FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

CYMOXANIL

1-(2-cyano-2-methoxyiminoacetyl)-3-ethylurea

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.

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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/ag/agp/agpp/pesticid/)
OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.

PART ONE

SPECIFICATIONS

CYMOXANIL

INFORMATION

ISO common name

Cymoxanil (E-ISO, (m) F-ISO, BSI, ANSI)

Synonyms

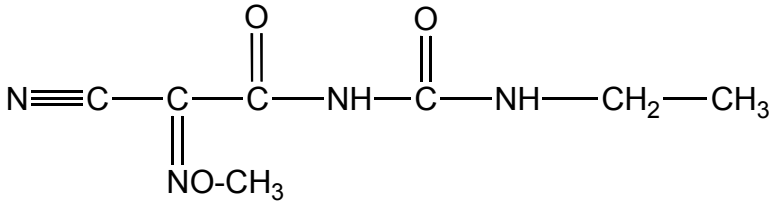
None

Chemical names

IUPAC: 1-(2-cyano-2-methoxyiminoacetyl)-3-ethylurea

CA: 2-cyano-*N*-[(ethylamino)carbonyl]-2-(methoxyimino)acetamide

Structural formula



Empirical formula

$C_7H_{10}N_4O_3$

Relative molecular mass

198.2

CAS Registry number

57966-95-7

CIPAC number

419

Identity tests

HPLC retention time; IR spectrum.

CYMOXANIL

TECHNICAL MATERIAL

FAO Specification 419/TC (March 2006*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports 419/2004 and 419/2005*. 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 reports* 419/2004 and 419/2005, *as PART TWO, form an integral part of this publication.*

1 Description

The material shall consist of cymoxanil together with related manufacturing impurities. It shall be a white to peach-coloured, homogeneous crystalline solid, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (CIPAC 419/TC/M/2, CIPAC handbook J, p.23, 2000)

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 **Cymoxanil content** (CIPAC 419/TC/M/3, CIPAC handbook J, p.23, 2000)

The cymoxanil content shall be declared (not less than 970 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/.

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WETTABLE POWDER

FAO Specification 419/WP (March 2006*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports 419/2004 and 419/2005*. 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 reports* 419/2004 and 419/2005, *as PART TWO, form an integral part of this publication.*

1 Description

The material shall consist of an homogeneous mixture of technical cymoxanil, complying with the requirements of FAO specification 419/TC (March 2006), together with filler(s) and any other necessary formulants. It shall be in the form of a fine powder free from visible extraneous matter and hard lumps.

2 Active Ingredient

2.1 **Identity tests** (CIPAC 419/WP/M/2, CIPAC handbook J, p.26, 2000)

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 **Cymoxanil content** (CIPAC 419/WP/M/3, CIPAC handbook J, p.26, 2000)

The cymoxanil 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:

Declared content, g/kg	Permitted tolerance
Above 500	± 25 g/kg

3 Physical Properties

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

Maximum: 2% retained on a 75µm test sieve.

3.2 **Suspensibility** (MT 184) (Notes 1 and 2)

A minimum of 70% of the cymoxanil found under 2.2 shall be in suspension after 30 minutes in CIPAC standard water D at 30 ± 2ºC (Note 3).

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

Maximum: 60 ml after 1 minute.

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

3.4 **Wettability** (MT 53.3.1) (Note 5)

The formulation shall be completely wetted in 1 minute, without swirling.

4 Storage Stability

4.1 **Stability at elevated temperature** (MT 46.3)

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 97% 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 (3.1);
- suspensibility (3.2);
- wettability (3.4).

Note 1 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in method MT184.

Note 2 The test will normally be carried out after the heat stability test 4.1.

Note 3 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, simpler methods such as gravimetric and solvent extraction determination may be used on a routine basis, provided that these methods have been shown to give equal results to those of the chemical assay method. In case of dispute, the chemical method shall be the “referee method”.

Note 4 The mass of sample to be used in the test should be at the highest rate of use recommended by the supplier.

Note 5 The product should be tested at 1.0 g. Although this amount of test substance is well below the 5.0 g sample size required by MT 53.3.1, it is still in excess of the maximum concentration recommended for use and is a sufficient quantity for accurate visual determination of wettability.

Note 6 Samples of the formulation taken before and after the storage test should be analyzed concurrently after the test in order to reduce analytical error.

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WATER DISPERSIBLE GRANULES

FAO Specification 419/WG (March 2006*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturers whose names are listed in the evaluation reports 419/2004 and 419/2005*. 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 reports* 419/2004 and 419/2005, *as PART TWO, form an integral part of this publication.*

1 Description

The material shall consist of an homogeneous mixture of technical cymoxanil, complying with the requirements of FAO specification 419/TC (March 2006), together with carriers and any other necessary formulants. It shall be in the form of granules for application after disintegration and dispersion in water. The product shall be dry, free flowing, nearly dust-free and free from visible extraneous matter, hard lumps.

2 Active Ingredient

2.1 **Identity tests** (CIPAC 419/WG/M/2, CIPAC handbook J, p.27, 2000)

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 **Cymoxanil content** (CIPAC 419/WG/M/3, CIPAC handbook J, p.27, 2000)

The cymoxanil 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:

Declared content, g/kg	Permitted tolerance
Above 250 up to 500 Above 500 Note: the upper limit is included in the lower range	± 5% of the declared content ± 25 g/kg

3 Physical Properties

3.1 **Wettability** (MT 53.3.1)

The formulation shall be completely wetted in 10 seconds, without swirling.

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

Maximum: 2% retained on a 75µm 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/ag/agp/agpp/pesticid/.

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

Dispersibility: minimum 75% after 1 minute of stirring.

3.4 **Suspensibility** (MT 184) (Notes 1 and 2)

A minimum of 70% of the cymoxanil found under .2.2 shall be in suspension after 30 minutes in CIPAC standard water D at 30 ± 2ºC.

3.5 **Persistent foam** (MT 47.2) (Note 3)

Maximum: 60 ml after 1 minute.

3.6 **Dustiness** (MT 171) (Note 4)

Nearly dust-free.

3.7 **Flowability** (MT 172)

A minimum of 99% of the product shall pass through a 5 mm test sieve after 20 drops of the sieve.

4 Storage Stability

4.1 **Stability at elevated temperature** (MT 46.3)

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 97% relative to the determined average content found before storage (Note 5) 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).

Note 1 The formulation should be tested at the highest and lowest rates of use recommended by the supplier, provided this does not exceed the conditions given in method MT184.

Note 2 Chemical assay is the only fully reliable method to measure the mass of active ingredient still in suspension. However, simpler methods such as 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, the chemical method shall be the “referee method”.

Note 3 The mass of sample to be used in the test should be at the highest rate of use recommended by the supplier.

Note 4 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, usually shows good correlation with the gravimetric method and can, therefore, be used as an alternative where the equipment is available. Where 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 5 Samples of the formulation taken before and after the storage test should be analyzed concurrently after the test in order to reduce analytical error.

PART TWO

EVALUATION REPORT

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EVALUATION REPORT 419/2005

Recommendations

The Meeting recommended that the existing FAO specifications for cymoxanil TC, WP and WG should be extended to include the products of Oxon Italia and that the TC description clause should be amended to encompass products from white to peach in colour.

Appraisal

Data provided by Oxon Italia were evaluated in support of the extension of existing (April 2005) FAO specifications for cymoxanil TC, WP and WG.

The manufacturer submitted confidential details of the manufacturing process, together with 5-batch analytical data and the manufacturing specifications (004/97; 001/2003). Mass balances were high (99.1-100.29%) and no unknowns were detected. These data were confirmed as essentially the same as those submitted by the company for registration in United Kingdom.

Comparing the Oxon Italia product with that of DuPont, the Meeting noted the occurrence of a new impurity at >1 g/kg, indicating that, on this criterion, the materials were not equivalent. The impurity is an intermediate in both manufacturing pathways. Oxon demonstrated that it does not interfere with the determination of cymoxanil using the CIPAC method and there was no evidence to suggest that it might increase or extend the hazards of cymoxanil.

In principle, *N*-nitrosamines might be formed in the manufacture of cymoxanil and the manufacturer therefore determined total *N*-nitrosamines in batches (96/829). The content of total *N*-nitrosamines was <1 mg/kg in all cases and the Meeting agreed that it was unnecessary to designate them as relevant impurities.

The toxicological and ecotoxicological profiles of cymoxanil TC produced by Oxon Italia indicated equivalence with DuPont cymoxanil. On this basis, the Meeting agreed that the former should be considered equivalent to the latter and that the additional impurity, found in Oxon Italia cymoxanil, should be designated non-relevant.

The Oxon TC was described as “whitish”, whereas the existing (April 2005) specification was for a peach-coloured material. The Meeting agreed that the description clause should be widened to encompass materials in the colour range white to peach coloured. Apart from this minor change, Oxon confirmed that its cymoxanil-based formulations (WP and WG) comply with the existing (April 2005) specifications. The Meeting acknowledged that this minor amendment to the TC specification required a consequential amendment of the WP and WG specifications, to reference the amended TC specification.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 419/2005

Table 1. Physico-chemical properties of pure cymoxanil (Oxon Italia)

Parameter	Value(s) and conditions	Purity %	Method	Reference
Vapour pressure	4.5×10^{-5} Pa at 25°C	99.1	92/69/EEC, A4, vapour pressure balance method	57/950183
Melting point, boiling point and/or temperature of decomposition	Melting point: 162°C Decomposition temperature: >206°C, melts without gas evolution	99.2	92/69/EE, A2	57/950183 374939
Solubility in water	0.88 g/l at 20°C at pH 4.0 0.78 g/l at 20°C at pH 7.0 2.70 g/l at 10°C at pH 10[1]	99.1-99.3	92/69/EEC A6, flask stirring method	57/950183 753 G
Octanol/water partition coefficient	log P_{OW} = 0.64 at 20°C, unbuffered. log P_{OW} = 1.3 at 20°C pH 3	99.1-99.3	92/96/EEC A8, shake flask and HPLC method	57/950183 754 G
Hydrolysis characteristics, half-life	>1 year at 20°C at pH 4.0 2.2 days at 20°C at pH 7.0 1.2 hours at 20°C at pH 9.0	>98.0, 99.1	92/96/EEC C7. SETAC. Procedures for assessing the environmental fate and ecotoxicity of pesticides. Aqueous hydrolysis (1995)	151/951108 308734
Photolysis characteristics	DT_{50} (sun test, pH 5, 25°C): 3.02 days DT_{50} (40˚N, summer): 12.11 days (extrapolated) Dark: about 92% present after 6-day exposure period (pH 5, 25°C)	98.0	SETAC. Procedures for assessing the environmental fate and ecotoxicity of pesticides. Aqueous hydrolysis (1995) US-EPA Pesticide assessment guidelines, subdivision N : Chemistry, Environmental	257759
Dissociation characteristics	pKa = 9.00	99.1	OECD 112 Volumetric titration	57/950183
Oxidizing characteristics	Under the conditions of this test cymoxanil technical does not possess oxidising properties. The original positive result was caused by the wick effect.	Not reported	EEC A17	58/950197

[1] Note: cymoxanil is hydrolyzed rapidly under alkaline conditions at 20°C.

Cymoxanil is an odorless white crystalline powder, with a density about 1.3x that of water. Cymoxanil has a fair solubility in water as well as in organic solvents.Bioaccumulation is most likely not relevant for cymoxanil, because its logPow is lower than 3 (log(Pow) cymoxanil = 0.64). In addition, cymoxanil degrades rapidly in an aqueous environment by hydrolytic process at pH >4 . Cymoxanil is sensitive to photodegradation.

Table 2. Chemical composition and properties of Oxon technical cymoxanil (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 99.1– 100.29%, with no unknowns detected.
Declared minimum cymoxanil content	970 g/kg
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 and/or TK	Melting point 162°C, decomposition occurs at >206°C, before boiling. Same results for purified and technical a.i. due to 99.2 and 99.1% purity, respectively)

Hazard summary

Cymoxanil has not been evaluated by IPCS and the FAO/WHO JMPR.

The WHO hazard classification of cymoxanil is: slightly hazardous, class III.

Cymoxanil was evaluated by the European Chemical Bureau in compliance with 67/548/EEC Directive. The EU classification is: harmful, dangerous for the environment, Xn, N, R 22, 43, 50/53, in accordance with Directive 2000/32/EC.

Formulations

The main formulation types produced by Oxon Italia are WP and WG and cymoxanil may be co-formulated with other fungicides, including mancozeb, folpet, chlorothalonil, copper salts and others. These formulations are registered and sold in many countries throughout the world including the European Union (Belgium, France, Greece, Hungary, Ireland, Italy, Malta, Portugal, Spain, The Netherlands, U.K.), South America (Argentina, Brazil, Colombia), Asia (Malaysia, Taiwan, Turkey), together with South Africa, Albania, Bulgaria, Israel, Romania, Switzerland.

Methods of analysis and testing

Oxon confirmed that the existing CIPAC methods for the determination of active ingredient content and for testing physical properties are satisfactory for use with their products.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: Oxon Italia provided written confirmation that the toxicological and ecotoxicological data included in the following summary were derived from cymoxanil having impurity profiles similar to those referred to in Table 2, above.

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

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Rat, CD strain (M/F)	oral	OECD 401 Cymoxanil TC (98.8%)	LD_{50} = 3100 mg/kg bw. 14-day observation. Mortality occurred among females only. Clinical signs: piloerection, abnormal body carriage, abnormal gait, body tremors, lethargy, decreased respiratory rate, pallor of the extremities, increased urine production, increased salivation clonic convulsions, walking on toes, unsteadiness, excitable behaviour, hair loss, prostration, cold body surfaces, protrusion of the eyes and dark yellow staining of urine.	62/940828/AC
Rat, CD strain (M/F)	dermal	OECD 402 Cymoxanil TC (97.6%)	LD_{50} >2000 mg/kg bw No mortality or clinical signs of systemic toxicity. Site of application showed no irritation or other dermal changes	41/940326/AC
Rat, CD strain (M/F)	inhalation	OECD 403 Cymoxanil TC (98.8%)	LC_{50} >3.90 mg/l One female died on day 1 following exposure. Clinical signs: exaggerated respiratory movements, staggering gait, vocalization, lethargy, red staining around the eyes, yellow staining around urogenital region, brown staining around snout, jaws, eyes, head and underbody, and matted fur.	83/950684
Rabbit, New Zealand white (M/F)	skin irritation	OECD 404 Cymoxanil TC (97.6%)	Non-irritant and no signs of toxicity or ill health.	42/940217/SE
Rabbit, New Zealand white (M/F)	eye irritation	OECD 405 Cymoxanil TC (97.6%)	Non-irritant and no signs of toxicity or ill health.	43/940244/SE
Guinea pig, Dunkin/Hartley strain (M)	skin sensitization	OECD 406, maximization test, Cymoxanil TC (99.4%)	Non-sensitizing.	29800123

Cymoxanil technical does not need to be classified for acute oral, dermal or inhalation toxicity (LD_{50} oral 3100 mg/kg bw, LD_{50} dermal >2000 mg/kg bw, LC_{50} inhalation >3.90 mg/l).

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

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Rat, Wistar strain (M/F)	feeding, sub-chronic toxicity, 90 d	OECD 408 (1981), 87/302/EEC part B (No. L133/8 Cymoxanil TC (98.8%)	NOEL (combined) = [45.6] mg/kg bw/day LOEL (combined) = [91.4] mg/kg bw/day	2143/96
Mouse, Swiss albino strain (M/F)	feeding, sub-chronic toxicity, 90 d	OECD 408 (1981), 87/302/EEC part B (No. L133/8) Cymoxanil TC (98.8%)	NOEL (combined) = [30.8] mg/kg bw/day NOAEL (combined) = [90.9] mg/kg bw/d	2144/96
Dog, Beagle strain (M/F)	feeding, sub-chronic toxicity, 90 d	OECD 409, OPPTS 870.3150, August 1998 (EPA 712-C-98-200) Cymoxanil TC (98.8%)	NOEL (combined) = [5.9] mg/kg bw/d LOEL (combined) = [9.8] mg/kg bw/day	2145/96
Rat, Wistar strain, (M/F)	feeding, carcinogenicity, 104 weeks	OECD 453, 87/302/EEC part B (No. L133/37), OPPTS 870.4300 (adopted : EPA 712-C-98-212) Cymoxanil TC (98.8%)	NOEL (overall combined) = 5.6 mg/kg bw/day No consistent changes attributable to cymoxanil. Incidental tumours were unrelated to cymoxanil.	2153/96
Mouse, Swiss albino strain, (M/F)	feeding, carcinogenicity, 80 weeks	OECD 451; 87/302/EEC, B: Carcinogenicity test (L133/32); OPPTS 870.4200 Cymoxanil TC (98.8%)	NOEL (overall combined) = 18.6 mg/kg bw/day No treatment-related mortality, clinical signs or pathology. Incidental tumours were unrelated to cymoxanil.	2152/96
Rat, Wistar strain strain (M/F)	feeding, 2-generation reproduction	OECD 416 Cymoxanil TC (98.8%)	NOAEL (parents combined) = 12.7 mg/kg bw/day NOAEL (offspring combined) = 13.3 mg/kg bw/day Except reduced body weight and decreased feed intake in P and F_1 generations at highest dose, no obvious adverse effects on the developing conceptus at any dose.	2155/96
Rat, Wistar strain (M/F)	teratogenicity and developmental toxicity	OECD 414 Cymoxanil TC (98.8%)	NOEL (parents) = 60 mg/kg bw/day NOEL (developing conceptus) = 120 mg/kg bw/day No primary teratogenic or embryotoxic potential at any dose.	2150/96
Rabbit, New Zealand White strain (M/F)	teratogenicity and developmental toxicity	OECD 414 Cymoxanil TC (98.8%)	NOEL (parents) = 15 mg/kg bw/day NOEL (developing conceptus) = 15 mg/kg bw/day No primary teratogenic or embryotoxic potential at any dose.	2151/96

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

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Rat, Wistar strain (M/F)	Repeated dose (28 d) dermal toxicity study	OECD 410 Cymoxanil TC (98.8%)	NOEL = 1000 mg/kg bw/day	2149/96

In the 90-d dietary toxicity study in rats, a NOEL of 500 ppm (42.6 mg/kg bw/day, males) was established based on a decreased relative kidney weight and changes in clinical biochemistry (calcium, total bilirubin) at 1000 ppm. At the higher dose level of 2000 ppm (181 mg/kg bw/day, combined sexes), reduced body weight and food consumption, a reduced red blood cell count and changes in clinical biochemistry (creatinine, albumine, calcium, inorganic phosphate, total bilirubin) were noted. These latter effects were not completely reversible after a recovery period of 28 d.

A NOEL of 150 ppm (28.7 mg/kg bw/day, males) was established in the 90-day dietary toxicity study in mice, based on increased incidences of vacuolar changes in the liver and increased creatinine levels at 450 ppm. At the highest dose level of 1350 ppm decreased body weight (gain) and food consumption, increased liver weight and increased incidences of vacuolar changes in the liver, and changes in clinical biochemistry (total bilirubin, creatinine, chloride, total protein) were noted. After a recovery period of 28 d, changes in creatinine and chloride, and the histopathological changes in liver were still present for the highest dose level group.

In the 90-day dietary toxicity study in dogs, the observation of reduced body weight gain, a decreased absolute and relative thymus weight and lymphoid atrophy in the thymus at 400 ppm resulted in a NOEL of 200 ppm, which corresponds to 4.9 mg/kg bw/day in males. In the 1-year dietary toxicity study in dogs, at the highest dose given to males (200 ppm, which corresponds to 5.6 mg/kg bw/day), all males showed a reduced body weight and one male showed lenticular degeneration in both eyes. No treatment-related effects were observed in the females administered the highest dose given to females (100 ppm, which corresponds to 2.9 mg/kg bw/day). The NOAEL in this study in dogs was defined to be 100 ppm, corresponding to 2.8 mg/kg bw/day in males. In rats, following repeated dermal exposure to Cymoxanil for 28 d, no effects were recorded at the highest dose administered (1000 mg/kg bw/day). No local dermal effects were observed at the site of application. A NOEL of 1000 mg/kg bw/day was established. Chronic toxicity and carcinogenicity studies in rats and mice showed some effects as decrease in body weights and food consumption, but no carcinogenic activity (incidental tumours were unrelated to the treatment). In the 2-year combined chronic toxicity/carcinogenicity study in rats, a NOEL of 100 ppm (4.7 mg/kg bw/day, males) was established, based on reduced food consumption and body weights at 500 ppm. No other treatment-related changes were noted. In the 18-month carcinogenicity study in mice, a NOEL of 120 ppm (18.6 mg/kg bw/day, females and combined sexes) was established, based on reduced food consumption and reduced body weights at 600 ppm. No other treatment-related changes were noted.

In the oral 2-generation reproduction study in rats, the NOEL for parental effects was 150 ppm, corresponding to 10.5 mg/kg bw/day for males and 14.9 mg/kg bw/day for females, based on reduced body weight and food consumption at 450 ppm. The NOEL for developmental effects was set at the same level, based on reduced body weight and survival index. No effects on fertility were observed.

No teratogenic effects were observed up to the highest dose tested in both teratogenicity studies in rats and rabbits. NOELs were therefore established on the basis of general toxicity effects.

In the oral teratogenicity study in rats, a NOEL of 60 mg/kg bw/day was set for maternal and developmental effects. Maternal effects included reduced body weights and food consumption. Developmental effects included an increased number of late resorptions and associated post-implantation loss and a decrease in fetal weights.

In the oral teratogenicity study in rabbits, an overall NOEL of 15 mg/kg bw/day was established based on reduced body weights and food consumption, and an increased incidence of the renal pelvis dilation and dilation of the ventricles of the heart, for maternal and developmental effects respectively.

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

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Salmonella typhimurium	*in vitro* gene mutation assay	OECD 471 Cymoxanil TC (98.8%)	Not mutagenic	2146/96
Chinese hamster ovary cells	*in vitro* gene mutation in mammalian cells	OECD 476. EEC Directive 87/302/EEC Cymoxanil TC (98.8%)	Not mutagenic	2147/96
Chinese hamster ovary cells	*in vitro* cytogenetic assay, mammalian chromosome aberrations	OPPTS 8705375 Cymoxanil TC (98.8%)	Negative	2148/96
Mouse, Wistar strain	*in vivo* micronucleus test	OECD 474 Cymoxanil TC (98.8%)	Negative	2611/99

Cymoxanil did not induce gene mutations in bacteria or in mammalian cells *in vitro* either in the presence or absence of metabolic activation. Cymoxanil did not induce chromosome aberrations in mammalian cells *in vitro* and did not show any mutagenic potential in a micronucleus test in mice *in vivo*. It was concluded that there are no indications for genotoxic properties of cymoxanil.

Table D. Ecotoxicology profile of Oxon cymoxanil technical material

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Oncorhyncus mykiss (rainbow trout)	96-h short-term toxicity, flow-through	OECD 203, 92/69/EEC C1 Cymoxanil TC (98.8%)	LC_{50} >4.9 x 10^{-2} g/l (measured)	107A/(c)/951882

Table D. Ecotoxicology profile of Oxon cymoxanil technical material

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Cyprinus carpio (common carp)	96-h short-term toxicity, flow-through	OECD 203 Cymoxanil TC (98.8%)	LC_{50} >0.1 g/l (measured)	257434
Daphnia magna (water flea)	48-h acute toxicity	OECD 202, 92/69/EEC C2 Cymoxanil TC	EC_{50} = 6.1 x 10^{-3} g/l (measured)	107A/(b)/950956
Selenastrum capricornutum (green alga)	algal growth inhibition test	OECD 201, 92/69/EEC C3 Cymoxanil TC (98.8%)	EC_{50} = 0.35 x 10^{-3} g/l (measured)	107A/(a)/950955
Eisenia foetida (earthworm)	acute toxicity, 14 d	OECD 207; 87/302/EEC, C.8. Cymoxanil TC (99.1%)	LC_{50} >1.0 g/kg dry soil	78A/950675
Soil micro-organisms	nitrogen transformation, carbon mineralisation	OECD 216 217 Cymoxanil TC (99.2%)	No effects at 1.6 10^{-3} g/kg soil	20031214/01
Activated sludge micro-organisms	respiration rate	EC Directive 87/302 Part C, OECD 209. Cymoxanil TC (98.8%)	EC_{50} = 19.4 x 10^{-3} g/l EC_{80} >32 x 10^{-3} g/l	308767
Apis mellifera (honey bee)	acute oral toxicity and acute contact toxicity	EPPO Guideline 170 Cymoxanil TC (98.9%)	LD_{50} oral >85.3 µg/bee LD_{50} contact >100 µg/bee	99063/01
Colinus virginianus (bobwhite quail)	acute oral toxicity	EPA Subdivision E, §71-1, 1982 and draft revised guideline 1988. Cymoxanil TC (99.1%)	LD_{50} >2 g/kg bw	69A/950758
Colinus virginianus (bobwhite quail)	sub-acute, 5-d dietary toxicity	EPA Subdivision E, §71-2, 1982 and draft guideline 1988; OECD 205 Cymoxanil TC (98.9%)	LC_{50} >5.2 g/kg diet NOEC = 1.3 g/kg diet	215/970985

Table D. Ecotoxicology profile of Oxon cymoxanil technical material

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Anas platyrhynchos (mallard duck)	acute oral toxicity	[EPA FIFRA 71-1, 1982; EPA FIFRA 71-1, 1989; EPA TSCA 797.2175, 1991; EPA OPPTS 850.2100, 1996; OECD 401, 1987; SETAC Procedure, pp 35-37, 1999 Cymoxanil TC (98.9%)	LD_{50} >2 g/kg bw	257377
Anas platyrhynchos (mallard duck)	sub-acute, 5-d dietary toxicity	U.S. EPA FIFRA 71-2 1982; U.S. EPA FIFRA 71-2 1989; U.S.EPA TSCA 797.2050 1991, U.S. EPA OPPTS 850.2200 1996; and OECD 205 1984 Cymoxanil TC (98.9%)	LC_{50} = 2.944 g/kg diet NOEC = 0.313 g/kg diet	257401
Colinus virginianus (bobwhite quail)	dietary reproduction and tolerance study.	U.S. EPA FIFRA 71-4 1989; U.S.EPA TSCA 797.2130 1991, U.S. EPA OPPTS 850.2300 1996; and OECD 206 1984 Cymoxanil TC (98.9%)	NOEC = 0.250 g/kg diet	262518

The lowest acute toxicity value for cymoxanil technical material to aquatic organisms was 0.35 mg/l, for green algae. Despite the high toxicity toward this species, when used in accordance with the label recommendations it was concluded that cymoxanil does not pose a significant risk to aquatic species.

The acute contact and oral toxicities of cymoxanil to honeybees was greater than the maximum dose administered, 85.3 and 100 µg/bee for oral or contact administration, indicating that the compound is poses low risks to foraging honey bees.

Cymoxanil is of low acute oral toxicity and low sub-acute (short-term dietary toxicity) to birds. The acute oral LD_{50} for bobwhite quail and mallard duck was greater than the highest dose administered, 2000 mg/kg. For bobwhite quail, the dietary LC_{50} was also greater than the highest concentration administered, 5200 ppm. No adverse parental effects were noted after exposure of breeding pairs of bobwhite quail to cymoxanil at dietary concentrations up to 1000 mg/kg diet. Adverse effects on egg production, eggshell quality, embryo viability, embryo survival and hatchability and offspring parameters (mortality, body weight and growth rate) were observed in birds receiving cymoxanil at 1000 mg/kg in the diet and the overall NOEC was considered to be 250 mg/kg diet. Cymoxanil is not expected to pose any significant acute and chronic risk to terrestrial vertebrates when applied at label recommended doses.

The LC_{50} of cymoxanil to earthworms was >1000 mg/kg soil, indicating no anticipated acute risk to earthworms. No significant effects of cymoxanil on soil microbial respiration and nitrogen transformation were observed at 600 g/kg and it is not expected to pose risks to soil microbial populations when applied at label recommended doses.

ANNEX 2. REFERENCES

Oxon Italia document No.	Year and title or published reference
001/2003	2003. Cymoxanil technical: analytical profile of OXON production.
004/97	1997. Cymoxanil tech.: analytical profile of Oxon production.
107A/(a)/950955	1996. Cymoxanil Technical: algal growth inhibition.
107A/(b)/950956	1996. Cymoxanil Technical: acute toxicity to *Daphnia magna.*
107A/(c)/951882	1996. Cymoxanil Technical: acute toxicity to rainbow trout (*Onchorhyncus mykiss*).
151/951108	1995. Cymoxanil: further investigation of the hydrolysis at pH 4.
20031214/01	2003. Assessment of the side effects of cymoxanil technical on the activity of the soil microflora.
2143/96	1999. Subchronic (90 day) oral toxicity study with Cymoxanil Technical in Wistar rats.
2144/96	1999. Subchronic (90 day) oral toxicity study with Cymoxanil Technical in Swiss albino mice.
2145/96	1999. Subchronic (90 day) oral toxicity study with Cymoxanil Technical in Beagle dogs.
2146/96	1997. Genetic toxicology: *Salmonella typhimurium* reverse mutation assay with Cymoxanil Technical.
2147/96	1998. Genetic toxicology: *In vitro* mammalian cell gene mutation test with Cymoxanil Technical.
2148/96	2000. *In vitro* mammalian chromosome aberration test with Cymoxanil Technical.
2149/96	1998. Repeated dose (28 day) dermal toxicity study with Cymoxanil Technical in Wistar rats.
215/970985	1997. Cymoxanil Technical: dietary LC50 to the bobwhite quail.
2150/96	1998. Teratogenicity study in Wistar rats with Cymoxanil Technical.
2151/96	1999. Teratogenicity study in rabbits with Cymoxanil Technical.
2152/96	2002. Carcinogenicity study with Cymoxanil Technical in Swiss albino mice.
2153/96	2003. Combined chronic toxicity and carcinogenicity study with Cymoxanil Technical in Wistar rats.
2155/96	2001. Two generation reproduction toxicity study with Cymoxanil Technical in Wistar rats.
257377	1999. Acute oral toxicity study in the mallard duck with Cymoxanil Technical.
257401	1999. 5-day dietary toxicity study in mallard duck with Cymoxanil Technical.
257434	1999. 96-hour acute toxicity study in carp with Cymoxanil Technical (flow-through).
257759	2000. Photodegradation of Cymoxanil in water.
2611/99	1999. Mutagenicity study – Micronucleus test in Swiss albino mice with Cymoxanil Technical.
262518	2000. Reproduction study in bobwhite quail with Cymoxanil Technical (by dietary admixture).
29800123	2003. Technical Cymoxanil: skin sensitization study in the guinea-pig (Magnusson Kligman maximization).
308734	2003. Aqueous hydrolysis of Cymoxanil.
308767	2001. Activated sludge respiration inhibition test with Cymoxanil Technical (contact time 3 hours).
374939	2003. Determination of the melting and boiling temperature of Cymoxanil Technical by differential scanning calorimetry.
41/940326/AC	1994. Cymoxanil Technical - Acute dermal toxicity to the rat.
42/940217/SE	1994. Cymoxanil – Skin irritation to the rabbit.
43/940244/SE	1994. Cymoxanil – Eye irritation to the rabbit
57/950183	1995. Cymoxanil (pure): physicochemical properties.

Oxon Italia document No.	Year and title or published reference
58/950197	1995. Cymoxanil (technical): Physico-chemical properties.
62/940828/AC	1995. Cymoxanil Technical - Acute oral toxicity to the rat.
69A/950758	1996. Cymoxanil Technical: acute oral toxicity (LD50) to the bobwhite quail.
753 G	2004. Cymoxanil: determination of the water solubility including effects of pH (4 to 10) on solubility.
754 G	2004. Cymoxanil: Determination of partition coefficient n-octanol/water (log Pow) at acid pH.
78A/950675	1995. Cymoxanil Technical: Acute toxicity (LC50) to the earthworm (*Eisenia foetida*).
83/950684	1996. Cymoxanil Technical - Acute inhalation toxicity in rats – 4-hour snout only exposure.
96/829	1996. Cymoxanil technical active substance: determination of dimethylsulfate and total N-nitrosamines.
99063/01	1999. Assessment of side effects of Cymoxanil Technical to the honey bees *Apis mellifera* L. in the laboratory.
CIPAC J	CIPAC Handbook, volume J. Analysis of technical and formulated pesticides, pp. 22-28. Eds. W. Dobrat and A. Martijn. Collaborative International Pesticides Analytical Council, Harpenden, U.K., 2000.

CYMOXANIL

EVALUATION REPORT 419/2004

Explanation

Data for Cymoxanil were evaluated in support of the review of existing FAO specifications for the technical material (TC), wettable powder (WP), and water dispersible granules (WG), which had been published in 2000 (AG:CP/366).

Cymoxanil is not under patent.

Cymoxanil has not been evaluated by the IPCS or the FAO/WHO JMPR. It was registered in Sweden in 2000 and a review process has been initiated in the EU (list 4B, Austria is the rapporteur member state).

The draft specification and the supporting data were provided by E. I. du Pont de Nemours and Company in 2003.

Uses

Cymoxanil is a foliar fungicide, with protective and curative action. It has contact and local systemic activity, and also inhibits sporulation. It is used in agriculture and horticulture against pathogens belonging to the order Peronosporales, namely *Phytophthora, Plasmopara* and *Peronospora* spp., which cause downy mildew and blight in a wide range of crops, such as grapes, tomatoes, and potatoes.

Identity of the active ingredient

ISO common name

Cymoxanil (E-ISO, (m) F-ISO, BSI, ANSI)

Synonyms

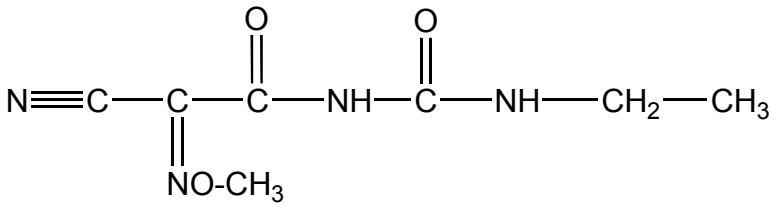
None

Chemical names

IUPAC: 1-(2-cyano-2-methoxyiminoacetyl)-3-ethylurea

CA: 2-cyano-*N*-[(ethylamino)carbonyl]-2-(methoxyimino)acetamide

Structural formula



Empirical formula

$C_7H_{10}N_4O_3$

Relative molecular mass

198.2

CAS Registry number

57966-95-7

CIPAC number

419

Identity tests

HPLC retention time; IR spectrum.

Physico-chemical properties of cymoxanil

Table 1. Physico-chemical properties of pure cymoxanil

Parameter	Value(s) and conditions	Purity	Method	Reference
Vapour pressure	1.5×10^{-4} Pa at 20°C	99.9%	OECD 104 EEC Method A4	2537-92
Melting point, boiling point and/or temperature of decomposition	Melting point: 162°C * Boiling point: not known Decomposition temperature: not known Sublimation temperature: 180°C	99.6%	OECD 102, Official Journal of the European Communities, Method A.1; and U.S. EPA OPPTS 830.7200	4286
Solubility in water	700 mg/l at 10°C at pH 5 620 mg/l at 10°C at pH 7 890 mg/l at 20°C at pH 5 780 mg/l at 20°C at pH 7 1200 mg/l at 30°C at pH 5 1000 mg/l at 30°C at pH 7	99.9%	U.S. EPA Pesticide Assessment Guidelines Subdivision D, 63-8	2526-92
Octanol/water partition coefficient	K_{OW} = 3.9 (log P = 0.59) at 20°C at pH 5 K_{OW} = 4.7 (log P = 0.67)at 20°C at pH 7	99.9%	EEC method A8, OECD 107	2581-92
Hydrolysis characteristics	Half-life = 148 days at 25°C at pH 5 Half-life = 34 hours at 25°C at pH 7 Half-life = 31 minutes at 25°C at pH 9	^{14}C cymoxanil	EPA Guideline Subdivision N Chemistry: Environmental Fate 161-1	3677-95
Photolysis characteristics	Artificial sunlight (xenon lamp): Half-life = 1.8 days at 25°C at pH 5 Half-life = 5.2 hours at 25°C at pH 7 Dark: Half-life = 148 days at 25°C at pH 5 Half-life = 12.6 hours at 25°C at pH 7	^{14}C cymoxanil	U.S. EPA Pesticide Assessment Guidelines Subdivision N, 161-2	1990-91
Dissociation characteristics	pKa = 9.7 ± 0.2	99.9%	OECD guideline 112	2589-92

Parameter	Value(s) and conditions	Purity	Method	Reference
Oxidizing characteristics	Classified as an oxidizer according to the results of the test, although cymoxanil does not have oxidizing properties.	Not reported	EEC A17	Not stated

* New data included provided to FAO but not yet assessed by a regulatory agency. The study was submitted to the Austrian authorities, as Rapporteur Member State for the EU in September, 2004, in support of product registration.

Cymoxanil was found to be non-flammable, not sensitive to thermal impact or friction stimuli, and negative for self-ignition. Cymoxanil was found to be an oxidizer, as defined by EEC A17, but for practical purposes it is not considered to have oxidizing properties.

Chemical composition and properties of technical cymoxanil

Table 2. Chemical composition and properties of cymoxanil 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 98.7-100.2%.
Declared minimum cymoxanil content	970 g/kg.
Relevant impurities ≥1 g/kg and maximum limits for them	None.
Relevant impurities <1 g/kg and maximum limits for them:	None.
Stabilizers or other additives and maximum limits for them:	None.
Melting temperature range of the TC	159-160 °C (Thomas Hoover melting point apparatus)

Toxicological summaries

Notes.

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from cymoxanil having impurity profiles similar to those referred to in the table above.
(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

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

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Male and female rat (Crl:CD®BR)	Acute oral	OECD 401, US EPA 81-1; cymoxanil technical (97.8%)	males LD_{50} = 760 mg/kg bw females LD_{50} = 1200 mg/kg bw	63-92
Male and female mouse (Crl:CD®-1[ICR]BR Mice)	Acute oral	OECD 401, US EPA 81-1, MAFF Japan 1985; cymoxanil technical (97.8%)	males LD_{50} = 1100 mg/kg bw females LD_{50} = 660 mg/kg bw	201-92

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Male and female rabbit (New Zealand White)	Acute dermal	OECD 402, US EPA 81-2, MAFF Japan 1985; cymoxanil technical (97.8%)	LD_{50} >2000 mg/kg bw (males and females)	149-92
Male and female rat (Crl:CD®BR)	Acute inhalation	OECD 403, US EPA 81-3, MAFF Japan 1985; cymoxanil technical (98.2%)	LC_{50} >5.06 mg/l (males and females)	83-92 RV1
Male and female rabbit (New Zealand White)	Skin irritation	EEC test method B4, OECD 404; cymoxanil technical (97.8%)	Dermal non-irritant	787-91 RV1
Male rabbit (New Zealand White)	Eye irritation	OECD 405, US EPA 81-4, MAFF Japan 1985, EEC 84/49 Method B5; cymoxanil technical (97.8%)	Ocular non-irritant	97-92
Male and female Guinea pig (Duncan-Hartley Albino)	Skin sensitization	OECD 406, US EPA 81-6, MAFF Japan 1985; cymoxanil technical (97.8%)	Non-sensitizing*	255-92

* Cymoxanil is presently classified as a skin sensitizer by the European Chemicals Bureau, on the basis of a study conducted by another manufacturer. No information was available on the purity/impurity profile of the cymoxanil tested in that study.

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

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Male and female rat (Crl:CD®BR)	90 day feeding study	OECD 408, US EPA 82-1, MAFF Japan 1985; cymoxanil technical (97.6%)	NOAEL = 750 ppm for males (47.6 mg/kg bw/day) and 750 ppm for females (59.9 mg/kg bw/day)	370-91 RV1
Male and female mouse (Crl:CD®-1[ICR]BR Mice)	90 day feeding study	OECD 408, US EPA 82-1, MAFF Japan 1985; cymoxanil technical (97.6%)	NOAEL <50 ppm for males (<8.25 mg/kg bw/day) and 50 ppm for females (11.3 mg/kg bw/day)	HLR 630-91 RV1
Male and female Beagle dog	90 day feeding study	OECD 409, US EPA 82-1, MAFF Japan 1985; cymoxanil technical (97.8%)	NOAEL = 100 ppm for males (3 mg/kg bw/day) and <100 ppm for females (<3 mg/kg bw/day)	797-92
Male and female Beagle dog	1 year feeding study	OECD 452, US EPA 83-1, MAFF Japan 1985; cymoxanil technical (97.8%)	NOAEL = 100 ppm for males (3.0 mg/kg bw/day) and 50 ppm for females (1.6 mg/kg bw/day)	65-94
Male and female rat (Crl:CD®BR)	28 day dermal study	EEC Method B.9, OECD 410, US EPA 82-2, MAFF Japan 1985; cymoxanil technical (97.8%)	NOAEL for systemic effects = 1000 mg/kg bw/day for males and females. NOAEL for local dermal effects = 500 mg/kg bw/day for males and 1000 mg/kg bw/day for females	Not stated

Species	Test	Duration and conditions or guideline adopted	Result	Reference
Male and female rat (Crl:CD®BR)	24 month feeding chronic toxicity/ oncogenicity study	OECD 453, US EPA 83-5, MAFF Japan 1985; cymoxanil technical (97.8%)	Not oncogenic NOEL = 100 ppm for males (4.08 mg/kg bw/day) and 100 ppm for females (5.36mg/kg bw/day)	678-93
Male and female mouse (Crl:CD-1®)	18 month feeding oncogenicity study	OECD 451, US EPA 83-2, MAFF Japan 1985; cymoxanil technical (97.8%)	Not oncogenic NOAEL = 30 ppm for males (4.19 mg/kg bw/day) and 30 ppm for females (5.83 mg/kg bw/day).	677-93
Male and female rat (Crl:CD®BR)	Two-generation reproductive toxicity study	OECD 416, US EPA 83-4, MAFF Japan 1985; cymoxanil technical (97.8%)	Parental NOAEL = 100 ppm (6.50 mg/kg bw/day for males and 7.85 mg/kg bw/day for female). Pup NOAEL = 100 ppm No effects on reproduction or fertility	568-93
Female rat (Crl:CD®BR)	Developmental toxicity study	OECD 414, US EPA 83-3, MAFF Japan 1985; cymoxanil technical (97.8%)	Maternal and foetal NOEL = 10 mg/kg bw/day Not uniquely toxic to the foetus Maternal NOAEL = 25 mg/kg bw/day*	744-92
Female rabbit (New Zealand White)	Developmental toxicity study	US EPA 83-3, in-house; cymoxanil technical (95.8%)	Maternal and foetal NOEL = 4 mg/kg bw/day Not uniquely toxic to the conceptus Maternal NOAEL 32 mg/kg bw/day*	467-82 SU1

* Evaluation by the US EPA (USEPA 2003). The European Chemicals Bureau concluded that R63 (possible risk of harm to the unborn child) was not warranted for this substance. The ECB classification of cymoxanil is: "Xn: harmful, R22: harmful if swallowed, R43: may cause sensitization by skin contact" (EU 2000). There have been no developmental toxicity studies subsequently conducted that would warrant reconsideration of the ECB decisions.

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

Species	Test	Conditions	Result	Reference
Salmonella typhimurium	*In vitro* bacterial gene mutation	OECD 471, US EPA 842, MAFF Japan 1985; cymoxanil technical (97.8%)	Negative	573-92
Human lymphocytes	*In vitro* chromosome aberration (clastogenicity)	OECD 473, US EPA 84-2, MAFF Japan 1985; cymoxanil technical (97.8%)	Positive with and without S-9 activation	835-92
CHO cells	*In vitro* mammalian cell mutagenicity (CHO/HGPRT)	OECD 476, US EPA 84-2; cymoxanil technical (97.8%)	Negative	826-92
Rat primary hepatocytes	*In vitro* unscheduled DNA synthesis (UDS)	OECD 482, US EPA 84-2; cymoxanil technical (97.8%)	Positive	796-92

Species	Test	Conditions	Result	Reference
Mouse bone marrow; Crl:CD®-1(ICR)BR	*In vivo* micronucleus	OECD 474, US EPA 84-2, MAFF Japan 1985; cymoxanil technical (97.8%)	Negative	827-92
Rat bone marrow (Sprague Dawley)	*In vivo* chromosome aberration (clastogenicity)	In house method; cymoxanil technical (98%)	Negative	3-83
Rat hepatocytes and spermatocytes	*In vivo* unscheduled DNA synthesis	OECD 482, US EPA 84-2; cymoxanil technical (97.8%)	Negative	169-94

Table 6. Ecotoxicology profile of technical cymoxanil

Species	Test	Duration and conditions	Result *	Reference
Daphnia magna (water flea)	48 hour acute toxicity	OECD 202; US EPA 72-4; cymoxanil technical (97.8%)	EC_{50} = 27 mg a.s./l NOEC = 15 mg a.s./l	736-92
Daphnia magna (water flea)	21-day chronic toxicity	OECD 202; US EPA 72-4; cymoxanil technical (97.8 %)	NOEC = 0.067 mg a.s./l	354-93 RV1
Selenastrum capricornutum (alga)	Growth and reproduction	OECD 201, EU Commission Directive 92/69/EEC Method C.3; US EPA 123-2; cymoxanil technical (97%)	NOEC = 0.622 mg a.s./l (based on cell density and growth rate) NOEC <0.622 mg a.s./l (based on area under the growth curve)	2498
Lemna gibba G3	Growth and reproduction	US EPA 122-2; cymoxanil technical (97.3%)	14 day EC_{50} >0.7 mg a.s./l (based on plant numbers) 14 day EC_{50} >0.7 mg a.s./l (based on plant biomass)	3775-96
Eisenia foetida (earthworm)	Acute 14 day soil exposure	OECD 207; cymoxanil technical (>96%)	LC_{50} = 2208 mg a.s./kg NOEC = 500 mg a.s./kg	8548
Apis mellifera (honey bee)	Acute dietary	US EPA 141-1; cymoxanil technical (97.8%)	48 hr acute LD_{50} >1000 ppm NOEL ≥1000 ppm	99-93
Apis mellifera (honey bee)	Acute contact	US EPA 141-1; cymoxanil technical (97.8%)	LD_{50} >25 µg a.s./bee NOEL = 25 µg a.s./bee	100-93
Lepomis macrochirus (bluegill sunfish)	96-hour static acute	OECD 203; US EPA72-1; cymoxanil technical (97.8%)	LC_{50} = 29 mg a.s./l NOEC = 17 mg a.s./l	834-92
Cyprinus carpio (common carp)	96-hour static acute	OECD 203; US EPA 72-1; cymoxanil technical (97.8%)	LC_{50} = 91 mg a.s./l NOEC = 47 mg a.s./l	734-92

Species	Test	Duration and conditions	Result *	Reference
Oncorhynchus mykiss (rainbow trout)	96-hour static acute	OECD 203; U.S. EPA 72-1; cymoxanil technical (97.8)	LC_{50} = 61 mg a.s./l NOEC = 28 mg a.s./l	735-92
Oncorhynchus mykiss (rainbow trout)	Chronic 21-day flow-through (unaerated)	OECD 204; cymoxanil technical (97.8%)	NOEC = 0.22 mg a.s./l, based on effects on length and wet weight	545-92
Oncorhynchus mykiss (rainbow trout)	90-day early-life stage (unaerated, continuous flow)	OECD 210; US EPA 72-4; cymoxanil technical (97.3%)	NOEC = 0.044 mg/l	411-96
Oncorhynchus mykiss (rainbow trout)	97-day early life stage (unaerated, continuous flow)	OECD 210; US EPA 72-4; cymoxanil technical (97.3%)	NOEC >120 µg/l	1013-96
Colinus virginianus (male and female northern bobwhite quail)	Acute oral toxicity	US EPA 71-1; cymoxanil technical (97.8%)	LD_{50} >2250 mg a.s./kg bw NOEL = 175 mg a.s./kg bw	136-92
Colinus virginianus (northern bobwhite quail chicks)	5-day dietary	US EPA 71-2; cymoxanil technical (97.8%)	LC_{50} >5620 ppm NOEC = 562 ppm	138-92
Colinus virginianus (male and female northern bobwhite quail)	One generation reproduction study	OECD 206; US EPA 71-4; cymoxanil technical (97.8%)	NOEC = 300 ppm a.s.	3507-95
Anas platyrhynchos (male and female mallard ducks)	Acute oral toxicity	US EPA 71-1; cymoxanil technical (97.8%)	LD_{50} >2250 mg a.s./kg bw NOEL = 292 mg a.s./kg bw	139-92
Anas platyrhynchos (mallard ducklings)	5 day dietary	US EPA 71-2; cymoxanil technical (97.8%)	LC_{50} >5620 ppm NOEC <562 ppm	137-92
Anas platyrhynchos (male and female mallard ducks)	One generation reproduction study	OECD 206; US EPA 71-4; cymoxanil technical (97.8%)	NOEC = 100 mg a.s./kg diet (ppm)	3508-95

* a.s. = active substance, i.e. data expressed as cymoxanil.

Cymoxanil has not been evaluated by the FAO/WHO JMPR or IPCS; however, it has been classified by WHO as Class III, slightly hazardous (WHO 2002). Existing FAO specifications for TC, WP and WG, established under the old procedure (FAO 1999), were published in 2000.

Cymoxanil does not meet the criteria established in the Recommendations on the Transport of Dangerous Goods (published by the United Nations Committee of Experts on the Transport of Dangerous Goods) and, therefore, is not considered to be dangerous/hazardous for transportation purposes.

Formulations and co-formulated active ingredients

The main formulation types available are water dispersible granules (WG) and wettable powder (WP). These formulations are registered and sold in many

countries throughout the world, including European Union countries, the USA, Brazil and Japan.

Methods of analysis and testing

The analytical method for the active ingredient (including identity tests) is a full CIPAC method (CIPAC J). Cymoxanil is determined by reversed-phase HPLC, using UV detection at 254nm and internal standardization with acetophenone.

The methods for determination of impurities were based on reversed-phase HPLC, using UV detection at 240 nm and external standardization.

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

Physical properties

The physical properties, the methods for testing them and the limits proposed for the WP and WG formulations, comply with the requirements of the FAO/WHO Manual (FAO/WHO 2002).

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as cymoxanil.

Appraisal

The Meeting considered data submitted by Du Pont de Nemours & Co. in support of a review of existing FAO specifications for cymoxanil TC, WP and WG, developed under the old procedure and published in 2000. The data provided were in accordance with the requirements of the manual (FAO/WHO 2002) and supported the proposed specifications.

Cymoxanil is not under patent. Is registered and sold in many countries throughout the world for use as a fungicide against downy mildews and blights in a wide range of agricultural crops.

Cymoxanil has not been evaluated by the IPCS or by FAO/WHO JMPR.

Cymoxanil is an odourless white to pale pink powdery crystalline solid, which melts at 162ºC and has a low vapour pressure. Cymoxanil is very weakly acidic (pKa 9.7) and is of relatively low water solubility (in the region of 1 g/l), which is not influenced by pH in the range 5-7 (no data were provided for pH 9) but which is increased by temperature in the range 10-30ºC. Cymoxanil is more soluble in organic solvents of intermediate or high polarity (Tomlin 2000). Cymoxanil hydrolyses very rapidly at pH

9, slightly less rapid at pH 7 and slowly at pH 5. It degrades rapidly by direct photolysis. The octanol/water partition coefficient is low, indicating a low potential for bioaccumulation.

The proposer provided the Meeting with commercially confidential information on the manufacturing process for cymoxanil and the concomitant impurities. Manufacturing specifications for the TC and data from 5 batches from each of three manufacturing plants (Wanguan and Limin, PRC; Middlesbrough, U.K.) were provided. Mass balances were high 99.2-99.8%, 99.3-100.2% and 98.7-100%, respectively. The data were similar to those submitted for registration in the Federal Republic of Germany.

The Meeting agreed with the manufacturer that none of the impurities should be considered relevant.

Cymoxanil can exist as E and Z isomers but the E isomer is overwhelmingly favoured thermodynamically and therefore the Z isomer is normally present only at very low levels. The Meeting agreed that it was not necessary to specify the isomer ratio.

Analytical methods for determination of cymoxanil in the TC, WP and WG are full CIPAC methods, in which the active ingredient is determined by reversed-phase HPLC, using UV detection at 254 nm and internal standardization. The methods used for determination of impurities were based on reversed-phase HPLC, using UV detection at 240 nm and external standardization. The physico-chemical properties of the technical active ingredient were determined using test OECD, EPA, and EEC test methods while those for the formulations were CIPAC procedures.

The proposed specifications for TC, WP and WG were in accordance with the requirements of the manual (FAO/WHO 2002) but some changes had been made to the existing specifications, as noted below.

The minimum active ingredient content of the TC had been increased from 935 to 970 g/kg, which was welcomed by the Meeting. The clause to limit water in the TC had been deleted.

Concentration ranges of >25 to 500 g/kg had been deleted from the WP specification and >25 to 250 from the WG specification, reflecting the products marketed by the proposer.

Although cymoxanil is hydrolyzed rather rapidly in neutral to alkaline solution, the manufacturer accepted that degradation in the formulated product did not occur in practice and the Meeting agreed that the clauses to restrict the water content and pH of the WP and WG should be deleted.

In the existing specifications for WP and WG, persistent foam was limited to 25 ml (MT47, 100 ml cylinder) and the proposed specifications limited it to 60 ml (MT 47.2, 250 ml cylinder), which the Meeting accepted as equivalent limits.

Cymoxanil has not been evaluated by the FAO/WHO JMPR or IPCS but it is classified by WHO as slightly hazardous (Class III). Cymoxanil is not considered as dangerous/hazardous for transportation purposes according to the criteria of the UN Committee of Experts on the Transport of Dangerous Goods.

Cymoxanil is currently classified as a skin sensitizer (R43) by the European Chemicals Bureau. The proposer stated that the classification was based on

cymoxanil produced by another manufacturer and that cymoxanil produced by Du Pont is not a skin sensitizer. The Meeting had no information on the impurity profile of the cymoxanil which produced the skin sensitization reaction.

In developmental toxicity tests, maternal and foetal NOELs were similar, indicating that the foetus was not uniquely sensitive to cymoxanil. In a recent US EPA evaluation of these studies (USEPA 2003), however, maternal NOELs were interpreted to be somewhat higher than the foetal NOELs. The European Chemicals Bureau (ECB) concluded that a R63 classification (possible risk of harm to the unborn child) was not warranted for this substance (EU 2000). The manufacturer explained that, in the course of the study, there was a concurrent spike (increase in apparent effect) in the control group of animals and stated there was no evidence to show that cymoxanil is a teratogen. The manufacturer stated that there had been no subsequent developmental studies conducted which warranted reconsideration of the ECB decision and the Meeting acknowledged the lack of any evidence to show that cymoxanil is teratogenic.

Cymoxanil is very toxic to the aquatic environment and moderately to slightly toxic to avian species and bees. WHO/PCS noted that the cymoxanil concentrations used in the studies of chronic toxicity to *Daphnia*, growth and reproduction of *Lemna*, and early life stage chronic toxicity to *Oncorhynchus*, were unnecessarily low (the maximum concentrations were well below the limit of water solubility) and therefore these studies did not enable these hazards to be characterized satisfactorily.

Recommendations

The Meeting recommended that the proposed specifications for cymoxanil TC, WP and WG, as amended, should be adopted by FAO.

References

DuPont document No.	Year and title or published reference
100-93	1993. An acute contact toxicity study with the honey bee.
1013-96	1997. DPX-T3217-113 (cymoxanil): Early life-stage toxicity to rainbow trout, *Oncorhynchus mykiss* (3 volumes).
136-92	1992. H-19,062-02: An acute oral toxicity study with the northern bobwhite.
137-92	1992. H-19,062-02: a dietary LC50 study with the mallard.
138-92	1992. H-19,062-02: A dietary LC50 study with the northern bobwhite.
139-92	1992. H-19,062-02: An acute oral toxicity study with the mallard.
149-92	1992. Acute dermal toxicity study with DPX-T3217-113 (cymoxanil) in rabbits.
169-94	1994. Determination of unscheduled DNA synthesis in rat hepatocytes and spermatocytes following *In vivo* exposure to DPX-T3217-113 (cymoxanil technical) by oral gavage.
1990-91	1993. Photodegradation of [2-14C]DPX-T3217 (cymoxanil) in pond water and sterile buffer pH 5.
201-92	1992. Acute oral toxicity study with DPX-T3217-113 (cymoxanil) in male and female mice.
2498	1999. Cymoxanil technical: growth and reproduction test with the freshwater alga, *Selenastrum capricornutum*.
2526-92	1993. Solubility of cymoxanil in pH 5, 7, and 9 aqueous buffers.

2537-92	1993. Vapor pressure determination of cymoxanil at 20 degrees C.
255-92	1992. Closed-patch repeated insult dermal sensitization study (maximization method) with DPX-T3217-113 (cymoxanil) in guinea pigs.
2581-92	1993. Octanol water partition coefficient of cymoxanil.
2589-92	1993. Dissociation constant of cymoxanil.
3507-95	1996. DPX-T3217-113 (cymoxanil): a reproduction study with the northern bobwhite (*Colinus virginianus*).
3508-95	1996. DPX-T3217-113 (cymoxanil): a reproduction study with the mallard (*Anas platyrhynchos*).
354-93 RV1	1993. Chronic toxicity of DPX-T3217-113 (cymoxanil) to *Daphnia magna*: 24-hour renewal (revision 1).
3677-95	1996. Hydrolysis of cymoxanil (DPX-T3217) in buffer solutions of pH 5, 7, and 9.
370-91 RV1	1993. Subchronic oral toxicity: 90-day study with DPX-T3217-107 (cymoxanil) feeding and neurotoxicity study in rats (Revision 1) (3 volumes).
3775-96	1996. Cymoxanil: influence on growth and reproduction of *Lemna gibba* G3.
3-83	1982. *In vivo* bone marrow cytogenetic assay in rats.
411-96	1996. DPX-T3217-113 (cymoxanil): Early-life stage toxicity to rainbow trout, *Oncorhynchus mykiss* (3 volumes).
4286	2000. Determination of the melting point/melting range for cymoxanil (DPX-T3217).
467-82 SU1	1994. Teratogenicity study of INT-3217 in New Zealand white rabbits (segment II evaluation) (supplement 1).
545-92	1992. Flow-through, 21-day toxicity of DPX-T3217-113 *(cymoxanil) to rainbow trout, Oncorhynchus* mykiss.
568-93	1995. Reproductive and fertility effects with DPX-T3217-113 (cymoxanil) multigeneration reproduction study in rats (signed statement).
573-92	1992. Mutagenicity testing of DPX-T3217-113 (cymoxanil) in the *Salmonella typhimurium* plate incorporation assay.
63-92	1992. Acute oral toxicity study with DPX-T3217-113 (cymoxanil) in male and female rats.
65-94	1994. Chronic toxicity study with DPX-T3217-113 (cymoxanil) one year feeding study in dogs.
677-93	1994. Oncogenicity study with DPX-T3217-113 (cymoxanil) eighteen- month feeding study in mice.
678-93	1994. Combined chronic toxicity/oncogenicity study with DPX-T3217-113 (cymoxanil) two-year feeding study in rats.
734-92	1992. Static, acute, 96-hour LC50 of DPX-T3217-113 (cymoxanil) to common carp, *Cyprinus carpio*.
735-92	1993. Static, acute, 96-hour LC50 of DPX-T3217-113 (cymoxanil) to rainbow trout, *Oncorhynchus mykiss*.
736-92	1993. Static, acute, 48-hour EC50 of DPX-T3217-113 (cymoxanil) to *Daphnia magna*.
744-92	1993. Developmental toxicity study of DPX-T3217-113 (cymoxanil) in rats.
787-91 RV1	1992. Primary dermal irritation study with DPX-T3217-113 (cymoxanil) in rabbits (Revision 1).
796-92	1993. Assessment of DPX-T3217-113 (cymoxanil technical) in the in vitro unscheduled DNA synthesis assay in primary rat hepatocytes.
797-92	1993. Subchronic oral toxicity: 90-day study with DPX-T3217-113 (cymoxanil) feeding study in dogs (3 volumes).
826-92	1993. Mutagenicity evaluation of DPX-T3217-113 (cymoxanil technical) in the CHO/HPRT assay.
827-92	1993. Mouse bone marrow micronucleus assay of DPX-T3217-113 (cymoxanil technical).
834-92	1993. Static, acute, 96-hour LC50 of DPX-T3217-113 (cymoxanil) to bluegill sunfish, *Lepomis macrochirus*.

835-92	1993. *In vitro* evaluation of DPX-T3217-113 (cymoxanil technical) for chromosome aberrations in human lymphocytes.
83-92 RV1	1992. Acute inhalation toxicity study with DPX-T3217-115 (cymoxanil) in rats (Revision 1).
8548	1991. Cymoxanil (tech) determination of acute toxicity (LC50) earthworms.
97-92	1992. Primary eye irritation study with DPX-T3217-113 (cymoxanil) in rabbits.
99-93	1993. A dietary LC50 toxicity study with the honey bee.
CIPAC J	CIPAC Handbook, volume J, Analysis of technical and formulated pesticides, pp. 22-28. Eds. W. Dobrat and A. Martijn. Collaborative International Pesticides Analytical Council, Harpenden, U.K., 2000.
EU 2000	European Commission Directive 2000/32/EC, May 2000. Adapting to technical progress for the 26th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.
FAO 1999	Manual on development and use of FAO specifications for plant protection products, 5th edition, 1999, Rome
FAO/WHO 2002	Manual on development and use of FAO and WHO specifications for pesticides, 1st edition, 2002, Rome
HLR 630-91 RV1	1993. Subchronic oral toxicity: 90-Day study with DPX-T3217-107 feeding study in mice (Revision 1) (2 Volumes).
Tomlin 2000	C.D.S. Tomlin, 2000. The pesticide manual, 12th ed., p.229. British Crop Protection Council, Farnham, U.K.
USEPA 2003	U.S. Environmental Protection Agency (EPA), 2003. 40 CFR part 180, Cymoxanil: pestidide tolerances. Federal Register, Vol. 68, No. 136, pp.41927-41936.
WHO 2002	The WHO recommended classification of pesticides by hazard and guidelines to classification 2000-2002, WHO, Geneva, 2002.