FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

CYPRODINIL

(4-cyclopropyl-6-methyl-pyrimidin-2-yl)-phenyl-amine

FOOD AND AGRICULTURE ORGANIZATION of THE UNITED NATIONS

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DISCLAIMER[1]

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.

FAO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may arise as a result of, or in connection with, the manufacture, sale, transportation, storage, handling, preparation and/or use of pesticides which are found, or are claimed, to have been manufactured to comply with these specifications.

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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.

Since 1999 the development of FAO specifications follows the **New Procedure**, described in the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products" (FAO Plant Production and Protection Page No. 149). 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 plant protection product in accordance with chapter 4, 5 and 6 of the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products".

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 specifications for plant protection products" 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 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/ps/en/)

PART ONE

SPECIFICATIONS

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CYPRODINIL

INFORMATION

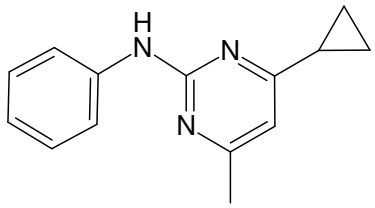
ISO common name
Cyprodinil (ISO 1750 published)

Chemical name(s)

IUPAC (4-cyclopropyl-6-methyl-pyrimidin-2-yl)-phenyl-amine
CA 4-cyclopropyl-6-methyl-N-phenyl-2-pyrimidinamine

Synonyms
None

Structural formula



Molecular formula
$C_{14}H_{15}N_3$

Relative molecular mass
225.3 g/mol

CAS Registry number
121552-61-2

CIPAC number
511

Identity tests
Retention times of cyprodinil in reversed phase HPLC or in GC using a widebore capillary column with flame ionization detection, respectively, and IR spectroscopy.

CYPRODINIL TECHNICAL MATERIAL

511/TC (May 2009)

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 (511/2009). It should be applicable to relevant products of these manufacturers but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for the products of other manufacturers. The evaluation report (511/2009) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist of cyprodinil together with related manufacturing impurities, in the form of white to yellow flakes and shall be free from visible extraneous matter and added modifying agent.

2 Active ingredient

2.1 **Identity tests** (CIPAC 511/TC/M/-, Note 1)

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

2.2 **Cyprodinil content** (CIPAC 511/TC/M/-, Note 1)

The cyprodinil content shall be declared (not less than 990 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

Note 1 Methods for the identification and determination of cyprodinil content in TC, EC and WG formulations were presented at the CIPAC Meeting in 2008 and provisionally adopted as CIPAC method. Prior to their publication in Handbook N, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org/prepubme.htm

CYPRODINIL EMULSIFIABLE CONCENTRATE

511/EC (May 2009)

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 (511/2009). It should be applicable to relevant products of these manufacturers but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for the products of other manufacturers. The evaluation report (511/2009) as PART TWO forms an integral part of this publication.

1. Description

The material shall consist of technical cyprodinil, complying with the requirements of FAO/WHO specification 511/TC (2009), dissolved in suitable solvents, together with any other necessary formulants. It shall be in the form of a clear to slightly hazy, stable homogeneous liquid, free from visible suspended matter and sediment, to be applied as an emulsion after dilution with water.

2. Active ingredient

2.1. **Identity tests** (CIPAC 511/EC/M/-, Note 1)

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

2.2. **Cyprodinil content** (CIPAC 511/EC/M/-, Note 1)

The cyprodinil 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 ± 2°C	Permitted tolerance
above 250 g/l up to 500 g/l	± 5% of the declared content

3. **Physical properties**

3.1. **Emulsion stability and re-emulsification** (MT 36.3)

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

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

3.2. **Persistent foam** (MT 47.2) (Note 3)

Maximum: 60 ml after 1 minute.

4. Storage stability

4.1. **Stability at 0°C** (MT 39.3)

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)

After storage at 54 ± 2°C for 14 days (Note 4), the determined average active ingredient content must not be lower than 95%, relative to the determined average content found before storage (Note 4) and the formulation shall continue to comply with the clause for:

- emulsion stability and re-emulsification (3.1).

Note 1 Methods for the identification and determination of cyprodinil

content in TC, EC and WG formulations were presented at the CIPAC Meeting in 2008 and provisionally adopted as CIPAC method. Prior to their publication in Handbook N, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org/prepubme.htm

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

Note 3 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 product taken before and after the storage stability test should be analyzed concurrently after the test in order to reduce the analytical error.

CYPRODINIL WATER DISPERSIBLE GRANULES

FAO Specification 511/WG (May 2009)

1 Description

The material shall consist of a homogeneous mixture of technical cyprodinil, complying with the requirements of the FAO/WHO specification 511/TC, together with carriers and any other necessary formulants. It shall be in the form of cylindrical granules with approximate diameter of 0.4 – 1.2 mm and length 2 – 8mm, for application after disintegration and dispersion in water. The formulation shall be dry, free-flowing, essentially non-dusty, and free from visible extraneous matter and hard lumps.

2 Active ingredient

2.1 **Identity tests** (CIPAC 511/WG/M/-, Note 1)

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

2.2 **Cyprodinil content** (CIPAC 511/WG/M/-, Note 1)

The cyprodinil content shall be declared (g/kg) and, when determined, the average content measured shall not differ from that declared by more than the appropriate tolerance, given in the table of tolerances.

Declared content	Permitted tolerance
Above 250 up to 500 g/kg	+/- 5% of the declared content
above 500 g/kg	± 25 g/kg
Note: In each range the upper limit is included	

3 Physical properties

3.1 **Wettability** (MT 53.3)

The formulation shall be completely wetted in 30 sec.

3.2 **Wet sieve test** (MT 185)

Maximum: 0.2% retained on a 75 µm test sieve.

3.3 **Degree of dispersion** (MT 174)

Dispersibility: minimum 60% after 1 minute of stirring.

3.4 **Suspensibility** (MT 168, MT 184) (Notes 2 & 3)

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

3.5 **Persistent foam** (MT 47.2) (Note 4)

Maximum: 30ml after 1 minute.

3.6 **Dustiness** (MT 171) (Note 5)

Essentially non-dusty.

3.7 **Flowability** (MT 172)

100% of the formulation shall pass through a 5 mm test sieve after 20 drops of the sieve.

3.8 **Attrition resistance** (MT 178.2)

Minimum: 85% attrition resistance.

4 Storage stability

4.1 Stability at elevated temperature (MT 46.3)

After storage at 54 ± 2°C for 14 days (Note 6), the determined average active ingredient content must not be lower that 95% relative to the determined average content found before storage (Note 6) and the formulation shall continue to comply with the clauses for:

- wet sieve test (3.2),
- degree of dispersion (3.3),
- suspensibility (3.4),
- dustiness (3.6),
- attrition resistance (3.8).

Note 1 Methods for the identification and determination of cyprodinil content in TC, EC and WG formulations were presented at the CIPAC Meeting in 2008 and provisionally adopted as CIPAC method. Prior to their publication in Handbook N, copies of the methods may be obtained through the CIPAC website, http://www.cipac.org/prepubme.htm

Note 2 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in methods MT 168 and MT 184.

Note 3 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, the simpler gravimetric method, MT 168, may be used on a routine basis provided that it has been shown to give equal results to those of chemical assay. In case of dispute, chemical assay shall be the "referee method".

Note4 The mass of sample to be used in the test should be specified at the highest rate recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 5 Measurement of dustiness must be carried out on the sample "as received" and, where practicable, the sample should be taken from a newly opened container, because changes in the water content of samples may influence dustiness significantly. The optical method, MT 171.2, usually shows good correlation with the gravimetric method, MT 171.1, and can, therefore, be used as an alternative where the equipment is available. Where the correlation is in doubt, it must be checked with the formulation to be tested. In case of dispute the gravimetric method shall be used.

Note 6 Analysis of the formulation, before and after the storage stability test, should be carried out concurrently (i.e. after storage) to reduce analytical error.

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EVALUATION REPORTS

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CYPRODINIL

FAO EVALUATION REPORT

Recommendation

The Meeting recommended that:

- The cyprodinil specifications for TC, EC and WG proposed by Syngenta, as amended, should be adopted as FAO specifications.

Appraisal

The meeting considered data submitted in 2007 by Syngenta Crop Protection AG, for the development of new FAO specifications for cyprodinil TC, EC and WG. The data and proposed specifications submitted were in accordance with the requirements of the revised 1st edition of the Manual on development and use of FAO and WHO specifications for pesticides (FAO/WHO Manual, 2006) and supported the draft specifications.

Cyprodinil is currently under patent in many countries.

Cyprodinil was evaluated by FAO/WHO JMPR in 2003 and by US EPA in 1998. It was evaluated/reviewed by the European Commission and was included in Annex I of Council Directive 91/414/EEC in April 2006.

Technical cyprodinil is a solid, and crystallizes in two different modifications which are designated as “modification A” and “modification B”, respectively. In the technical material, both forms may exist. These modifications show somewhat differing physical-chemical properties like melting point etc. (see Table 1). The crystallization taking place at the end of the manufacturing process is controlled in such a way that predominantly the B modification is formed. This modification shows better stability on storage in the bulk material.

Cyprodinil shows a rather low vapour pressure (crystal modification A: 5.1×10^{-4} Pa crystal modification B: 4.7×10^{-4} Pa at 25°C). It is moderately soluble in water; the solubility is influenced by pH in the range between 5 and 9. Its octanol/water partition coefficient (log P_{ow}=4.0) is not significantly pH dependent and shows that the molecule is lipophilic, with possibility of bioaccumulation. Cyprodinil is hydrolytically stable in the pH range 4 to 9. The estimated/extrapolated half-life in water under sterile conditions and in the dark is longer than 1 year at 25°C at pH 4, 5, 7 and 9, respectively.

However, cyprodinil is rapidly degraded in water when exposed to UV light with a half live of 13.5 days. The pK_a (base) is 4.44, leading to protonation at pH below this value and being present as a free base at pH above pH 4.4. This explains the weak pH dependence of the P_{ow} with pH at 5, 7 and 9.

The main formulation types available are emulsifiable concentrate (EC) and water dispersible granules (WG).

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on all impurities present at or

above 1g/kg and their manufacturing limits in the TC. Mass balances ranged from 1001-1007 g/kg in the five batch data. None of the manufacturing impurities considered are, on the basis of information available, of toxicological or environmental concern. These data were declared to be identical to those submitted for registration in Switzerland. The question of the formation of nitrosamines in the manufacturing process was discussed by the Meeting. Based on information provided by the company, the presence of nitrosamines in the TC at levels above 0.5 µg/kg can be excluded. Nitrosamines are therefore not considered as being relevant impurities in cyprodinil TC and formulations.

Residual water in the TC may become a relevant impurity when the material is to be used for EC formulations. However, the manufacturing process leads to a TC with very low water content so the water clause becomes obsolete.

The analytical method for determination of cyprodinil in TC, EC and WG relies on reversed phase HPLC with UV detection at 254 nm. The method and its collaborative validation were presented at the 2008 CIPAC Meeting in Braunschweig, Germany, and adopted as provisional CIPAC Method. Three different identity tests for cyprodinil are provided: retention time in HPLC, in GC and comparison of IR spectra

Methods to elaborate the physical-chemical properties of the formulation were CIPAC, and all other methods were EU, OECD and EPA.

Issues relating to TC only

A clause for water content was considered unnecessary despite of the TC being used for preparation of EC formulations as the manufacturing process leads to low water content. Similarly, clauses for pH or acidity/alkalinity were considered unnecessary as cyprodinil is not prone to rapid hydrolysis catalysed by excess acid or base.

Issues relating to WG only

The WG is produced with a technology (extrusion) leading to a low dustiness but the limit of the attrition resistance is 85 %, which is considered rather low but may be associated with the production process. On the other the limits for the degree of dispersion and suspensibility are at minimum of 60 which may be attributed to the fact that cyprodinil is often coformulated calling for a certain compromise to guarantee acceptable limits for all actives in the WG formulation.

Issues relating to EC only

No clauses on pH or alkalinity/acidity were considered necessary. The Meeting noted that the limit for persistent foam at maximum value of 60 ml but justified by the company due to the fact that cyprodinil is coformulated with other fungicides.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 511/2009

Uses

Cyprodinil, a member of the anilinopyrimidine group, is a systemic foliar broad spectrum fungicide. It acts as an inhibitor of methionine biosynthesis and interferes in the fungal life cycle by inhibition of penetration and by disruption of mycelial growth in the plant. It has registered uses in many countries on many crops (e.g. agriculture, horticulture, viticulture).

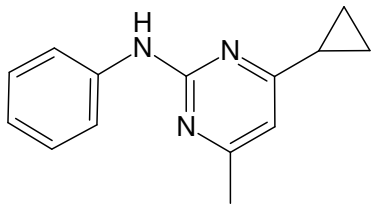
Identity of the active ingredient

ISO common name
Cyprodinil (ISO 1750 published)

Chemical name(s)
IUPAC
(4-cyclopropyl-6-methyl-pyrimidin-2-yl)-phenyl-amine
CA
4-cyclopropyl-6-methyl-N-phenyl-2-pyrimidinamine

Synonyms
none

Structural formula



Molecular formula
$C_{14}H_{15}N_3$

Relative molecular mass
225.3 g/mol

CAS Registry number
121552-61-2

CIPAC number
511

Identity tests
Retention times of cyprodinil in reversed phase HPLC or in GC using a widebore capillary column with flame ionization detection, respectively and IR spectroscopy.

Physico -chemical properties of pure cyprodinil (*Table 1*)

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)
Vapour pressure Ref. CGA219417/0107 (1992)	Crystal modification A: 5.1×10^{-4} Pa at 25 °C crystal modification B: 4.7×10^{-4} Pa at 25 °C	99.9 %	OECD 104, EEC A.4 by extrapolation
Melting point, boiling point and/or temperature of decomposition Ref. CGA219417/0110 (1992), CGA219417/0107 (1992), CGA219417/0825 (1997) and CGA219417/0115 (1992)	Melting point: 75.9 °C Melting point of crystal mod. A: 71.3 °C Melting point of crystal mod. B: 76.4 °C Boiling point: >360 °C at 101.325 kPa (at a reduced pressure of 1.96 Pa cyprodinil boils at 100.9 °C) Decomposition temperature: No decomposition between room temperature and 150 °C (with and without air)	99.9 % 99.9 % 99.2 %	OECD 102, EEC A.1 OECD 103, EEC A.2 OECD 113
Solubility in water Ref. CGA219417/0338 (1994) and CGA219417/0106 (1992)	In buffer solution: 20 mg/l at 25 °C at pH 5.0 13 mg/l at 25 °C at pH 7.0 15 mg/l at 25 °C at pH 9.0 In pure water: 16 mg/l at 25 °C at pH 7.6	99.9 %	OECD 105, EEC A.6
Octanol/water partition coefficient Ref. CGA219417/0105 (1992)	log P_{OW} = 3.9 at 25 °C at pH 5.0 log P_{OW} = 4.0 at 25 °C at pH 7.0 log P_{OW} = 4.0 at 25 °C at pH 9.0	99.9 %	OECD 107
Hydrolysis characteristics Ref. CGA219417/0462 (1995) and CGA219417/0144 (1992)	Pyrimidyl ring ^{14}C-labelled cyprodinil: No degradation at 25 °C in buffered sterilised solutions at pH 5, 7 and 9 within 32 days (in the dark) Phenyl ring ^{14}C-labelled cyprodinil: No degradation at 50 °C in buffered sterilised solutions at pH 4, 7 and 9 within 5 days (in the dark) Estimated/extrapolated half-life > 1 year at 25 °C at pH 4, 5, 7 and 9	98.7 % 99.2 % (radio-chemical purity)	EPA 161-1 EPA 161-1, OECD 111

Photolysis characteristics Ref. CGA219417/0268 (1994) and CGA219417/0292 (1994)	The photolytic half-lives of cyprodinil were determined at 25 °C in various sterile aqueous solutions using xenon arc light irradiation. The findings were quite variable and sometimes a lag phase was observed. The selected results given below are representative overall values, expressed in Florida (at latitude 30°N) Summer Sunlight Equivalent (FSSE) days. Half-life: 13.5 days (FSSE) for pyrimidiyl ring ^{14}C-labelled cyprodinil in aqueous buffer at pH 7.3 (c_o = 4.7 ppm). Half-life: 21.5 days (FSSE) for phenyl ring ^{14}C-labelled cyprodinil in bi-distilled water (c_o = 4.0 ppm). Dark control experiments showed only negligible degradation of cyprodinil.	98 % > 99 % (radio-chemical purity)	EPA 161-2
Dissociation characteristics Ref. CGA219417/0108 (1992) and CGA219417/0878 (1998)	pKa = 4.44 at 20 °C This constant describes the protonation of cyprodinil (neutral form) in aqueous solution. Thus the neutral form is predominantly present at pH above 4.44, the protonated form of cyprodinil at pH below 4.44.	99.9 %	OECD 112

Chemical composition and properties of cyprodinil technical materials (TC and or TK) (*Table 2*)

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 100.1 – 100.7 %.
Declared minimum [a.i.] content	990 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	73 - 76°C

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

Table 3. ***Toxicology profile of the cyprodinil technical material, based on acute toxicity, irritation and sensitization***

Species	Test	Duration and conditions or guideline adopted	Result cyprodinil technical
Rat (m,f)	Acute Oral LD_{50}, (OECD 401) Ref. CGA219417/0020	14d observation period; purity= 99.5%; one dose level= 2000 mg/kg bw.	LD_{50} >2000 mg/kg bw
Rat (m,f)	Acute Dermal LD_{50}, (OECD 402) Ref. CGA219417/0021	14d observation period; purity= 99.5%; limit dose= 2000 mg/kg bw	LD_{50} > 2000 mg/kg bw
Rat (m,f)	Acute Inhalation (4h) LC_{50}, (OECD 403) Ref. CGA219417/0026	4h exposure, 14d observation period; purity= 99.5%; nominal concentration= 1684 mg/m^3, analytical concentration= 1203 mg/m^3	LC_{50} > 1200 mg/m^3
Rabbit	Skin irritation, (OECD 404) Ref. CGA219417/0022	1-72 h; purity= 99.5%; dose= 0.5g/animal	Non-irritating
Rabbit	eye irritation, (OECD 405) Ref. CGA219417/0023	1-72 h; purity= 99.5%; 40 mg/eye	Non-irritating
Guinea – pig	skin sensitization (maximization test), (OECD 406) Ref. CGA219417/0746	48h; purity= 99.2%; dose= 50% ;see study for details	Sensitization of 45 % of test animals. “May cause sensitization by skin contact”

Cyprodinil is not classified as dangerous if swallowed, in contact with skin or by inhalation, and is not irritating to skin or eyes. The substance is classified as “may cause sensitisation by skin contact”.

Table 4. ***Toxicology profile of technical cyprodinil based on repeated administration (sub-acute to chronic)***

Species	Test	Duration and conditions or guideline adopted	Result cyprodinil technical
Rat	Short term toxicity Ref. CGA219417/0045	3m dietary; OECD 408, Tif:RAIf, (SPF) rat; purity= 99.5%; dose levels: 0, 50, 300, 2000, 12000 ppm	NOEL = 50 ppm (3.14/3.24 mg/kg bw/d)
Dog	Short term toxicity Ref. CGA219417/0044	3m dietary; OECD 409; FIFRA 82-1, Beagle dog; purity= 99.5%; dose levels: 0, 200, 1500, 7000, 20000 ppm	NOAEL = 7000ppm (210/232 mg/kg bw/d)
Dog	Short term toxicity Ref. CGA219417/0122	1 year dietary; FIFRA 83-1, OECD 452, Beagle dog; purity= 99.6%; dose levels: 0, 25, 250, 2500, 15000 ppm	NOEL = 2500ppm (65.5/68.0 mg/kg bw/d)
Mouse	Carcinogenicity Ref. CGA219417/0239	18m dietary; FIFRA 83-2, OECD 451,; animals: Tif:MAGf; purity= 99.6%; dose levels: 0, 10, 150, 2000, 5000ppm	No carcinogenic effects NOEL = 2000ppm (212.4/196.3 mg/kg bw/d)
Rat	Chronic toxicity / Carcinogenicity Ref. CGA219417/0252	2 year dietary, FIFRA 83-5, OECD 453, 1981; animals: Tif:RAIf; purity= 99.6%; dose levels: 0, 5, 75, 1000, 2000 ppm	Not carcinogenic NOEL =75 ppm (2.70/3.22 mg/kg bw/d)

Species	Test	Duration and conditions or guideline adopted	Result cyprodinil technical
Rat	Reproductive toxicity Ref. CGA219417/0162	2 generation, dietary; OECD 416, FIFRA 83-4; animals: animals: Tif:RAI rat ; purity= 99.5%; dose levels: 0, 10, 100, 1000, 4000 ppm	No effects on reproductive parameters NOAEL reproductive, parental,offspring =1000 ppm (51.0-144.6 /70.6-153.5 mg/kg bw/d)
Rat	Developmental toxicity Ref. CGA219417/0027	Gavage feeding; OECD 414, FIFRA 83-3; animals: Tif:RAIf rat; purity= 99.5%; dose levels: 0, 20, 200, 1000 mg/kg bw/day	Not teratogenic NOEL for maternal toxicity = 200 mg/kg bw/d NOEL for developmental toxicity = 200 mg/kg bw/d
Rabbit	Developmental toxicity Ref. CGA219417/0039	Gavage feeding; OECD 414, FIFRA 83-3; animals: Russian Chbb:HM (SPF); purity= 99.5%; dose levels: 0, 5, 30, 150, 400 mg/kg bw/day	Not teratogenic NOEL for maternal toxicity = 150 mg/kg bw/d NOEL for developmental toxicity = 400 mg/kg bw/d

Table 5. ***Mutagenicity profile of technical cyprodinil based on in vitro and in vivo tests***

Species	Test	Conditions / Dose levels	Result cyprodinil
Bacterial gene mutation	Salmonella/E.coli in vitro (OECD 471) Ref. CGA219417/0025	0 to 5000 µg/plate, +/- activation; purity= 99.5%	Not mutagenic
Chinese hamster	Gene mutation in V79 cells in vitro (OECD 476) Ref. CGA219417/0028	0 to 30 µg/ml, - activation 0 to 150 µg/ml, + activation; purity= 99.5%	Not mutagenic
Chinese hamster	Cytogenetic test in Chinese hamster cells in vitro (OECD 473) Ref. CGA219417/0040	0 to 200 µg/ml, - activation 0 to 200 µg/ml, + activation; purity= 99.5%	Not clastogenic
Rat hepatocytes	DNA repair on rat hepatocytes in vitro (OECD 482) Ref. CGA219417/0058	0 to 4800 µg/ml; purity= 99.5%	Not genotoxic

Species	Test	Conditions / Dose levels	Result cyprodinil
Mouse somatic cells	Micronucleus test mouse bone marrow in vivo (OECD 474) Ref. CGA219417/0029	0, 1250, 2500, 5000 mg/kg bw; purity= 99.5%	Not clastogenic

Cyprodinil was tested for different endpoints including gene mutation, chromosome aberration and DNA-damage in bacteria in vitro and in mammalian cells in vitro and in vivo. No mutagenic effects were noted in any test in vitro and in vivo.

Table 6. **Ecotoxicology profile of cyprodinil**

Species	Test	Duration and conditions	Result cyprodinil
Anas platyrhynchos (mallard duck)	Acute oral Ref. CGA219417/0062	Observation: 14 days; EPA Pesticide Assessment Guidelines, E, 1982; purity: 99.5%; Treatment levels: 125, 250, 500, 1000 and 2000 mg a.s./kg bw	LD_{50} = > 500 mg/kg bw Vomiting at dose levels of 1000 mg/kg and above
Colinus virginianus (Bobwhite quail)	Acute oral CGA219417/0067	Observation: 14 days; EPA Pesticide Assessment Guidelines, E, 1982; purity: 99.5%; Treatment levels: 125, 250, 500, 1000 and 2000 mg a.s./kg bw	LD_{50} = > 2000 mg/kg bw
Anas platyrhynchos (Mallard duck)	Short term CGA219417/0068	Treatment 5d / observation 3 d; EPA Pesticide Assessment Guidelines, E, 1982; purity: 99.5%; Treatment levels: 163, 325, 650, 1300, 2600, 5200 mg/kg feed	LC_{50} = > 5200 mg/kg feed
Colinus virginianus (Bobwhite quail)	Short term CGA219417/0066	Treatment 5d / observation 3 d; EPA Pesticide Assessment Guidelines, E, 1982; purity: 99.5%; Treatment levels: 163, 325, 650, 1300, 2600 and 5200 mg/kg feed	LC_{50} = > 5200 mg/kg feed
Colinus virginianus (Bobwhite quail)	Reproduction CGA219417/0478	EPA Pesticide Assessment Guidelines Section 71-4 (1982); purity:=99.2%; Treatment levels: 100, 300, 600 mg/kg diet	NOAEC= 600mg/kg diet

Species	Test	Duration and conditions	Result cyprodinil
Anas platyrhynchos (mallard duck)	Chronic reproduction test CGA219417/0477	EPA Pesticide Assessment Guidelines Section 71-4 (1982); purity.=99.2%; Treatment levels: 100, 300, 600 mg/kg diet	NOAEC =600mg/kg diet
Oncorhynchus mykiss (Rainbow trout)	Acute, CGA219417/0486	96h static exposure/ freshwater; OECD 203 purity: 99.2%; dose= 0.28, 0.511, 0.86, 1,48, 2.72 mg/l	LC_{50} = 2.41 mg a.s./l
Lepomis macrochirus (Bluegill sunfish)	Acute, CGA219417/0507	96h static exposure/ freshwater; OECD 203 purity: 99.2%; dose= 0.285, 0.445, 0.922, 1.35, 2.55 mg/l	LC_{50} = 2.17 mg a.s./l
Lepomis macrochirus (Bluegill sunfish)	Acute, CGA219417/0651	96h flow-through exposure/ freshwater; OECD 203 purity: 99.8%; dose= 0.631, 1.00, 1.64, 2.70, 4.68 mg/l	LC_{50} = 3.2 mg a.s./l
Pimephales promelas *Fathead Minnow*	Early-life-stage CGA219417/0653	Early-life-stage toxicity; 36d flow-through exposure, US-EPA FIFRA 72-4(a); purity: 99.2%; dose= 0.114, 0.231, 0.455, 0.940 and 1.91 mg/L	NOEC=0.231 mg a.s/l

Species	Test	Duration and conditions	Result cyprodinil technical
Daphnia magna (Water flea)	Acute CGA219417/0461	Static freshwater, 48h exposure; US-EPA FIFRA 72-2(2) 1982; purity: 96.2 radiolabelled material ; dose= 0.022, 0.034, 0.061, 0.081 and0.126 mg/l	EC_{50} = 0.033 mg a.s./l

Daphnia magna (Water flea)	Chronic CGA219417/0543	Flow-through, 21 days exposure; US-EPA FIFRA 72-4(b) 1982; purity: 92.8%; dose= 0.0082, 0.019, 0.040, 0.079 and 0.147 mg/l	NOEC = 0.0082 mg a.s./l
Pseudokirchneriella subcapitata (Freshwater Green Algae)	Growth inhibition CGA219417/1030	72h exposure; OECD 201; purity: 99.4%; dose= 0.41, 0.94, 2.00, 4.41 and 9.47 mg/l	E_rC_{50} = 5.2 mg a.s./l E_bC_{50} = 2.6 mg a.s./l

Species	Test (observed Endpoints)	Duration and conditions	Result cyprodinil
Chironomus riparius	Spiked sediment exposure, emergence rate & development of midge CGA219417/1003	27 days exposure; OECD proposal of 1998; BBA Guideline 1995, purity: 99.4%; spiked sediment 20, 40, 80, 160, and 320 mg/kg	Sediment exposure: NOEC = 80 mg a.s./kg sediment
Apis mellifera (Honeybee)	Contact; Mortality / behaviour CGA219417/0532	48 hours exposure; EPPO 170 (1992); purity: 99.4%; Contact doses: of 54, 89, 196, 396, and 784 µg/bee	Contact LD_{50} = > 784 µg a.s./bee
Eisenia foetida	Acute toxicity, Mortality /	14 days exposure; OECD 207; purity: 99.6%;	LC_{50} = 192 mg a.i./kg soil

(Earthworm)	behaviour, CGA219417/0015	dose= 12.3, 37, 111, 333 and 1000 mg/kg soil	
Aerobic bacteria *(Sewage treatment plant sludge)*	Oxygen consumption CGA219417/0085	3 h exposure; 87/302/EEC; purity: 99.2%; dose= 1.1, 3.3, 10.5, 32.1, and 105.0 mg ai/l	EC_{50} > 100 mg ai/l

The results of extensive tests demonstrate the low acute and short-term toxicity of cyprodinil to birds.

Based on acute toxicity tests in the laboratory cyprodinil is classified as toxic to fish and algae and very toxic to crustaceans. Toxicity to the midge *Chironomus riparia* was low after application to sediment. In experiments in freshwater ponds a rapid dissipation of cyprodinil from the water phase was observed and toxicity to aquatic organisms was significantly reduced compared to laboratory results. Various assessments demonstrate that the risk to aquatic organisms is acceptable after recommended use in agriculture.

Cyprodinil has a low acute toxicity to honeybees and earthworms.

Cyprodinil was evaluated by the FAO/WHO JMPR in 2003.

Toxicity Class WHO (cyprodinil, proposed): III

Cyprodinil is classified by Xi; R43; N; R50/53; S-2; S-24; S-37; S-46; S-60; S-61 by the Directive 67/458/EEC 31st ATP.

Formulations and co-formulated active ingredients

The main formulation types available are WG and EC.

These WG formulations are registered and sold in many countries throughout the world.

The EC formulation is registered and sold in the United Kingdom. It is in the registration process in various other European countries.

Methods of analysis and testing

The analytical method for determination of cyprodinil is based on reversed phase HPLC with external standardisation and UV detection. The method including three identity tests based on retention time comparison in HPLC, in widebore capillary GC and comparison of IR spectra was presented at the 2008 CIPAC Meeting in Braunschweig, Germany and accepted as provisional CIPAC Method.

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

Physical properties

The physical properties, the methods for testing them and the limits proposed for the WG and EC formulations, comply with the requirements of the FAO/WHO Manual (revised 1st edition, 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 cyprodinil.

ANNEX 2: References

CGA219417/0107	1992. Report on vapour pressure curve.
CGA219417/0110	1992. Report on melting point / melting range.
CGA219417/0825	1997. Report on boiling point / boiling range.
CGA219417/0115	1992. Report on thermal stability and stability in air.
CGA219417/0338	1994. Report on solubility in pure water.
CGA219417/0106	1992. Report on water solubility (buffer solutions).
CGA219417/0105	1992. Report on octanol / water partition coefficient.
CGA219417/0462	1995. Hydrolysis of pyrimidinyl [^{14}C] CGA 219417 in aqueous buffered solutions at pH 5, 7 and 9.
CGA219417/0144	1992. Hydrolysis determination of [U-^{14}C-phenyl] CGA 219417 at different pH values.
CGA219417/0268	1994. Aqueous photolysis of pyrimidyl-labelled CGA 219417 under laboratory conditions.
CGA219417/0292	1994. Aqueous photolysis of phenyl labeled CGA 219417 under laboratory conditions.
CGA219417/0108	1992. Report on dissociation constant in water.
CGA219417/0878	1998. CGA 219417 - Dissociation constant.
CGA219417/0020	1990. Acute oral toxicity in the rat.
CGA219417/0021	1990. Acute dermal toxicity in the rat.
CGA219417/0026	1991. Acute inhalation toxicity in the rat.
CGA219417/0022	1990. Acute dermal irritation/corrosion study in the rabbit.
CGA219417/0023	1990. Acute eye irritation/corrosion study in the rabbit.
CGA219417/0746	1996. Skin sensitization test in the Guinea pig - Maximization test.
CGA219417/0045	1991. 3-Month oral toxicity study in rats (administration in food).
CGA219417/0044	1991. 3-Month subchronic oral toxicity study in Beagle dogs.
CGA219417/0122	1992. 12-Month chronic dietary toxicity study in Beagle dogs.
CGA219417/0025	1990. Salmonella and Escherichia/Liver-Microsome Tes
CGA219417/0028	1990. Gene mutation test with Chinese hamster cells V 79 (OECD CONFORM)
CGA219417/0040	1991. Cytogenetic test on Chinese hamster cells in vitro (EC-conform)
CGA219417/0058	1991. Autoradiographic DNA repair test on rat hepatocytes (OECD conform) in vitro.
CGA219417/0029	1990. Micronucleus Test, Mouse in vivo study.
CGA219417/0239	1994. 18-months carcinogenicity study in mice.
CGA219417/0252	1994. 24-Months carcinogenicity and chronic toxicity study in rats.
CGA219417/0162	1993. Two-generation reproduction toxicity study in rats with CGA 219417 technical (dietary administration).
CGA219417/0027	1991. Developmental Toxicity (Teratogenicity) Study in Rats
CGA219417/0039	1991. Developmental Toxicity (Teratogenicity) Study in Rabbits with CGA 219`417 tech. (Oral Administration)
CGA219417/0062	1992. Acute oral toxicity (LD50) to mallard duck
CGA219417/0067	1992. Acute oral toxicity (LD50) to bobwhite quail

CGA219417/0068	1992. Subacute dietary toxicity (LC50) to Mallard duck
CGA219417/0066	1992. Subacute dietary toxicity (LC50) to Bobwhite quail
CGA219417/0477	1995. Effects on reproduction in mallard duck after dietary administration
CGA219417/0478	1995. Effects on reproduction in bobwhite quail after dietary administration
CGA219417/0486	1995. Acute toxicity of CGA 219417 to the rainbow trout *Oncorhynchus mykiss*
CGA219417/0507	1995. Acute toxicity of CGA 219417 to the bluegill sunfish *Lepomis macrochirus.*
CGA219417/0651	1995. Acute flow-through toxicity of CGA 219417 to the bluegill sunfish *Lepomis macrochirus.*
CGA219417/0653	1995. Early-life-stage toxicity of CGA219417 to the fathead minnow, *Pimephales promelas.*
CGA219417/0461	1995. Acute flow-through toxicity of CGA219417 to the daphnid, *Daphnia magna.*
CGA219417/0543	1995. Chronic toxicity of CGA 219417 to the daphnid, *Daphnia magna.*
CGA219417/1030	1995. Toxicity of CGA219417 to Green algae (Growth Inhibition test).
CGA219417/1003	2000. Toxicity test of CGA219417 on sediment-dwelling *Chironomus riparius* (syn. Chironomus thummi) under static conditions.
CGA219417/0532	1995. Acute toxicity of CGA219417 to the honey bee, *Apis mellifera*.
CGA219417/0015	1990. Report on the acute toxicity test of CGA219417 technical to earthworm (Eisenia foetida foetida).
CGA219417/0085	1992. Report on the test for inhibitory concentrations on aerobic bacteria of CGA219417.