection at 288 nm. The method(s) for determination of impurities are based on HPLC with UV detection.

Test methods for determination of physical-chemical properties of the technical active ingredient were OECD, EPA or EC, respectively.

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE CONTENT OF ACTIVE INGREDIENT

The active ingredient content is expressed as flumioxazin.

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 flumioxazin 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 3: Toxicology profile of the flumioxazin technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Purity %[2]	Guideline, duration, doses and conditions	Result	Study number
Rat male/female	oral	94.8	EPA-FIFRA 540/9, 82, 025 0, 5000 mg/kg bw	LD_{50}: >5000 mg/kg bw	[301] SBT-00-0006
Rat male/female	dermal	94.8	EPA-FIFRA 540/9, 82, 025 0, 2000 mg/kg bw	LD_{50}: >2000 mg/kg bw	[302] SBT-00-0007
Rat male/female	inhalation	98.3	EPA-FIFRA 81-3 4-hr exposure 0, 1550, 3930 mg/m^3	LC_{50}: >3930 mg/m^3 (max. feasible concentration)	[303] SBT-00-0011
Rabbit male/female	skin irritation	94.8	EPA-FIFRA (1982) 4-hr exposure	Non-irritating	[304] SBT-90-0005
Rabbit male/female	eye irritation	94.8	EPA-FIFRA (1982)	Non-irritating	[304] SBT-90-0005
Guinea pig male	skin sensitisation	94.8	EPA-FIFRA 81-6 Maximization test (Magnusson & Kligman)	Non-sensitizing	[305] SBT-90-0008

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

Table 4: Toxicology profile of the flumioxazin technical material based on repeated administration (subacute to chronic)

Species	Test[3]	Purity %	Guideline, duration, doses and conditions	Result	Study number
Mouse male/female	Sub-chronic / 28-d / diet	94.8	EPA-FIFRA 82-1 4 weeks 0. 1000, 3000, 10000 ppm (equivalent to: 0, 151.5, 419.9, 1366.5 mg/kg bw/d for male, 0, 164.5, 481.6, 1698.3 mg/kg bw/d for female)	Effects: Increase in absolute and/or relative liver weight	[306] SBT-00-0014
Rat male/female	Sub-chronic / 90-d / diet	98.4	EPA-FIFRA 82-1 13 weeks 0, 30, 300, 1000, 3000 ppm (equivalent to: 0, 2.28, 20.71, 69.70, 243,5 mg/kg bw/d for male, 0, 2.21, 21.72, 71.53, 229.6 mg/kg bw/d for female)	NOAEL: 69.70 mg/kg bw/d (male), 71.53 mg/kg bw/d (female) LOAEL: 243.5 mg/kg bw/d (male), 229.6 mg/kg bw/d (female)	[307] SBT-91-0002
Rat male/female	Sub-chronic / 90-d / diet	94.8	EPA-FIFRA 82-1 13 weeks 0, 30, 300, 1000, 3000 ppm (equivalent to: 0, 1.9, 19.3, 65.0, 196.7 mg/kg bw/day for male, 1, 2.2, 22.4, 72.9, 218.4 mg/kg bw/day for female)	NOAEL: 19.3 mg/kg bw/d (male), 2.2 mg/kg bw/d (female) LOAEL: 65.0 mg/kg bw/d (male), 22.4 mg/kg bw/d (female)	[308] SBT-10-0023
Dog male/female	Sub-chronic / 90-d / oral (capsule)	94.8	EPA-FIFRA 82-1 13 weeks 0, 10, 100, 1000 mg/kg bw/d	NOAEL: 10 mg/kg bw/d (male & female) LOAEL: 100 mg/kg bw/d (male & female)	[309] SBT-30-0038
Dog male/female	Chronic / 1-y / oral (capsule)	94.8	EPA-FIFRA 83-1 1 year 0, 10, 100, 1000 mg/kg bw/d	NOAEL: 10 mg/kg bw/d (male & female) LOAEL: 100 mg/kg bw/d (male & female)	[310] SBT-30-0039

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

Rat male/female	Dermal toxicity / 21-d	94.8	EPA-FIFRA 82-2 21 days 0, 100, 300, 1000 mg/kg bw/d	NOAEL: 1000 mg/kg bw/d (male), 300 mg/kg bw/d (female) LOAEL: 1000 mg/kg bw/d (female)	[311] SBT-11-0026
Rat male/female	Chronic toxicity & carcinogenicity / 2-y / diet	94.8	EPA-FIFRA 83-5 2 years 0, 50, 500, 1000 ppm (equivalent to: 0, 1.8, 18.0, 36.5 mg/kg bw/d for male, 0, 2.2, 21.8, 43.6 mg/kg bw/d for female)	NOAEL: 1.8 mg/kg bw/d (male), 2.2 mg/kg bw/d (female) LEL: 18 mg/kg bw/d (male), 21.8 mg/kg bw/d (female) Not carcinogenic	[312] SBT-30-0040
Mouse male/female	Carcinogenicity / 18-m / diet	94.8	EPA-FIFRA 83-2 78 weeks 0, 300, 3000, 7000 ppm (equivalent to: 0, 31.1, 314.9, 754.1 mg/kg bw/d for male, 0, 36.6, 346.4, 859.1 mg/kg bw/d for female)	NOAEL: 31.1 mg/kg bw/d (male), 36.6 mg/kg bw/d (female) LEL: 314 mg/kg bw/d (male), 346.4 mg/kg bw/d (female) Not carcinogenic	[313] SBT-30-0048
Rat male/female	Reproduction / dose-range finding / one generation	94.8	EPA-FIFRA 83-4, OECD 416, JMAFF 4200 0, 100, 500, 1000, 5000 ppm	Parental NOEL: <100 ppm Offspring NOEL: 100 ppm	[314] SBT-11-0018
Rat male/female	Reproduction / dose-range finding / one generation	94.8	EPA-FIFRA 83-4, OECD 416, JMAFF 4200 0, 100, 200, 300, 400, 500 ppm	Parental NOEL: 200 ppm Offspring NOEL: 200 ppm	[315] SBT-11-0019
Rat male/female	Reproduction / two generation	94.8	EPA-FIFRA 83-4, OECD 416, JMAFF 4200 0, 50, 100, 200, 300 ppm	Parental NOAEL: 200 ppm Reproductive NOAEL: 200 ppm Offspring NOAEL: 100 ppm	[316] SBT-21-0035

Rat female	Teratogenicity / oral / dose-range finding	98.2	EPA-FIFRA 83-3 0, 30, 100, 200, 500 mg/kg bw/d	Because of the high degree of embryolethality at 100 mg/kg bw/d and greater, 30 mg/kg bw/d was recommended as the maximum dose for the definitive study.	[317] SBT-90-0037
Rat female	Teratogenicity / oral	94.8	EPA-FIFRA 83-3 0, 1, 3, 10, 30 mg/kg bw/d	Maternal NOAEL: >30 mg/kg bw/d	[318] SBT-00-0012
Rabbit female	Teratogenicity / oral / dose-range finding	94.8	EPA-FIFRA 83-3 0, 300, 500, 1000, 1500 mg/kg bw/d	Maternal NOAEL: >1500 mg/kg bw/d	[319] SBT-11-0016
Rabbit female	Teratogenicity / oral	94.8	EPA-FIFRA 83-3 0, 300, 1000, 3000 mg/kg bw/d	Maternal NOAEL: 1000 mg/kg bw/d Developmental NOAEL: 3000 mg/kg bw/d	[320] SBT-11-0017
Rat female	Teratogenicity / dermal / dose-range finding	94.8	EPA-FIFRA 83-3 0, 100, 200, 400, 800 mg/kg bw/d	Maternal NOAEL: >800 mg/kg bw/d	[321] SBT-00-0015
Rat female	Teratogenicity / dermal	94.8	EPA-FIFRA 83-3 0, 30, 100, 300 mg/kg bw/d	Maternal NOAEL: >300 mg/kg bw/d	[322] SBT-10-0021

Table 5: Mutagenicity profile of the flumioxazin technical material based on *in vitro* and *in vivo* tests

Species	Test	Purity %[4]	Guideline, duration, doses and conditions	Result	Study number
---	Stability study *in vitro*	radiolabelled: >99 non-radiolabelled: 94.9	In-house method Under Ames conditions: 1000 µg/plate Under chromosomal aberration conditions: 0.2 mM	Stable for 2 days under Ames conditions, degraded with a half-life of about 1 hour under chromosomal aberration conditions.	[323] SBT-20-0036
Salmonella typhimurium / Escherichia coli	Bacterial reverse mutation *in vitro*	94.8	EEC B.13/14 -/+S9: 0, 50, 100, 200, 500, 1000, 2000 µg/plate	-/+S9: Negative	[324] SBT-90-0004
Chinese hamster ovary cells (CHO-K1)	Chromosomal aberration *in vitro*	98.2	EPA-FIFRA 84-2 -/+S9: 0, 10.6, 35.4, 70.9 µg/mL	-S9: Negative +S9: Positive	[325] SBT-80-0049
Chinese hamster V79 cells	*hprt* forward mutation *in vitro*	99.6	OECD 476, EC No.440/2008 B.17 -/+S9: 0, 14.1, 28.1, 56.3, 112.5, 225 µg/mL -S9: 0, 14.1, 28.1, 56.3, 112.5, 225 µg/mL +S9: 0, 28.1, 56.3, 112.5, 337.5, 450 µg/mL	-/+S9: Negative	[326] SBT-0111
Mouse bone marrow cells	Bone marrow micronucleus, *in vivo*	98.4	EPA-FIFRA 84-2 0, 300, 1000, 5000 mg/kg	Negative	[327] SBT-80-0050
Rat bone marrow cells	Bone marrow chromosomal aberration *in vivo*	94.8	EPA-FIFRA 84-2 Male: 0, 1250, 2500, 5000 mg/kg Female: 0, 1250, 2500, 4400, 5000 mg/kg	Negative	[328] SBT-00-0009
Rat hepatocytes	Unscheduled DNA synthesis *in vivo*	94.8	EPA-FIFRA 84-4 0, 1250, 2500, 5000 mg/kg	Negative	[329] SBT-00-0013

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

Table 6: Ecotoxicology profile of the flumioxazin technical material

Species	Test	Purity %[5]	Guideline, duration, doses and conditions	Result	Study number
Bobwhite quail (*Colinus virginianus*)	Acute oral	94.8	EPA-FIFRA 71-1 14 days 0, 292, 486, 810, 1350, 2250 mg/kg bw	LD_{50}: >2250 mg/kg bw	[401] SBW-01-0003
Mallard duck (*Anas platyrhyn-chos*)	Acute oral	94.8	EPA-FIFRA 71-1 14 days 0, 292, 486, 810, 1350, 2250 mg/kg bw	LD_{50}: >2250 mg/kg bw	[402] SBW-11-0005
Bobwhite quail (*Colinus virginianus*)	Dietary / 5-d	94.8	EPA-FIFRA 71-2, ASTM E 857-81 5 days 0, 562, 1000, 1780, 3160, 5620 ppm	LC_{50}: >5620 ppm (>1870 mg/kg bw/d)	[403] SBW-11-0010
Mallard duck (*Anas platyrhyn-chos*)	Dietary / 5-d	94.8	EPA-FIFRA 71-2, ASTM E 857-81 5 days 0, 562, 1000, 1780, 3160, 5620 ppm	LC_{50}: >5620 ppm (>2130 mg/kg bw/d)	[404] SBW-11-0011
Bobwhite quail (*Colinus virginianus*)	Reproduction / one-generation	94.8	EPA-FIFRA 71-4 21 weeks 0, 100, 250, 500 ppm	NOEC: 500 ppm (49.8 mg/kg bw/d)	[405] SBW-41-0016
Mallard duck (*Anas platyrhyn-chos*)	Reproduction / one-generation	94.8	EPA-FIFRA 71-4 21 weeks 0, 100, 250, 500 ppm	NOEC: 250 ppm (31 mg/kg bw/d)	[406] SBW-41-0018
Rainbow trout (*Oncorhynchus mykiss*)	Acute Flow-through	94.8	EPA-FIFRA 72-1 96 hours 0, 0.56, 0.92, 2.0, 2.9, 5.4 mg a.s./L	LC_{50}: 2.3 mg a.s./L	[407] SBW-90-0001
Bluegill sunfish (*Lepomis macro-chirus*)	Acute Flow-through	94.8	EPA-FIFRA 72-1 96 hours 0, 2.1, 3.9, 6.3, 9.4, 21 mg a.s./L	LC_{50}: >21 mg a.s./L	[408] SBW-90-0002
Rainbow trout (*Oncorhynchus mykiss*)	Chronic Flow-through	94.3	OECD 204 21 days 0, 0.20, 0.37, 0.61, 1.2, 2.4 mg a.s./L	NOEC: 0.37 mg a.s./L	[409] SBW-21-0009

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

Water flea (*Daphnia magna*)	Acute Flow-through	94.7	EPA-FIFRA 72-2 48 hours 0, 3.7, 6.0, 5.1, 6.0, 9.3 mg a.s./L	EC_{50}: 5.9 mg a.s./L	[410] SBW-21-0007
Water flea (*Daphnia magna*)	Chronic Flow-through	radiolabelled: 98.5 non- radio-labelled: 94.8	EPA-FIFRA 74-2 21 days 0, 0.015, 0.028, 0.057, 0.107, 0.205 mg a.s./L	NOEC: 0.057 mg a.s./L	[411] SBW-41-0014
Water flea (*Daphnia magna*)	Chronic Semi-static	99.0	OECD 211 21 days 0, 0.050, 0.10, 0.20, 0.40, 0.80 mg a.s./L (nominal)	NOEC: 0.10 mg a.s./L	[412] SBW-0050
Green alga (*Pseudokirchneriella subcapitata*)	Chronic Static	radiolabelled: 99.7 non- radio-labelled: 99.5	EPA-FIFRA 122-2, 123-2 72 hours 0, 0.00012, 0.00033, 0.00079, 0.0020, 0.0049 mg a.s./L	EC_{50}: 0.000852 mg a.s./L	[413] SBW-0030
Green alga (*Pseudokirchneriella subcapitata*)	Chronic Static	94.3	OECD 201 72 hours 0, 0.00054, 0.0011, 0.0021, 0.0043, 0.0085 mg a.s./L (nominal)	EC_{50}: 0.0012 mg a.s./L	[414] SBW-21-0008
Diatom (*Navicula pellicu-losa*)	Chronic Static	radiolabelled: 99.7 non- radio-labelled: 99.5	EPA-FIFRA 122-2, 123-2 120 hours 0, 0.000042, 0.000074, 0.00015, 0.00031, 0.00061, 0.0012, 0.0024 mg a.s./L	EC_{50}: 0.0015 mg a.s./L	[415] SBW-0028
Duckweed (*Lemna gibba*)	Chronic Semi-static	radiolabelled: 99.7 non- radio-labelled: 99.5	EPA-FIFRA 122-2, 123-2 14 days 0, 0.000051, 0.00011, 0.00022, 0.00044, 0.00087, 0.0017 mg a.s./L	EC_{50}: 0.00035 mg a.s./L	[416] SBW-0027
Sediment dwelling invertebrates (*Chironomus ripari-us*)	Chronic Static	99.0	ASTM E 1398-94, DoE 3460 P2 23 days 0, 0.01, 0.05, 0.09, 0.22, 0.74 mg a.s./kg	NOEC: 0.73 mg a.s./kg	[417] SBW-0042
Honeybee (*Apis mellifera*)	Acute contact	94.8	EPA-FIFRA 141-1 48 hours 0, 14, 23, 38, 63, 105 µg a.s./bee	LD_{50}: >105 µg a.s./bee	[418] SBW-01-0004

Earthworm (*Eisenia fetida*)	Acute	94.8	OECD 207 14 days 0, 61, 123, 246, 491, 982 mg/kg soil	LC_{50}: >982 mg/kg soil	[419] SBW-11-0006
Nitrogen transformation / Carbon mineralisation	28 days	99.4	EPPO guideline	No effect at 1.75 mg a.s./kg d.w.soil (equivalent to 1.2 kg a.s./ha)	[420] SBW-41-0020

ANNEX 2

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