FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

CYROMAZINE

N-cyclopropyl-1,3,5-triazine-2,4,6-triamine

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

INTRODUCTION

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

From 1999, the development of FAO specifications has followed 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 plant protection product reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are to be provided by the manufacturer(s) according to the requirements of Appendix A, annex 1 or 2 of the "Manual on the development and use of FAO and WHO specifications for pesticides" 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/agriculture/crops/core-themes/theme/pests/pm/jmps/en/

PART ONE

SPECIFICATIONS

CYROMAZINE

CYROMAZINE

INFORMATION

ISO common name

Cyromazine (E-ISO, F-ISO, BSI, ANSI)

Synonyms

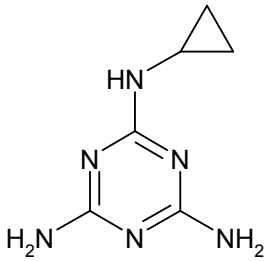
none

Chemical name(s)

IUPAC *N*-cyclopropyl-1,3,5-triazine-2,4,6-triamine

CA *N*-cyclopropyl-1,3,5-triazine-2,4,6-triamine

Structural formula



Molecular formula

$C_6H_{10}N_6$

Relative molecular mass

166.2

CAS Registry number

66215-27-8

CIPAC number

420

Identity tests

HPLC retention time, GC retention time and IR spectrum

CYROMAZINE TECHNICAL MATERIAL

FAO specification 420/TC (March 2010)*

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 (420/2007). It should be applicable to relevant products of 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 the products of other manufacturers. The evaluation report (420/2007) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist of cyromazine together with related manufacturing impurities, in the form of white to beige powder, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (420/TC/M-, CIPAC Handbook M, p. 54, 2009)

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

2.2 **Cyromazine content** (420/TC/M-, CIPAC Handbook M, p. 54, 2009)

The cyromazine content shall be declared (not less than 950 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/pm/jmps/ps/en/.

CYROMAZINE SOLUBLE CONCENTRATE

FAO Specification 420/SL (March 2010)*

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 (420/2007). 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 (420/2007), as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of technical cyromazine, complying with the requirements of FAO specification 420/TC (March 2010), together with any other necessary formulants. It shall be in the form of a clear or opalescent liquid, free from visible suspended matter and sediment, to be applied as a true solution of the active ingredient in water.

2 Active ingredient

2.1 Identity tests (420/SL/M-, CIPAC Handbook M, p. 54, 2009)

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

2.2 Cyromazine content (420/SL/M-, CIPAC Handbook M, p. 54, 2009)

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

Declared content in g/kg or g/l at 20 ± 2°C	Tolerance
above 25 up to 100 Note: the upper limit is included in the range	± 10% of the declared content

3 Physical properties

3.1 Solution stability (MT 41, CIPAC Handbook F, p.131, 1995)

The formulation, after the stability test at 54°C (see clause 4.2) and following dilution (Note 2) with CIPAC standard water D and standing at 30 ± 2°C for 18 h, shall give a clear or opalescent solution, free from more than a trace of sediment and visible solid particles. Any visible sediment or particles produced shall pass through a 45 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/pm/jmps/ps/en/.

3.2 **Persistent foam** (MT 47.2, CIPAC Handbook F, p.152, 1995) (Note 3)

Maximum: 30 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 4).

Note 1 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 2 The concentration for the test should not be higher than the highest concentration recommended in the instructions for use.

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

Note 4 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

CYROMAZINE WATER SOLUBLE POWDER

FAO Specification 420/SP (March 2010)*

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 (420/2007). 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 (420/2007), as PART TWO, forms an integral part of this publication.

1 Description

The formulation shall consist of an emulsion of technical cyromazine, complying with the requirements of FAO specification 420/TC (March 2010), together with any necessary formulants. It shall be in the form of a fine powder free from visible extraneous matter and hard lumps, and to be applied as a true solution of the active ingredient after solution in water, but which may contain insoluble inert ingredients.

2 Active ingredient

2.1 **Identity tests** (420/SP/M-, CIPAC Handbook M, p. 54, 2009)

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

2.2 **Cyromazine content** (420/SP/M-, CIPAC Handbook M, p. 54, 2009)

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

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

3 Physical properties

3.1 **Wettability** (MT 53.3, CIPAC Handbook F, p.164, 1995)

The formulation shall be completely wetted in 1 min. without 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/agriculture/crops/core-themes/theme/pests/pm/jmps/ps/en/.

3.2 **Degree of dissolution and solution stability** (MT 179, CIPAC Handbook H, p.307, 1998) (Note 1)

Residue of formulation retained on a 75 µm test sieve after dissolution in CIPAC Standard Water D at 30 ± 2°C:
Maximum: 0.5% after 5 min.
Maximum: 0.5% after 18 hours.

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

Maximum: 50 ml after 1 min.

4 Storage stability

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

After storage 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 clauses for:

- wettability (3.1),
- degree of dissolution and solution stability (3.2).

Note 1 This test will detect coarse particles which arise from impurities in the technical material and/or are present as inert ingredients, which could cause blockage of nozzles or filters in the application equipment.

Note 2 The mass of the sample to be used in the test should be specified at 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.

PART TWO

EVALUATION REPORTS

CYROMAZINE

CYROMAZINE

FAO/WHO EVALUATION REPORT 420/2007

Recommendations

The meeting recommended that:

(i) the specifications for cyromazine TC, SL and SP (active ingredient content in the range 100-750 g/kg), proposed by Syngenta Crop Protection AG, should be adopted by FAO.

(ii) the specifications for cyromazine TC and SP (active ingredient content 750 g/kg), proposed by Syngenta Crop Protection AG, should be adopted by WHO, subject to satisfactory completion of the WHOPES evaluation.

Appraisal

The Meeting considered data for cyromazine, submitted by Syngenta Crop Protection AG in support of new FAO specifications (TC, SL, SP) and new WHO specifications (TC, SP).

Cyromazine was evaluated by the FAO/WHO JMPR in 1990, 1991, 1992, 2006 (JMPR 2006), by the USA EPA in 1985 and 2003 (US EPA 2003) and most recently by the EU in 2009 (EU 2009). It is no longer under patent.

Cyromazine is a crystalline solid which is moderately soluble in water and methanol but has low solubility in organic solvents of low polarity. It is not susceptible to hydrolysis (in the pH range 4-9) or photolysis. It is moderately basic, with pKa 5.2.

The Meeting was provided with commercially confidential information of the manufacturing process for cyromazine, the manufacturing specifications for the TC and 5-batch analytical data on the purity and impurities ≥1 g/kg. Mass balances were high (99.0-99.9%) and no unidentified impurities were detected. The manufacturer confirmed in writing that the data were identical to those submitted for registration in Japan but, for reasons beyond the control of FAO/WHO and the manufacturer, this was not confirmed independently. The manufacturer stated that the data package submitted to FAO and WHO would form the basis of all future submissions for registration/re-registration throughout the world.

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

Analytical methods for determination of cyromazine in the TC, SL and SP are full CIPAC methods, published in 2009. The content of cyromazine is determined by reversed-phase HPLC, using UV detection and external standardization.

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

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 420/2007

Uses

Cyromazine is an insect growth regulator, with contact action, interfering with moulting and pupation. It is used in agriculture, particularly on vegetables to control leaf-miners but also to treat manure to control flies. It is also intended for use in public health applications for vector control (against mosquitoes).

Identity of the active ingredient

ISO common name

Cyromazine (E-ISO, F-ISO, BSI, ANSI)

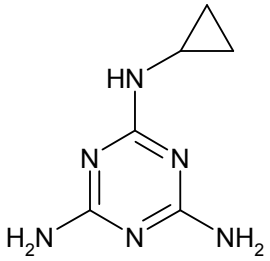
Synonyms

none

Chemical name(s)

IUPAC & CA: *N*-cyclopropyl-1,3,5-triazine-2,4,6-triamine

Structural formula



Molecular formula

$C_6H_{10}N_6$

Relative molecular mass

166.2

CAS Registry number

66215-27-8

CIPAC number

420

Identity tests

HPLC retention time, GC retention time and IR spectrum

Physico-chemical properties of cyromazine

Table 1. Physico-chemical properties of pure cyromazine

Parameter	Value(s) and conditions	Purity %	Method	Reference
Vapour pressure	4.48 x 10^{-7} Pa at 25°C (from fit of measurements at 89.8-170.0°C)	99.3	EEC A4	AG-87-36P
Melting point	223.2°C, with decomposition	99.2	EEC A1	60991
Solubility in water at 25°C	13 g/l at 25°C (pure water, pH 7.9) In buffered water: 8.0 g/l at pH 5.3 13 g/l at pH 7.1 13 g/l at pH 9.0	99.2 99.6	EEC A6	107935, EA-163050
Octanol/water partition coefficient at 25°C	log P_{OW} = -0.36 ± 0.012 at pH 5.4 -0.069 ± 0.009 at pH 7.0 -0.039 ± 0.009 at pH 9	99.6	OECD 107 EEC A8	EA-163050
Hydrolysis characteristics	No degradation was observed during 28 d at 30, 50 and 70°C at pH 5, 7 and 9, respectively.	97.2	In-house adaptation of USEPA guideline and OECD 101	17/79
Photolysis characteristics	No photochemical degradation expected as the molar extinction coefficient at 290 nm <<10 l/mol·cm A study in pH 7 buffer at 25°C under Xenon arc light showed practically no degradation	 99.2	In-house adaptation of OECD 101, USEPA FIFRA Subdiv. N, USEPA-540/9-82-021, Section 161-2 & USEPA 540/09-90-078	108953 99RF05
Dissociation characteristics	pK_a = 5.22 at 20°C Charge within the protonated molecule is resonant	99.6	OECD 112	AG-92-5P, PP92/5P:DCW

Table 2. Chemical composition and properties of technical cyromazine (TC)	
Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 99.0-99.9% and no unidentified impurities were reported.
Declared minimum cyromazine content	950 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 or boiling temperature range of the TC	Melting point: ~223°C, with decomposition. The melting point of the TC is similar to that of pure material, as the purity is high

Hazard summary

The WHO hazard classification of cyromazine is “unlikely to present any acute hazard in normal use” (WHO 2004).

The FAO/WHO JMPR established an ADI for cyromazine of 0-0.06 mg/kg bw/d and an acute RfD of 0.1 mg/kg bw (JMPR 2006).

In the EU, cyromazine does not have a hazard classification according to Regulation (EC) 1272/2008, because it is of low acute toxicity, it is not an irritant to skin or eye and has no sensitizing, genotoxic or carcinogenic potential (EU 2008).

Formulations and co-formulated active ingredients

The main formulation types available are SP (water soluble powder) and SL (soluble concentrate). These formulations are registered and sold in many countries in South America and Europe, as well as some countries in the Middle East, Asia and Africa.

Cyromazine is not co-formulated with other pesticides.

Methods of analysis and testing

The analytical methods for cyromazine (including identity tests) in TC, SL and SP are full CIPAC methods (CIPAC 2009). The content of cyromazine is determined by reversed-phase HPLC, using UV detection and external standardization.

Physical properties

The physical properties, the methods for testing them and the limits proposed for the EC and EW formulations comply with the requirements of the FAO/WHO 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 cyromazine.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

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

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

Species	Test	Duration and conditions	Result	Reference
Rat, Sprague-Dawley (f)	Acute oral	OPPTS 870:1100 (2002) ≅ OECD 425 (2001); single dose by oral gavage, 14-d observation; dose 2000 mg/kg bw; purity 97.2%	LD_{50} >2000 mg/kg bw (f)	PSL 15876
Rat, Sprague-Dawley (m,f)	Acute dermal	OPPTS 870:1200 (2002) ≅ OECD 402 (1987); single application, in place for 24 h, 14-d observation; dose 2000 mg/kg bw; purity 97.2%	LD_{50} >2000 mg/kg bw (m,f)	PSL 15877
Rat, HSD:SD (m,f)	Acute inhalation	92/69/EEC B.2 ≅ OECD 403 (1981) ≅ FIFRA § 81-3; single 4-h dose, 17-d observation. Dose 744 or 3600 mg/m^3; purity 96.5%	LC_{50} >3600 mg/m^3 (m,f)	0971-94
Rat, Alpk(APfSD) (m,f)	Acute inhalation	OPPTS 870:1300 (1998) ≅ OECD 403 (1981) ≅ 92/69/EEC B.2; single 4-h dose, 17-d observation; dose 2000 mg/m^3; purity 97.3%	LC_{50} >2000 mg/m^3 (m,f)	HR2504
Rabbit, NZ White (m,f)	Skin irritation	OPPTS 870:2500 (1998) ≅ OECD 404 (2002); dose ~0.5 g to shorn flank; purity 97.2%	Non-irritant	PSL 15879
Rabbit, NZ White (f)	Eye irritation	OPPTS 870:2400 (1998) ≅ OECD 405 (2002); dose 0.1 ml (0.06g) in one eye; purity 97.2%	Non-irritant	PSL 15878
Guinea pig, Himalayan Spotted (GOHI) (m,f)	Skin sensitization	96/54/EC B.6 ≅ OECD 406 (1992) ≅ OPPTS 870.2600. Induction (intradermal injection) day 1: i) 1:1 saline/FCA; ii) 5% cyromazine in vehicle; iii) 5% cyromazine in 1:1 saline/FCA. Topical induction day 8: dermal application of 75% cyromazine under occlusive dressing for 48 h. Challenge day 22: 50% cyromazine under occlusive dressing for 24 h. Purity 97.4%	Non-sensitizer	782627

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

Species	Test	Duration and conditions	Result	Reference
Rat (m,f)	90-d oral (feeding)	87/302/EEC B.26 ≅ OECD 408 (1981) ≅ FIFRA § 82-1 (study predated the guidelines but would have been compliant);doses 30, 300, 1000 or 3000 ppm; +4 week reversibility; purity 96.3%	NOAEL = 25 mg/kg bw/d (300 ppm) LOAEL = 79 mg/kg bw/d (1000 ppm) based on reduced body weight gain	382-052
Dog (m,f)	1-year oral (feeding)	87/302/EEC B.27 ≅ OECD 409 (1981) ≅ FIFRA § 82-1 (study predated the guidelines but would have been compliant); doses 0, 30, 300, 1000 or 3000 ppm; purity 96.3%	NOAEL = 34 mg/kg bw/d (1000 ppm) LOEL = 98 mg/kg bw/d (3000 ppm)	382-048
Dog (m,f)	Oral (feeding)	67/548/EEC B.30 ≅ OECD 452 (1981) ≅ FIFRA § 83-1(b); 1-year; doses 0, 50, 200, 800 or 3500 ppm; purity 97.5%	NOAEL = 5.74 mg/kg bw/d (200 ppm) (m) 24.9 mg/kg bw/d (800 ppm) (f) LOAEL = 22.8 mg/kg bw/d (800 ppm) (m) (haematology 110 mg/kg bw/d (3500 ppm) (f)	962001
Rabbit (m,f)	21-d percutaneous	92/69/EEC B9 ≅ OECD 410 (1992) ≅ FIFRA § 82-2; exposed 6-h/d, repeated 5x weekly for 3 weeks, daily observations ended 1 d after last exposure; doses 50, 500, 2000 mg/kg/d; purity 94.6%	NOAEL ≥2000mg/kg bw/d LOAEL >2000mg/kg bw/d	3805-85
Rat, (m,f)	28-d inhalation	92/69/EEC B.8 ≅ OECD 412 (1981); exposed nose-only to TC as aerosol 4-h daily for 28 consecutive days, additional control and highest dose groups also maintained for 3-week recovery period; doses 0, 58, 206 or 706 mg/m^3 air; purity 97.5%	NOAEL not determined LOAEL = 58 mg/m^3 (non-specific toxicity)	861472
Mouse (m,f)	24-month carcinogenicity and chronic toxicity	87/302/EEC B.32 ≅ OECD 451 (1981) ≅ FIFRA § 83-2 (study predated the guidelines but would have been compliant); dietary administration; doses 0, 50, 1000, 3000 ppm; purity 95.3 & 95.5%	NOAEL = 126 mg/kg bw/d (1000 ppm) LOAEL = 384 mg/kg bw/d (3000 ppm) based on body weight gain; no increase in neoplastic or pre-neoplastic lesions; not carcinogenic.	382-082

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

Species	Test	Duration and conditions	Result	Reference
Rat (m,f)	24-month carcinogenicity and chronic toxicity	87/302/EEC B.33 ≅ OECD 453 (1981) ≅ FIFRA § 83-5 (study predated the guidelines but would have been compliant); dietary administration; doses 0, 30, 300, 3000 ppm; additional groups in control and highest dose group were fed control diet for a four-week recovery period prior to termination after 1 year of dosing; purity 95.3 & 95.5%	NOAEL = 14.7 mg/kg bw/d (300 ppm) LOAEL = 156 mg/kg bw/d (3000 ppm) based on body weight gain. No increase in neoplastic or pre-neoplastic lesions. Not carcinogenic.	382-081
Rat (m,f)	Oral (feeding), 2-generation reproduction	87/302/EEC B.35 ≅ OECD 416 (1983) ≅ FIFRA § 83-4 (study predated the guidelines but would have been compliant); diet contained 0, 30, 1000 or 3000[1] ppm; purity 95.3%	NOAEL (maternal) = 2.0 mg/kg bw/d (30 ppm) NOAEL (offspring) = 65 mg/kg bw/d (1000 ppm) LOAEL (maternal) = 65 mg/kg bw/d (1000 ppm) LOAEL (offspring) = 215 mg/kg bw/d (3000 ppm) (pup weight)	382-086
Rat (f)	Teratogenicity	87/302/EEC B.31 ≅ OECD 414 (1981) ≅ FIFRA § 83-3 (study predated the guidelines but would have been compliant); dosed by gavage on days 6-19 (inclusive) of gestation; doses 0, 100, 300, 600 mg/kg bw/d; purity 96.3%	Cyromazine did not cause teratogenic effects. LOAEL = 300 mg/kg bw/d based on maternal & foetal weight and reduced ossification, clinical signs	382-070
Rabbit (f)	Teratogenicity	87/302/EEC B.31 ≅ OECD 414 (1981) ≅ FIFRA § 83-3 (study predated the guidelines but would have been compliant); dosed by gavage as single daily dose on days 6-27 (inclusive) of gestation; doses 0, 25, 50, 75 mg/kg/ bw/d (exp. 1) & 0, 10, 30, 60 mg/kg/ bw/d (exp. 2); purity 96.3%	Cyromazine did not cause teratogenic effects. NOAEL (maternal) = 10 mg/kg bw/d NOAEL (foetal) = 25 mg/kg bw/d LOAEL (maternal) = 25 mg/kg bw/d based on maternal mortality and body weight loss LOAEL (foetal) = 30 mg/kg bw/d	382-072/072A

[1] Maximum dietary dose initially 4000 ppm, reduced to 3000 ppm after 4 weeks feeding to F_0 parents.

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

Species	Test	Duration and conditions	Result	Reference
Rabbit (f)	Teratogenicity	87/302/EEC B.31 ≅ OECD 414 (1981) ≅ FIFRA § 83-3 (study predated the guidelines but would have been compliant); dosed by gavage as single daily dose on days 7-19 (inclusive) of gestation; doses 0, 5, 10, 30, 60 mg/kg/ bw/d); purity 95.2%	No teratogenic effects observed at ≤30 mg/kg bw/d. At 60 mg/kg bw/d teratogenic potential could not be evaluated due to severe maternal toxicity. NOAEL (maternal) = 10 mg/kg bw/d NOAEL (foetal) = >30 <60 mg/kg bw/d LOAEL (maternal) = 25 mg/kg bw/dbased on body weight loss and reduced food consumption LOAEL (foetal) = 30 mg/kg bw/d	WIL-82001
Rabbit (f)	Teratogenicity	87/302/EEC B.31 ≅ OECD 414 (1981) ≅ FIFRA § 83-3; dosed by gavage as single daily dose on days 7-19 (inclusive) of gestation; doses 0, 5, 10, 30 mg/kg/ bw/d); purity 95.2%	Cyromazine did not cause teratogenic effects. NOAEL (maternal) = 10 mg/kg bw/d NOAEL (foetal) = 30 mg/kg bw/d LOAEL (maternal) = 30 mg/kg bw/d based on body weight loss LOAEL (foetal) = >30 mg/kg bw/d	WIL-82008

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

Species	Test	Duration and conditions	Result	Reference
S. typhimurium TA1535, TA1537, TA98, TA100	*In vitro* gene mutation	67/548/EEC B.13/14 (2000) ≅ OECD 471 (1997) ≅ OPPTS 870.5100 (1998); tests 1 & 2, 0 to 5000 µg/plate, ± S9 activation; purity 97.5%	Negative	871713
S. typhimurium TA1538 and *Escherichia coli* WP2uvrA	*In vitro* gene mutation	67/548/EEC B.13/14 (2000) ≅ OECD 471 (1997) ≅ OPPTS 870.5100 (1998); tests 1 & 2, 0 to 5000 µg/plate, ± S9 activation; purity 97.5%	Negative	901445
Saccharomyces cerivisiae D7	Mutagenicity assay *in vitro*	67/548/EEC B.15 and B16 (1988) ≅ OECD 480 and 481 (1986) ≅ OPPTS 870.5575 (1998); 0 to 3000 µg/ml, ± S9 activation; purity 98.9%	Negative	831167
Mouse lymphoma cells L5178Y TK	Mammalian gene mutation test *in vitro*	67/548/EEC B.17 (2000) ≅ OECD 476 (1997) ≅ OPPTS 870.5300 (1998); 0 to 500 µg/ml, ± S9 activation; purity 96.2%	Negative	840942
Chinese hamster V79 cells	*In vitro* gene mutation test	67/548/EEC B.17 (2000) ≅ OECD 476 (1997) ≅ OPPTS 870.5300 (1998); 0 to 4000 µg/ml, -S9 0 to 1000 µg/ml, +S9 activation; purity 98.9%	Negative	840798
Human lymphocytes	*In vitro* mammalian cytogenetic test	67/548/EEC B.10 (2000) ≅ OECD 473 (1997) ≅ OPPTS 870.53575 (1998); 0 to 1000 µg/ml, ± S9; purity 96.2%	Negative	850013
Rat primary hepatocytes	*In vitro* DNA repair assay	Not in full compliance with 67/548/EEC B.18 (2000) ≅ OECD 482 (1986) ≅ OPPTS 870.5550 (1998); 0-1 mg/ml for 18 h.	Negatve	042782
Mouse primary hepatocytes	*In vitro* DNA repair assay	67/548/EEC B.18 (2000) ≅ OECD 482 (1986) ≅ OPPTS 870.5550 (1998); 0-1 mg/ml for 18 h.	Negative	050382
Chinese hamster	Nucleus anomaly test *in vivo*	67/548/EEC B.12 (2000) ≅ OECD 474 (1997) ≅ OPPTS 870.5395 (1998); 2 oral doses on consecutive days, doses 0, 2000, 4000, 8000 mg/kg bw; purity 98.9%	Negative	79-1347

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

Species	Test	Duration and conditions	Result	Reference
Mouse	*In vivo* micronucleus test in bone marrow	67/548/EEC B.12 (2000) ≅ OECD 474 (1997) ≅ OPPTS 870.5395 (1998); Single oral dose of 0, 360 or 1080 mg/kg bw; purity 96.3%.	Negative	861345
Mouse, strain C57 B1/6	Mammalian spot test	67/548/EEC B.22 (1988) ≅ OECD 484 (1986); single injected dose to females (10^{th} day after conception); dose 0, 150, 300 or 600 mg/kg bw; purity 96.2%	Negative	850616
Mouse, NMRI-derived (Tif:MAGf [SPF])	Dominant lethal study	67/548/EEC ≅ OECD 478 (1984) ≅ FIFRA § 84-2; single oral dose by gavage; doses 0, 226 or 678 mg/kg bw; purity 98.9%	Negative	790033

Table D. Ecotoxicology profile of cyromazine technical material

Species	Test	Duration and conditions	Result	Reference
Mallard duck	Acute oral toxicity	Guideline not defined. Single dose administered by intubation (14 d); doses 0, 398, 631, 1000, 1590 or 2510 mg/kg; purity 95.6%	LD_{50} >2510 mg/kg bw (highest concentration tested) NOEL <398 mg/kg bw	108-190
Bobwhite quail	Acute oral toxicity	Guideline not defined. Single dose administered by intubation (14 d); doses 0, 398, 631, 1000, 1590 or 2510 mg/kg; purity 95.6%	LD_{50} = 1785mg/kg bw NOEL = 398 mg/kg bw	108-189
Mallard duck	Short-term dietary toxicity	Guideline not defined. Dietary inclusion for 5 d (test duration 8 d); doses: 0, 562, 1000, 1780, 3160 or 5620 mg/kg diet; purity 95.6%	LC_{50} >5620 mg/kg feed NOEL <562 mg/kg feed	108-188
Bobwhite quail	Short-term dietary toxicity	Guideline not defined. Dietary inclusion of TC for 5 d (test duration 8 d); doses; 0, 562, 1000, 1780, 3160 or 5620 mg/kg diet; purity 95.6%	LC_{50} >5620 mg/kg feed NOEL = 562 mg/kg feed	108-187
Bobwhite quail	Sub-chronic toxicity & reproduction	FIFRA Guideline 71-4, 1982; dietary inclusion for 20 weeks; doses 0, 75, 300 or 1200 mg/kg diet; purity 96.3%	NOEL ≥1200 mg/kg feed	108-265
Mallard duck	Sub-chronic toxicity & reproduction	FIFRA Guideline 71-4 (1982); dietary inclusion for 19 weeks; doses 0, 75, 300 or 1200 mg/kg diet; purity 96.3%	NOEL = 300 mg/kg feed	108-266
Common carp	Acute toxicity, static	OECD guideline 203 (1992) & JMAFF (2-7-1) (2001) & EU Commission Directive 92/69/EEC, C.1 (1992); 96-h; doses 0 or 100 mg/l; purity 97.5%	LC_{50} >100 mg/l NOEC = 100 mg/l	848755
Channel catfish	Acute toxicity, static	EPA-660/3-75-009 (1975); 96-h; doses 0, 10, 18, 32, 56 or 100 mg/l; purity 95.6%	LC_{50} >100 mg/l NOEC = 100 mg/l	UCES-11506-04-04
Fathead minnow	Early life stage test, flow-through	Guideline not defined. 32 d; Nominal doses 0, 17,43, 77, 147 or 290 mg/l; purity 93.4%	NOEC = 14 mg/l LOEC = 36 mg/l	PB906
Daphnia magna (water flea)	Acute toxicity, static	EPA-660/3-75-009 (1975); 48-h; doses 0, 10, 18, 32, 56 or 100 mg/l; purity 95.6%	EC_{50} >100 mg/l NOEC = 10 mg/l	UCES-11506-04-03

Table D. Ecotoxicology profile of cyromazine technical material

Species	Test	Duration and conditions	Result	Reference
Daphnia magna (water flea)	Acute toxicity, static	OECD guideline 202, part 1 91884) & JMAFF (2-7-2-1) (2001) & EU Commission Directive 92/69/EEC, C.2 (1992); 48-h; doses 0, 1.0, 2.2, 4.6, 10, 22, 46 or 100 mg/l; purity 97.5%	EC_{50} >100 mg/l NOEC = 4.6 mg/l	848805
Chironomus riparius larvae	Acute toxicity, static	ASTM (1986). E729 – 96a[1]; 48-h; doses 0 or 120 mg/l; purity 97.4%	EC_{50} >120 mg/l NOEC = 120 mg/l	BL7532/B
Daphnia magna (water flea)	Chronic toxicity, flow-through	EPA-660/3-75-009; 21-d; nominal doses 0.23, 0.46, 0.91, 1.82 or 3.64 mg/l; purity 93.4%	$NOEC_{(mortality)}$ = 0.64 mg/l $NOEC_{(reproduction\ and\ length\ of\ surviving\ adults)}$ = 0.31 mg/l $LOEC_{(mortality)}$ = 0.96 mg/l $LOEC_{(reproduction\ and\ length\ of\ surviving\ adults)}$ = 0.64 mg/l	B906
Scenedesmus subspicatus (green alga)	Effects on growth, static	In accordance with the AFNOR- T 90-304 (August 1980); 120-h; doses 100, 150, 230, 340, 510, 760 or 1000 mg/l; purity 99.5%	EC_{50} = 124 mg/l	81-07-94
Chironomus riparius larvae	Chronic toxicity to sediment dwelling species	BBA 1995 & OECD 219[2]; 26-d; static water-sediment system (spiked water phase); doses 0, 6.3, 12.5, 25, 50 or 100 µg/l; purity 97.4%	NOEC = 25 µg/l LOEC = 50 µg/l	851893
Apis mellifera (honey bee)	Acute oral & contact toxicity	EPPO 170 (1992); single oral or topically applied dose; 48-h observation; oral doses 0, 80, 120, 160, 200, 240 or 280 µg/bee; contact doses 0, 25, 50, 100, 150 or 200 µg/bee; purity 98%	oral LD_{50} = 186 µg/bee contact LD_{50} = >200 µg/bee	94 10 48 017
Eisenia foetida (earthworm)	Toxicity	OECD 207 (1984); artificial soil; 14-d; concentrations 0, 62.5, 125, 250, 500 or 1000 mg/kg (soil dw); purity 96.2%	EC_{50} >1000 mg/l NOEC <62.5 mg/l	85 12 26
Eisenia foetida (earthworm)	Chronic toxicity & reproduction	BBA-Richtlinie VI, 2-2, 1994 (Draft ISO/DIS 11268-2, 1993); artificial soil; 56-d; concentrations 0, 12.3, 37, 111, 333 or 1000 mg/kg (soil dw); purity 98.2%	$NOEC_{(adult\ mortality\ and\ biomass)}$ = 1000 mg/kg $NOEC_{(reproduction)}$ = 333 mg/kg	952501

[1] Standard guide for conducting acute toxicity tests with fishes, macro-invertebrates and amphibians. ASTM, West Conshohoken, PA, USA.

[2] Proposal for a BBA-Guideline, 1995: "Effects of plant protection products on the development of sediment-dwelling larvae of *Chironomus riparius* in a water-sediment system". OECD guidelines for testing of chemicals, proposal for a new guideline 219, draft document February 2001: "Sediment-water Chironomid toxicity test using spiked water".

Table D. Ecotoxicology profile of cyromazine technical material

Species	Test	Duration and conditions	Result	Reference
Soil non-target micro-organisms	Microbial soil respiration	Guideline not stated; single application; 28 d; concentrations 0, 1, 10 or 100 mg/kg; purity 93.7%	NOAEC = 100 mg/kg	CGA72662/0074
Soil non-target micro-organisms	Microbial nitrogen fixation	Guideline not stated; single application; 28 d; concentrations 0, 1, 10 or 100 mg/kg; purity 93.7%	NOAEC = 100 mg/kg	CGA72662/0075
Soil non-target micro-organisms	Soil nitrification	Guideline not stated; single application; 28 d; concentrations 0, 1, 10 or 100 mg/kg; purity 93.7%	NOAEC = 100 mg/kg	CGA72662/0072

ANNEX 2. References

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107935	2001. Water solubility of CGA 72662 (pure water).
108-187	1980. CGA 72662, Eight-day dietary LC50 - bobwhite quail.
108-188	1980. Eight-day dietary LC50 - Mallard duck CGA 72662 technical.
108-189	1980. Acute oral LD50 - Bobwhite quail CGA 72662.
108-190	1980. Acute oral LD50 - Mallard duck CGA 72662 technical.
108-265	1989. A one-generation reproduction study with the Bobwhite.
108-266	1989. A one-generation reproduction study with the Mallard (*Anas platyrhynchos*).
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850013	1985. CGA 72662 tech: Chromosome studies on human lymphocytes in vitro.
850616	1986. CGA 72662 tech.: Mammalian spot test, mouse, 8 weeks.
85 12 26	1986. Report on the Test for Acute Toxicity of CGA 72662 Technical to *Eisenia foetida*.
851893	2004. Effects of CGA72662 (Cyromazine tech.) on the development of sediment-dwelling larvae of *Chironomus riparius*.

Syngenta number or other reference	Author, year and title of report or publication details
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