FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

FLUSILAZOLE

bis(4-fluorophenyl)(methyl)(1*H*-1,2,4-triazol-1-ylmethyl)silane

FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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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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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

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INFORMATION

ISO common name

flusilazole (BSI, ANSI, E-ISO)

Chemical name(s)

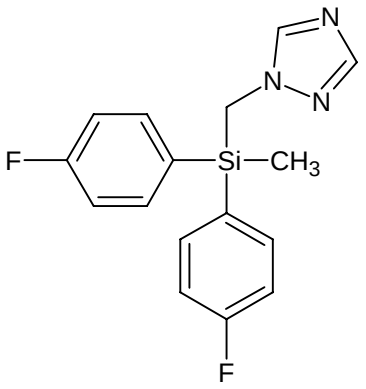
IUPAC bis (4-fluorophenyl)(methyl)(1*H*-1,2,4-triazol-1-ylmethyl)silane

CAS 1-[[bis(4-fluorophenyl)methylsilyl]methyl]-1*H*-1,2,4-triazole

Synonyms

DPX-H6573
IN-H6573

Structural formula



Molecular formula

$C_{16}H_{15}F_2N_3Si$

Relative molecular mass

315.4

CAS Registry number

85509-19-9

CIPAC number

435

Identity tests

Capillary GC retention time; IR spectrum

FLUSILAZOLE TECHNICAL MATERIAL

FAO specification 435/TC (April 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 reports (*435/2007*). 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 (*435/2007*), as PART TWO, forms an integral part of this publication.*

1 Description

The material shall consist of flusilazole together with related manufacturing impurities, in the form of odourless white crystals, and shall be free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (435/TC/(M)/2, CIPAC Handbook H, p.172, 1998)

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

2.2 **Flusilazole content** (435/TC/(M)/3, CIPAC Handbook H, p.172, 1998)

The flusilazole content shall be declared (not less than 925 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/ag/agp/agpp/pesticid/.

FLUSILAZOLE EMULSIFIABLE CONCENTRATE

FAO specification 435/EC (April 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 (435/2007)*. 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* (435/2007)*, as PART TWO, forms an integral part of this publication.*

1 Description

The material shall consist of technical flusilazole, complying with the requirements of FAO specification 435/TC (April 2008), dissolved in suitable solvents, together with any other necessary formulants. It shall be in the form of a stable homogeneous liquid, free from visible suspended matter and sediment, to be applied as an emulsion after dilution in water.

2 Active ingredient

2.1 Identity tests (435/EC/(M)/2, CIPAC Handbook H, p. 176, 1998)

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

2.2 Flusilazole content (435/EC/(M)/3, CIPAC Handbook H, p. 176, 1998)

The flusilazole content shall be declared (g/kg or g/l at 20 ± 2°C, Note 1) and, when determined, the average content measured shall not differ from that declared by more than the following tolerance:

Declared content, g/kg or g/l at 20 ± 2ºC	Tolerance
above 250 up to 500 Note. the upper limit is included in the range	± 5% of the declared 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/ag/agp/agpp/pesticid/.

3 Physical properties

3.1 **Emulsion stability and re-emulsification** (MT 36.3, CIPAC Handbook K, p.137, 2003)

The formulation, when diluted at 30 ± 2ºC with CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of stability, MT 36.3
0 h	Initial emulsification complete
0.5 h	"Cream", maximum: 0 ml
2.0 h	"Cream", maximum: 0 ml "Free oil", maximum: 0 ml
24 h	Re-emulsification complete
24.5 h	"Cream", maximum: 2 ml "Free oil", maximum: 0 ml
Note: In applying MT 36.3, tests after 24 h are required only where results at 2 h are in doubt.	

3.2 **Persistent foam** (MT 47.2, CIPAC Handbook F, p. 152, 1995) (Note 2)

Maximum: 10 ml after 1 min.

4 Storage Stability

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

After storage at 0 ± 2°C for 7 days, the volume of solid and/or liquid which separates shall not be more than 0.3 ml.

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 3) and the formulation shall continue to comply with the clause for:

- emulsion stability and re-emulsification (3.1)

Note 1 If the buyer requires both g/kg and g/l at 20ºC, then in case of dispute the analytical results shall be calculated as g/kg.

Note 2 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 3 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.

FLUSILAZOLE EMULSION, OIL IN WATER

FAO specification 435/EW (April 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 (435/2007). 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 (435/2007), as PART TWO, forms an integral part of this publication.

1 Description

The formulation shall consist of a white to off-white emulsion of technical flusilazole, complying with the requirements of FAO specification 435/TC (April 2008), in an aqueous phase together with suitable formulants. After gentle agitation, the formulation shall be homogeneous (Note 1) and suitable for dilution in water.

2 Active Ingredient

2.1 **Identity tests** (435/EW/(M)/2, CIPAC Handbook H, p. 177, 1998)

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

2.2 **Flusilazole content** (435/EW/(M)/3, CIPAC Handbook H, p. 177, 1998)

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

Declared content g/kg or g/l at 20 ± 2ºC	Tolerance
Above 25 up to 100	± 10% of the declared content
Above 100 up to 250	± 6% of the declared content
Note: the upper limit is included in each range	

3 Physical properties

3.1 **Pourability** (MT 148.1, CIPAC Handbook J, p. 133, 2000)

Maximum “residue”: 3.5%.

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

3.2 **Emulsion stability and re-emulsification** (MT 36.3, CIPAC Handbook K, p.137, 2003)

The formulation, when diluted at 30 ± 2ºC (Note 3) with CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of stability, MT 36.3
0 h	Initial emulsification complete
0.5 h	"Cream", maximum: 0 ml
2.0 h	"Cream", maximum: 0 ml "Free oil": maximum: 0 ml
24 h	Re-emulsification complete
24.5 h	"Cream", maximum: 2 ml "Free oil": maximum: 0 ml
Note: in applying MT 36.3, tests after 24 h are required only where results at 2 h are in doubt.	

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

Maximum: 10 ml after 1 min.

4 Storage stability

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

After storage at 0 ± 2°C for 7 days, no separation of particulate or oily matter shall be visible after gentle agitation.

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 6) and the formulation shall continue to comply with the clause for:

- emulsion stability and re-emulsification (3.2)

Note 1 All physical and chemical tests listed in this specification are to be performed with a laboratory sample taken after the recommended homogenization procedure.

Before sampling to verify the formulation quality, the commercial container must be inspected carefully. On standing, emulsions may develop a concentration gradient, which could even result in the appearance of a clear liquid on the top (sedimentation of the emulsion) or on the bottom (creaming up of the emulsion). Therefore, before sampling, the formulation must be homogenized 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.

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

Note 3 The formulation should be tested at the highest and lowest rates of use recommended by the supplier

Note 4 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 5 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

FLUSILAZOLE

FLUSILAZOLE

FAO/WHO EVALUATION REPORT 435/2007

Recommendations

The Meeting recommended that:

(i) the existing FAO specifications for flusilazole TC, WG, EC and EW should be withdrawn;

(ii) the specifications for flusilazole TC, EC, EW, proposed by DuPont Crop Protection (USA), as amended, should be adopted by FAO.

Appraisal

The Meeting considered data on flusilazole, provided by DuPont Crop Protection (USA), in support of proposed a revision of existing (1997) full FAO specifications for flusilazole TC, EC and EW. The existing FAO full specification for flusilazole WG was not supported in the revision. The data submitted were in accordance with the requirements of the FAO/WHO Manual (FAO/WHO 2006).

Flusilazole is a fungicide which is not under patent.

Flusilazole was included in the Annex I of EU Council Directive 91/414/EEC in December 2006. It has been subjected to periodic re-evaluation by the FAO/WHO JMPR (JMPR 2007), which established an ADI of 0-0.007 mg/kg bw/d and an ARfD of 0.02 mg/kg bw. Its WHO hazard classification is class III, 'slightly hazardous' (WHO, 2005).

Flusilazole is a white, crystalline solid of low vapour pressure. It is very weakly basic (pKa 2.5) but its water solubility (which is low) and octanol/water partition coefficient are unaffected by pH in the range 5-9. Flusilazole is stable to hydrolysis at pH 5, 7 and 9 at 25°C. In simulated sunlight very slow photolysis occurred (half-life 60-80 days at pH 7) but this was not evident in natural sunlight.

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on all impurities present at or above 1 g/kg and their manufacturing limits in the TC. Mass balances were 98.87-99.20%. These data, together with the hazard data also provided, were confirmed as identical to those evaluated for registration of flusilazole in Germany (Steer 2007).

The Meeting requested further information on the identity and maximum limit of an impurity which occurred at much lower values in the five batches than limit in the manufacturing specification. The manufacturer explained that it is actually a mixture of four components. The Meeting also requested clarification of the identity and levels of three other impurities, listed in the manufacturing specification (<0.1 g/kg) but which did not occur in the 5-batch data. The manufacturer explained that the limits in the specification were established using data from 20 years of manufacture, while the five batches provided represented the current production. Although data on such low-level impurities are not strictly required by the JMPS, the manufacturer had included them in order to be consistent with the information provided to regulatory authorities.

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

The Meeting considered aspects of the proposed specifications.

TC. The existing (1997) specification included a clause to limit material insoluble in acetone. The manufacturer explained that this was really a process monitoring specification, unrelated to relevant impurities as presently defined by the JMPS. The proposed new specification described the TC as a white crystalline solid, whereas the existing specification described it as tan to light brown, presumably reflecting an improvement in product purity although the lower limit of 925 g/kg remained unchanged. The Meeting agreed with the proposed specification.

EC and EW. The existing specifications included clauses to limit the pH range to 3 to 7 and the manufacturer proposed that the range should be pH 4 to 9. Noting that flusilazole is very stable to hydrolysis, the Meeting questioned the need for such a clause and the manufacturer agreed to its deletion.

The proposed 95% limits for stability at elevated temperature were slightly lower than the 97% in the existing specifications.

EC. The Meeting noted that the proposed limits for emulsion stability (0, 0 and 2 ml at 0.5, 2.0 and 24.5 h, respectively) represented a considerable improvement on those in the existing specification (5, 6 and 5 ml at 0.5, 2.0 and 24.5 h, respectively).

Although the existing specification included no clause for persistent foam, this was included in the proposed specification (in accordance with the guideline given in the FAO/WHO manual) and the limit of 10 ml after 1 min was well within the acceptable range.

EW. The Meeting noted that the proposed limit for pourability, 3.5%, was slightly higher than the 2.5% given in the existing specification.

The Meeting noted that the proposed limits for cream in the test for emulsion stability (0 ml at 2.0 and 24.5 h) were lower those of the existing specification (1 ml at 2.0 and 24.5 h).

The identity of flusilazole is determined by capillary GC retention time and by its IR spectrum. The capillary GC-FID methods for determination of flusilazole in TC, EC and EW are full CIPAC methods. Test methods for determination of physico-chemical properties of the technical active ingredient and formulations were OECD and CIPAC, as indicated in the specifications.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 435/2007

Uses

Flusilazole is a fungicide with curative and preventative activity against many pathogens of crop plants. It is used as a whole plant spray treatments in agriculture, horticulture and viticulture for control of diseases such as eyespot, mildew and rust of cereals; *Cerocspora* and rust of sugar beet; leaf spots of oilseed rape; scab and mildew of pome and stone fruit; mildew and black rot of grapes; and sigatoka disease of bananas.

Identity of the active ingredient

ISO common name

flusilazole (BSI, ANSI, E-ISO)

Chemical name(s)

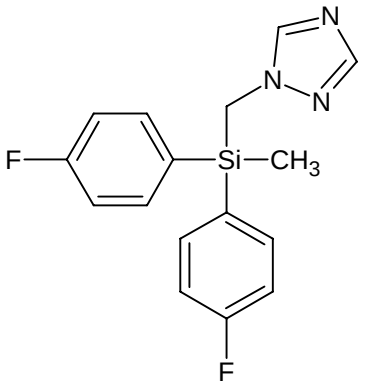
IUPAC bis (4-fluorophenyl)(methyl)(1*H*-1,2,4-triazol-1-ylmethyl)silane

CAS 1-[[bis(4-fluorophenyl)methylsilyl]methyl]-1*H*-1,2,4-triazole

Synonyms

DPX-H6573
IN-H6573

Structural formula



Molecular formula

$C_{16}H_{15}F_2N_3Si$

Relative molecular mass

315.4

CAS Registry number

85509-19-9

CIPAC number

435

Identity tests

Capillary GC retention time; IR spectrum

Physico-chemical properties of flusilazole

Table 1. Physico-chemical properties of pure flusilazole

Parameter	Value(s) and conditions	Purity %	Method	Reference
Vapour pressure	3.9×10^{-5} Pa at 25°C (extrapolated)	99	Gas saturation method, USEPA Pesticide Assessment Guidelines Subdivision D, 63-9	AMR 1201-88
Melting point	53.2 ± 0.1°C	99	OECD Method 102, determination of melting point/melting range method, USEPA OPPTS 830.7200	DuPont-2664
Decomposition temperature	288 ± 6.0°C	99	OECD Method 102, determination of melting point/melting range method, USEPA OPPTS 830.7200	DuPont-2664
Relative Density	1.30 g/ml at 20°C	98.8	OECD 109, pycnometer method, OPPTS 830.7300	DuPont-2665
Solubility in water	4.02×10^{-2} g/l at 20°C pH = 6.25 (de-ionized water)	99	OECD 105, shake flask method, OPPTS 830.7840	DuPont-2666
Solubility in organic solvents at 20°C	*n*-heptane = 6.713 ± 0.1 mg/ml acetone, ethyl acetate, dichloromethane, toluene, *n*-octanol, *o*-xylene: >250 mg/ml	98.2	OECD 105, shake flask method and preliminary solubility test; EEC A.6, OPPTS 830.7840	DuPont-16267
Octanol/water partition coefficient	log K_{ow} = 3.81 at 20°C pH 5 log K_{ow} = 3.87 at 20°C pH 7 log K_{ow} = 3.81 at 20°C pH 9	99	OECD 107, shake flask method, OPPTS 830.7550	DuPont-2663
Hydrolysis characteristics	Stable at pH 5, 7 and 9 at 25°C Stable at pH 5, 7 and 9 at 25°C	99, (triazole label) 99, (phenyl label)	USEPA pesticide assessment guidelines subdivision D, series 161-1	AMR 159-83
Photolysis characteristics	In simulated sunlight at pH 7, slow degradation with 60-80 days half-life In natural sunlight, no photo-degradation detected with either label	99, (triazole label) 99, (phenyl label)	USEPA pesticide assessment guidelines subdivision D, series 161-2 USEPA pesticide assessment guidelines subdivision D, series 161-2	AMR 393-85 AMR 1236-88
Dissociation characteristics	pKa = 2.5 ± 0.1	99	OPPTS 830.7370	H6573.B

Table 2. Physico-chemical properties of flusilazole 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 98.87–99.20%.
Declared minimum flusilazole content	925 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	Data not available

Hazard summary

Flusilazole was evaluated for toxicology by the FAO/WHO JMPR in 1989 and 1995; for residues in 1989, 1990, 1991 and 1993; and was subjected to periodic re-evaluation scheduled for 2007. The 2007 JMPR established an ADI of 0-0.007 mg/kg bw/d and an ARfD of 0.02 mg/kg bw (JMPR 2007).

The WHO hazard classification for flusilazole is class III, 'slightly hazardous' (WHO 2004).

Flusilazole was included in the Annex I of EU Council Directive 91/414/EEC in December 2006.

Formulations

The main formulation types available are EC and EW. These formulations are registered and sold in many countries throughout the world.

Methods of analysis and testing

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, EEC, EPA, OPPTS and ASTM, while those for the formulations were EEC and CIPAC.

Methods for determination of active ingredient identity are full CIPAC methods. Flusilazole is determined by capillary GC-FID with benzophenone as internal standard.

Containers and packaging

No extraordinary container or package issues need to be considered.

Expression of the active ingredient

The active ingredient is expressed as flusilazole, in g/kg or in g/l.

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 flusilazole having impurity profiles similar to those referred to in Table 2, above.

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

Species	Test	Duration and conditions, purity	Result	Reference
Rat, Cr1:CD®, (m,f)	Acute oral	Single dose followed by 14-d observation. Doses: males 200 to 1300 mg/kg; females 500 to 1500 mg/kg. OECD 401, EEC B.1; USEPA subdivision F, 81-1. Flusilazole TC 97.0% purity	LD_{50} = 1110 mg/kg (m) 674 mg/kg (f)	Dupont-3749
Rabbit, New Zealand White (m,f)	Acute derma	Single dose followed by 14-d observation. Dose 2000 mg/kg. OECD 402, EEC B.3; USEPA subdivision F, 81-2. Flusilazole TC 95.5 % purity)	LD_{50} >2000 mg/kg	HLO-288-83
Rat, Cr1:CD® (m,f)	Acute Inhalation	4-h inhalation followed by 14-d observation. Doses 6.4 to 7.7 mg/l OECD 401, EEC B.1; USEPA subdivision F, 81-1. Flusilazole TC 92.7% and 95.1% purity	LC_{50} >6.4 mg/l*	HLR-1-85
Guinea pig, Duncan-Hartley Albino (m,f)	Acute skin irritation	48-h. OECD 404; USEPA subdivision F, 81-5 and 81-6 Flusilazole TC 90% purity	Mild skin irritant	HLR-626-82 RE
Rabbit, New Zealand White (m,f)	Acute eye irritation	72-h. EEC B.5 of Directive 92/69/EEC; OECD 405; MAFF Japan 4200; USEPA subdivision F, Series 81-4 Flusilazole analytical standard 99% purity	Non-irritant	Dupont-1300
Guinea pig, Duncan-Hartley Albino (m,f)	Acute skin sensitization	48-h. EEC B.6 of Directive 92/69/EEC ; USEPA subdivision F 81-6; Buehler method Flusilazole TC 97.7% purity	Not a sensitizer	HLR-34-88

* The LC_{50} could not be calculated from the data available: it was >6.4 mg/l but evidently <7.7 mg/l. For classification purposes, the acute inhalation hazard is represented by >6.4 mg/l.

Table B. Toxicology profile of technical flusilazole (sub-acute to chronic)

Species	Test	Duration and conditions, purity	Result	Reference
Rabbit, New Zealand white (m,f)	21-dose dermal	21-d, doses 0 to 200 mg/kg bw/d. EEC B.28; USEPA subdivision F, 82-2. Flusilazole TC 94.8% purity	NOEL (skin irritation) = 5 mg/kg bw NOAEL (systemic) = 200 mg/kg bw**	HLR-744-86
Rat, Cr1:CD® (m,f)	Oral	90-d, doses 0 to 750 ppm. Directive 87/302/EEC part B, 90-d oral rodent. Flusilazole TC 96.7% purity	NOEL and NOAEL = 125 ppm 9 mg/kg/ bw (m) 11 mg/kg/ bw (f)	HLR-483-83

** Only minimal clinical signs observed at the highest dose tested, 200 mg/kg bw/d: diarrhoea in 1/10 males, lung noise in 1/10 females. No clinical effects or histopathology considered to be adverse, hence systemic NOAEL = 200 mg/kg bw.

Table B. Toxicology profile of technical flusilazole (sub-acute to chronic)

Species	Test	Duration and conditions, purity	Result	Reference
Mouse, Cr1:CD-1® (ICR) (m,f)	Oral (#1)	90-d, doses 0 to 1000 ppm, USEPA subdivision F, 82-1 part B, 90-d oral rodent; Directive 87/302/EEC, part B, 90-d oral rodent Flusilazole TC 96.7% purity	NOEL and NOAEL = 75 ppm (m) 25 ppm (f) 9 mg/kg/ bw (m) 12 mg/kg bw (f)	HLR-341-83
Dog, beagle (m,f)	Oral	90-d, doses 0 to 750/500 ppm. Directive 87/302/EEC, part B, 90-d oral non-rodent Flusilazole TC 93% purity	NOEL = 25 ppm (m,f) NOAEL = 25 ppm (m) 125 ppm (f) 0.9 mg/kg bw (m) 4.3 mg/kg bw (f)	HLR-461-83
Rat, Cr1:CD® (m,f)	Long-term feeding and 2-generation reproduction (#1)	2-year, doses 0 to 250 ppm. Directive 87/302/EEC, part B, combined chronic toxicity and carcinogenicity test. Two-generation reproduction study added to protocol. Flusilazole TC 95.6% purity	Systemic NOAEL = 50 ppm 2.0 mg/kg bw (m) 2.6 mg/kg bw (f) Not carcinogenic	HLR-32-86RV1
Rat, Cr1:CD® (m,f)	Long-term feeding study (#2)	2 year, doses 0 to 750 ppm. Directive 87/302/EEC, part B, combined chronic toxicity and carcinogenicity test. Acetone solution containing 62.6% technical flusilazole, 95% purity	Bladder transitional cell tumours and Leydig cell adenomas observed. NOAEL (neoplasms) = 125 ppm (m) 5.03 mg/kg bw = 375 ppm (f) 20.5 mg/kg bw	HLR-527-92 RV1
Mouse, Cr1:CD-1® (ICR) (m,f)	Long-term feeding study (#1)	18-month, doses 0 to 200 ppm. Directive 87/302/EEC, part B, carcinogenicity test Flusilazole TC 93% and 95.6% purity	Systemic NOAEL = 25 ppm (m,f) 3.4 mg/kg bw (m) 4.6 mg/kg bw (f) Not carcinogenic	HLR-278-85
Mouse, Cr1:CD-1® (ICR) (m,f)	Long-term feeding study (#2)	18-month, doses 0 to 1000 ppm (m) 0 to 2000 ppm (f). Directive 87/302/EEC, part B, carcinogenicity test. Acetone solution containing 62.6% technical flusilazole, 95% purity	Liver tumours observed. NOAEL (neoplasms) = 500 ppm (m) 14.3 mg/kg bw = 100 ppm (f) 4.38 mg/kg bw	HLR-35-92
Dog, beagle (m,f)	Long-term feeding study in non-rodent	1-year, doses 0 to 75 ppm. Directive 87/302/EEC, part B, chronic toxicity test; OECD 408 Flusilazole TC 92.4% purity	NOAEL = 20 ppm 0.7 mg/kg bw NOEL = 5 ppm 0.2 mg/kg bw, based on minimal, non-adverse effects on liver histopathology at 20 ppm.	HLR-461-85
Rat, Cr1:CD® (f)	Teratogenicity (dietary administration)	21-d, doses 0 to 900 ppm. OECD 414; Directive 87/302/EEC, part B, teratogenicity in rodents Flusilazole TC 94.8% purity	NOAEL = 50 ppm 4.6 mg/kg bw (maternal and developmental toxicity)	HLR-431-84, HLR-431-84 SU1

Table B. Toxicology profile of technical flusilazole (sub-acute to chronic)

Species	Test	Duration and conditions, purity	Result	Reference
Rat, Cr1:CD® (f)	Teratogenicity (oral gavage)	21-d, doses 0 to 250 mg/kg bw/d. OECD 414; Directive 87/302/EEC, part B, teratogenicity in rodents. Flusilazole TC 93% purity	Maternal NOAEL = 10 mg/kg bw Foetal NOAEL <10 mg/kg bw Malformation at maternally toxic dose. Foetal variations and toxicity at LOAEL.	HLR-444-83
Rat, Cr1:CD® (f)	Teratogenicity (oral gavage)	21-d, doses 0 to 250 mg/kg bw/d. OECD 414; Directive 87/302/EEC, part B, teratogenicity in rodents. Flusilazole TC 95.6% purity	Maternal NOAEL = 10 mg/kg bw Foetal NOAEL = 2 mg/kg bw Malformation at maternally toxic dose. Foetal variations and toxicity at LOAEL.	HLR-142-84
Rat, Cr1:CD® (f)	Teratogenicity (oral gavage)	22-d, doses 0 to 50 mg/kg bw/d. OECD 414; Directive 87/302/EEC, part B, teratogenicity in rodents Flusilazole TC 94.8% purity	Maternal NOAEL = 10 mg/kg bw Foetal NOAEL = 2 mg/kg bw No malformations. Foetal variations and toxicity at LOAEL.	Dupont-2287
Rat, Cr1:CD® (f)	Teratogenicity (oral gavage)	22-d, doses 0 to 100 mg/kg bw/d. OECD 414; Directive 87/302/EEC, part B, teratogenicity in rodents, modified to include additional maternal toxicity measurements. Flusilazole TC 94.8% purity	Maternal NOAEL = 2 mg/kg bw Foetal NOAEL = 2 mg/kg bw Maternal and foetal NOEL = 0.5 mg/kg bw Malformation in presence of maternal effects. Foetal variations and toxicity at LOAEL.	HLR-654-85 RV1
Rat, Cr1:CD® (f)	Teratogenicity (dermal administration)	21-d, doses 0 to 250 mg/kg/d. OECD 414; Directive 87/302/EEC, part B, teratogenicity in rodents, modified to include additional maternal toxicity measurements. Flusilazole TC 95% purity	Maternal NOAEL = 2 mg/kg bw Foetal NOAEL = 2 mg/kg bw No malformations. Foetal variations and toxicity at LOAEL.	HLO-1998-01504
Rabbit, New Zealand white (f)	Teratogenicity (dietary administration)	29-d, doses 0 to 1200 ppm. OECD 414; Directive 87/302/EEC, part B, teratogenicity in non-rodents	Maternal NOAEL = 21.2 mg/kg bw Foetal NOAEL = 2.8 mg/kg bw No malformations. Foetal toxicity at LOAEL.	HLR-337-85

Table B. Toxicology profile of technical flusilazole (sub-acute to chronic)

Species	Test	Duration and conditions, purity	Result	Reference
Rabbit, New Zealand white, (f)	Teratogenicity (oral gavage)	29-d, doses 0 to 12 mg/kg bw/d. OECD 414; Directive 87/302/EEC, part B, teratogenicity in non-rodents. Flusilazole TC 94.8% purity	Maternal NOAEL >12 mg/kg bw Foetal NOAEL >12 mg/kg bw No malformations or effects at highest dose tested.	HLR-333-84
Rabbit, New Zealand white (f)	Teratogenicity (oral gavage)	29-d, doses 0 to 35 mg/kg bw/d. OECD 414; Directive 87/302/EEC, part B, teratogenicity in non-rodents. Flusilazole TC 94.8% purity	Maternal NOAEL = 12 mg/kg bw Foetal NOAEL = 12 mg/kg bw No malformations. Maternal and foetal toxicity at LOAEL.	HLR-669-85
Rabbit, New Zealand white (f)	Teratogenicity (oral gavage)	29-d, doses 0 to 30 mg/kg bw/d. OECD 414; Directive 87/302/EEC, part B, teratogenicity in non-rodents. Flusilazole TC 94.9% purity	Maternal NOAEL = 7 mg/kg bw Foetal NOAEL >30 mg/kg bw No malformations. Maternal and foetal toxicity at LOAEL.	HLR-216-90
Rat, Cr1:CD® (m,f)	Multi-generation study	2-year, doses 0 to 250 ppm. USEPA assessment guideline subdivision F, series 83-4; Directive 87/302/EEC, part B. Two-generation reproductive toxicity test. Flusilazole TC 94% purity	NOAEL = 50 ppm (R) 5 ppm (P) 0.35 mg/kg/d (m,f) (P) 2.9 mg/kg/d (m) (R) 3.5 mg/kg/d (f) (R) No effects on fertility. Reduced litter size and offspring body weights, increased gestation length. [R = reproductive toxicity; P = parental (maternal) toxicity]	HLR-424-90

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

Species	Test	Duration and conditions	Result	Reference
Salmonella typhimurium TA100, TA1535, TA97, TA98[c]	*In vitro* bacterial mutagenicity (Ames)	0 to 250 µg/plate in DMSO[b] (with and without S-9[a]), purity 97.7%	negative	HLR 59-88
Salmonella typhimurium TA100[d], TA1535, TA97, and TA98	*In vitro* bacterial mutagenicity (Ames)	0 to 300 µg/plate in acetone (with and without S-9[a]), purity 95.0%	negative	HLR-33-91
Chinese hamster ovary cells[e]	*In vitro* mammalian cell mutagenicity (CHO/HGPRT)	0 to 0.50 mM in DMSO[b] (with and without S-9[a]), purity 95.5%	negative	HLR-449-83
Human lymphocytes[f]	*In vitro* chromosome aberration (clastogenicity)	0 to 100 µg/ml in DMSO[b] (with and without S-9[a]), purity 94.8%	negative	HLR- 745-86, HLR-745-86 Rev1
Rat bone marrow[g]	*In vivo* chromosome aberration in somatic cells	Rat (m,f): 0, 50 150, 500 mg/kg bw in corn oil, purity not stated	negative	HLO-480-83
Mouse bone marrow[h]	*In vivo* chromosome aberration in somatic cells	Mouse (m,f): 0, 375 mg/kg bw in corn oil, purity 92.5%	negative	HLO-437-84
Rat primary hepatocytes[i]	*In vitro* unscheduled DNA synthesis	1×10^{-5} to 1.1×10^{2} mM in DMSO, purity 95.5%	negative	HLR-209-83, HLR-209-83 SU1

a. S-9: rat liver supernatant (centrifuged at 9000 g) from Sprague-Dawley rats pre-treated with Aerochlor® 1254.
b. DMSO: dimethylsulfoxide.
c. Test conducted in duplicate; TA 98 utilized for cytotoxic concentration screen; positive controls were : 2-aminoanthracene (2AA); sodium azide (NAAZ); 2-nitrofluorene (2NF); acridine (ICR-191).
d. Test conducted in duplicate; TA 100 utilized for cytotoxic concentration screen; positive controls were: 2AA; NAAZ; 2NF; ICR-191.
e. Tests conducted without S9 in 4 trials and with S9 in 3 trials; positive controls were methanesulfonic acid ethyl ester (EMS) and 9,10-dimethylbenzanthracene (DMBA).
f. Lymphocytes from 2 healthy volunteers in 2 trials. Positive control mitomycin C (MMC) and cyclophosphamide (CP).
g. Purity of test material not known, assumed to be 100%. Twenty male and female SD rats administered 0, 50, 150, or 500 mg/kg bw; bone marrow harvested 6, 12, 24, 48 h after dosing. Positive control with cyclophosphamide-dosed animals. Minimal clinical signs of toxicity observed at 500 mg/kg bw after 24 h and had reversed in most animals by 48 h.
h. Fifteen male and female CD-1 mice administered flusilazole in corn oil at 375 mg/kg bw. At 24, 48 and 72 h post dosing, bone marrow collected from 5 mice/sex/dose, slides prepared and evaluated for relative proportions of polychromatic erythrocytes with micronuclei.
i. Livers from Sprague-Dawley rats perfused, cells harvested and cultured. Two trials evaluated. Incorporation of ^{3}H-thymidine was monitored as an indicator of DNA repair/synthesis. Criterion for slide evaluation: increase above background in silver grain counts in developed film emulsion in 25 randomly selected nuclei. Positive control DMBA (1 mM).

Table D. Ecotoxicology profile of technical flusilazole

Species	Test	Duration and conditions	Result	Reference
Lepomis macrochirus (bluegill sunfish)	Acute toxicity	96-h, static. No regulatory guidelines cited. Flusilazole TC 95.5% purity	LC_{50} >1.71 mg/l NOEC = 0.52 mg/l	HLR-133-83
Oncorhynchus mykiss (rainbow trout)	Acute toxicity	96-h, static. No regulatory guidelines cited. Flusilazole TC 95.5% purity	LC_{50} = 1.2 mg/l NOEC = 0.23 mg/l	HLR-108-83
Daphnia magna (water flea)	Acute toxicity	48-h, static. No regulatory guidelines cited. Flusilazole TC 95.5% purity	EC_{50} = 3.4 mg/l NOEC = 1.8 mg/l	HLR-111-83
Daphnia magna (water flea)	Chronic toxicity	21-d, flow-through. USEPA pesticide assessment guidelines, subdiv. E, 72-4 Flusilazole TC 94.85% purity	NOEC = 0.27 mg/l (mean measured concentration) LOEC = 0.57 mg/l	HLR-579-86
Pimephales promelas (fathead minnow)	Chronic toxicity	252-d, flow-through. USEPA pesticide assessment guidelines, subdiv. E, 72-5 Flusilazole TC 94.7% purity	NOEC = 0.025 mg/l (mean measured concentration) MATC = 0.033 mg/l	HLO-606-85
Selenastrum capricornutum (green alga)	Growth and reproduction	120-h. OECD 201; FIFRA, Subdivision J, 122-2. Flusilazole TC 97% purity	EC_{50} = 6.4 mg/l NOEC = 2.0 mg/l	DPT/171 F871605
Eisenia foetida (earthworm)	Acute toxicity	14-d. OECD 207; Directive EEC 79/831. Flusilazole TC 95%, 99.8%, 97.7% purity	LC_{50} >88 mg/kg NOEC >100 mg/kg	ABM 86-1, ABM 86-1 Rev. 1, ABM 86-1 SU1
Apis mellifera (honey bee)	Acute contact toxicity	48-h. FIFRA subdivision L, series 141-1, hazard evaluation: nontarget insects Flusilazole TC 95.6% purity	LD_{50} >165 µg/bee	ABM-84-6
Anas platyrhynchos (mallard duck)	Acute oral toxicity	14-d. Pesticide assessment guidelines, FIFRA subdivision E, 71-1; hazard evaluation, wildlife & aquatic organisms Flusilazole TC 99% purity	LD_{50} >1590 mg/kg bw NOEL = 398 mg/kg bw	HLO-424-83
Colinus virginianus (bobwhite quail)	Dietary toxicity	5-d. Pesticide assessment guidelines, FIFRA subdivision E, 71-2; hazard evaluation, wildlife & aquatic organisms. Flusilazole TC 99% purity	LC_{50} > 5620 ppm NOEL >562 ppm	HLO-386-83
Anas platyrhynchos (mallard duck)	Dietary toxicity	5-d. Pesticide assessment guidelines, FIFRA subdivision E, 71-2; hazard evaluation, wildlife & aquatic organisms Flusilazole TC 99% purity	LC_{50} = 1584 ppm NOEC <562 ppm	HLO-385-83

ANNEX 2. REFERENCES

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