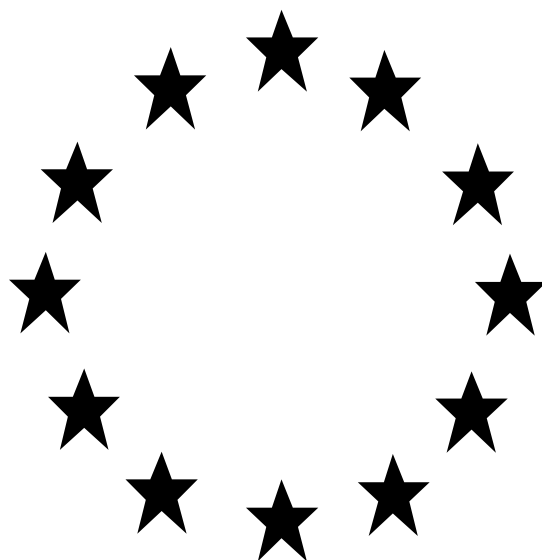




Draft Assessment Report (DAR)

- public version -

**Initial risk assessment provided by the rapporteur Member State
Austria for the existing active substance**

CYMOXANIL

**of the third stage (part B) of the review programme
referred to in Article 8(2) of Council Directive 91/414/EEC**

Volume 3, Annex B, part 1, B.1 – B.5

October 2007

Federal Office for Food Safety

Spargelfeldstraße 191
1226 Vienna
Austria

Monograph prepared in the context of inclusion of following active substance in Annex I of the
Council Directive 91/414/EEC

Cymoxanil



Volume 3

Annex B

Summary, Scientific Evaluation and Assessment

Draft: June 2007

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Annex B

Cymoxanil

B.1 Identity

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

B.1 Identity

B.1.1 Identity of the active substance (Annex IIA 1)

B.1.1.1 Name and address of applicant(s) for inclusion of the active substance in Annex I (Annex IIA 1.1)

Applicant A:

Name: Du Pont de Nemours (Deutschland) GmbH

Address: DuPont Strasse 1
61350 Bad Homburg, Germany

Contact Person: [REDACTED]

Telephone: [REDACTED]

Telefax: [REDACTED]

e-mail: [REDACTED]

Alternate Contact: [REDACTED]

Telephone: [REDACTED]

Telefax: [REDACTED]

Manufacturer of the active ingredient:

Name: [REDACTED]

Address: [REDACTED]

Contact Person: [REDACTED]

Telephone: [REDACTED]

Telefax: [REDACTED]

Location of plants: see confidential information, Volume 4, Annex C

Applicant B:

Name: OXON Italia SpA
Address: Via Sempione 195
20016 Pero (MI), Italy

Contact Person: [REDACTED]
Telephone: [REDACTED]
Telefax: [REDACTED]
e-mail: [REDACTED]

Alternate Contact: [REDACTED]
[REDACTED]
[REDACTED]
Telephone: [REDACTED]
Telefax: [REDACTED]
e-mail: [REDACTED]

Manufacturer of the active ingredient:

Name: [REDACTED]
Address: [REDACTED]
[REDACTED]
Contact Person: [REDACTED]
Telephone: [REDACTED]
Telefax: [REDACTED]
e-mail: [REDACTED]

Location of plants: see confidential information, Volume 4, Annex C

B.1.1.2 ISO common name and synonyms (Annex IIA 1.3)

Cymoxanil

B.1.1.3 Chemical name (Annex IIA 1.4)

IUPAC: 1-(2-cyano-2-methoxyiminoacetyl)-3-ethylurea
CA: 2-cyano-N-[(ethylamino)carbonyl]-2-(methoxyimino)acetamide

B.1.1.4 Manufacturer's development code number (Annex IIA 1.5)

Applicant A (DuPont): DPX-T3217, IN-T3217, T3217
Applicant B (Oxon): No specific manufacturer's code number was defined

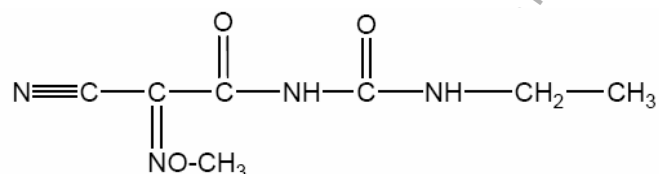
B.1.1.5 CAS, EC (EEC) and CIPAC numbers (Annex IIA 1.6)

CAS: 57966-95-7
EEC: 261-043-0
CIPAC: 419

B.1.1.6 Molecular formula, molecular mass and structural formula (Annex IIA 1.7)

Molecular formula: $C_7H_{10}N_4O_3$

Structural formula:



Molecular mass: 198.2 g/mol

B.1.1.7 Manufacturer of the active substance (Annex IIA 1.2)

Confidential information, see Volume 4, Annex C

B.1.1.8 Method or methods of manufacture (Annex IIA 1.8)

Confidential information, see Volume 4, Annex C

B.1.1.9 Specification of the purity of the active substance (Annex IIA 1.9)

FAO Specification 419/TC (April 2005): 970 g/kg (declared minimum content of technical material).

Applicant A (DuPont): 970 g/kg (minimum purity)

Applicant B (Oxon): 970 g/kg (minimum purity)

From an analytical point of view, the technical material of both applicants is equivalent (for details see Volume 4, Annex C).

B.1.1.10 Identity of inactive isomers, impurities and additives (Annex IIA 1.10)

Confidential information, see Volume 4, Annex C

B.1.1.11 Analytical profile of batches (Annex IIA 1.11)

Confidential information, see Volume 4, Annex C

B.1.2 Identity of the plant protection product (Annex IIIA 1)

Applicant A (DuPont):

Name: Du Pont de Nemours (Deutschland) GmbH
Address: DuPont Strasse 1
61350 Bad Homburg, Germany

Contact Person: [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Telephone: [REDACTED]
Telefax: [REDACTED]
e-mail: [REDACTED]

Alternate Contact: [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Telephone: [REDACTED]
Telefax: [REDACTED]

Manufacturer of the active ingredient:

Name: [REDACTED]
Address: [REDACTED]
[REDACTED]

Contact Person: [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Telephone: [REDACTED]
Telefax: [REDACTED]

Location of plants: see confidential information, Volume 4, Annex C

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Applicant B:

Name: OXON Italia SpA
Address: Via Sempione 195
20016 Pero (MI), Italy
Contact Person: [REDACTED]
Telephone: [REDACTED]
Telefax: [REDACTED]
e-mail: [REDACTED]

Manufacturer:

Address: [REDACTED]
[REDACTED]
[REDACTED]
Contact Person: [REDACTED] a
Telephone: [REDACTED]
Telefax: [REDACTED]
e-mail: [REDACTED]

Location of plant: see above

B.1.2.1 Current, former and proposed trade names and development code numbers (Annex IIIA 1.3)

Applicant A (DuPont):

Trade name: Tanos®
Code number: DPX-KP481 50WG

Applicant B (Oxon):

Trade names: SIPCAM C50 (UK registered)
LIFE 50 WP (Italy proposed)
Code numbers: SIP40904 (years 1999-2000)
Cymoxanil 50 WP (years 2000-2002)

B.1.2.2 Manufacturer or manufacturers of the plant protection product (Annex IIIA 1.2)

Confidential information, see Volume 4, Annex C

B.1.2.3 Type of the preparation and code (Annex IIIA 1.5)

Applicant A (DuPont): Water Dispersible Granule (WG)

Applicant B (Oxon): Wettable Powder (WP)

B.1.2.4 Function (Annex IIA 3.1; Annex IIIA 1.6)

Fungicide

B.1.2.5 Composition of the preparation (Annex IIIA 1.4)

Applicant A (DuPont):

DPX-KP481 50WG contains 250 grams of Cymoxanil active substance per kg and 250 grams famoxadone active substance per kg.

Information with respect to formulants is included with all other confidential information in Volume 4, Annex C.

Applicant B (Oxon):

Cymoxanil 50% WP contains 500 grams of Cymoxanil active substance per kg.

Information with respect to formulants is included with all other confidential information in Volume 4, Annex C.

B.1.3 Reference relied on

See Volume 4, Annex C.

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Annex B

Cymoxanil

B.2 Physical and chemical properties

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B.2 Physical and chemical properties**B.2.1 Physical and chemical properties of the active substance (Annex IIA 2)****Applicant (A): DuPont****Applicant (B): Oxon**

PAI..... Pure active ingredient

TGAI..... Technical grade active ingredient

Table B.2.1-1 Summary of the physical and chemical properties of Cymoxanil

Study	Method	Material / Purity	GLP	Results	Conclusion/Comment	Reference
B.2.1.1 Melting point, freezing point or solidification point (IIA 2.1.1)	EEC A.1., OECD 102, (capillary method), DSC	DPX-T3217-151, 99.6 %	Y	(A): 162 °C ± 0.0 °C	Acceptable	Huntley 2000, (DuPont 4286)
		Lot 817, 99.1%, PAI	Y	(B): 161.5 °C, 162.0 °C	Acceptable	Betteley 1995a, (OXN 57/950183)
		Lot 19800042, 99.2%, TGAI	Y	(B): 161 °C	Acceptable	Van der Baan-Treur 2003, (Notox 374939)
B.2.1.2 Boiling point (IIA 2.1.2)	–	–	–	Not applicable. Cymoxanil is not a liquid.	–	–
B.2.1.3 Temperature of decomposition or sublimation (IIA 2.1.3)	EEC A.1., OECD 102, OECD 103 (DSC, TGA)	DPX-T3217-101, 99.9%	Y	(A): Cymoxanil is thermally stable. No decomposition or chemical transformation observed through the melting point (162 °C). 100% weight loss at 225 °C.	Acceptable	Schmuckler, LeSieur 1993, (DuPont AMR 2620-93)
		Lot 19800042, 99.2%, TGAI	Y	(B): thermally stable, no decomposition or chemical transformation observed through the melting point (161 °C). Endothermic effects observed about above 206 °C, indicating evaporation of test substance and resulting in a dark brown to black residue.	Acceptable	Van der Baan-Treur 2003, (Notox 374939)

Study	Method	Material / Purity	GLP	Results	Conclusion/Comment	Reference
B.2.1.4 Relative density (IIA 2.2)	EEC A3, OECD 109, OPPTS 830.7300 (Pychnometer)	DPX-T3217-151, 99.6 % Lot 817, 99.1%, PAI	Y	(A): 1.3238 ± 0.006 (20.4 ± 0.1 ° C) (B): 1.3281 (20 ± 0.5 ° C)	Acceptable Acceptable	Huntley, Lowe 2000, (DuPont 3821) Betteley 1995a, (OXN 57/950183)
B.2.1.5 Vapour pressure (IIA 2.3.1)	EEC A4, OECD 104 (Vapour pressure balance)	DPX-T3217-101, 99.9%, Lot 817, 99.1%, PAI	Y	(A): 1.50 x 10 ⁻⁴ Pa (20 ° C) (B): 4.50 x 10 ⁻⁵ Pa (25 ° C)	Acceptable Acceptable	Schmuckler, Cooke 1993 (DuPont AMR 2537-92) Betteley 1995a, (OXN 57/950183)
B.2.1.6 Volatility, Henry's law constant (IIA 2.3.2)	Calculation Calculation (Bond estimation method)	-	N Y	(A): H = 3.3 x 10 ⁻⁵ Pa.m ³ .mol ⁻¹ (pH 5, VP=1.50 x 10 ⁻⁴ Pa, solubility 0.890 g/L) H = 3.8 x 10 ⁻⁵ Pa.m ³ .mol ⁻¹ (pH 7, VP=1.50 x 10 ⁻⁴ Pa, solubility 0.780 g/L) (B): H = 3.308 x 10 ⁻⁵ Pa.m ³ .mol ⁻¹ (25° C)	Acceptable. For (A) not calculated at pH 9, due to rapid hydrolysis. Acceptable	Schmuckler, 1993 (DuPont AMR 2726-93) Betteley 1995a, (OXN 57/950183)
B.2.1.7 Appearance: physical state (IIA 2.4.1)	OPPTS 830.6303 EEC 2.3	DPX-T3217-151, 99.6 % PAI, Lots DPX-T3217-202, 203, 204, 205, TGAI Lot 817, 99.1% PAI Lot 805, 98.8% TGAI	Y Y Y	(A): solid (A): solid (all tested TGAI lots) (B): solid (B): solid	Acceptable Acceptable Acceptable	Moore 2003 (DuPont 11983) Betteley 1995a, (OXN 57/950183) Betteley 1995b, (OXN 58/950197)
B.2.1.8 Appearance: colour (IIA 2.4.1)	OPPTS 830.6302 EEC 2.3	DPX-T3217-151, 99.6 % PAI, Lots DPX-T3217-202, 203, 204, 205, TGAI Lot 817, 99.1% PAI Lot 805, 98.8% TGAI	Y Y Y	(A): white (A): pale pink or pale peach (all tested TGAI lots) (B): white (Munsell 5Y 9.0/1.0) (B): white (Munsell 5 Y 9.0/1.8)	Acceptable Acceptable Acceptable	Moore 2003, (DuPont 11983) Betteley 1995a, (OXN 57/950183) Betteley 1995b, (OXN 58/950197)

Study	Method	Material / Purity	GLP	Results	Conclusion/Comment	Reference
B.2.1.9 Appearance: odour (IIA 2.4.2)	OPTTS 830.6304 (organoleptic) EEC 2.3	DPX-T3217-151, 99.6 %, PAI,	Y	(A): odourless	Acceptable	Moore 2003, (DuPont 11983)
		Lots DPX-T3217-202, 203, 204, 205, TGAI	Y	(A): odourless (all tested TGAI lots)	Acceptable	Betteley 1995a, (OXN 57/950183)
		Lot 817, 99.1% PAI	Y	(B): odourless	Acceptable	Betteley 1995b, (OXN 58/950197)
		Lot 805, 98.8% TGAI	Y	(B): odourless	Acceptable	Moore, 1998 (DuPont AMR 4865-98)
B.2.1.10 Spectra of the active substance (IIA 2.5.1)	OPPTS 830.7050, OECD 101	DPX-T3217-151, 99.6%	Y	(A): ϵ in $[\text{L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}]$ λ_{max} [nm]: 244, ϵ = 9333.20 (25° C, pH 1.5) λ_{max} [nm]: 244, ϵ = 9296.80 (25° C, pH 6.9) (B): ϵ in $[\text{L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}]$ λ_{max} [nm]: 240, ϵ = 9287.6 (acid conditions) λ_{max} [nm]: 240, ϵ = 9419.3 (neutral conditions) λ_{max} [nm]: 240, ϵ = 7739.7 (alkaline conditions)	Acceptable. (A) no determination of ϵ at pH > 10, due to rapid hydrolysis.	Betteley 1995a, (OXN 57/950183)
		Lot 817, 99.1% PAI	Y			
Spectra of the active substance	IR, NMR, MS	DPX-T3217-151, 99.6%	Y	(A): IR: Key absorption bands are consistent with given structure of Cymoxanil. NMR: Spectrum is consistent with given structure of Cymoxanil. MS: Characteristic mass spectrum obtained by chemical desorption ($[\text{M}+\text{H}]^+$ ion at m/z 199) is consistent with molecular mass of Cymoxanil.	Acceptable	Schmuckler, 1998 (Cymo/Pro 6)
		Lot 817, 99.1% PAI	Y	(B): IR: The spectrum is consistent with given structure of Cymoxanil. NMR: Spectrum is consistent with given structure of Cymoxanil. MS: Characteristic mass spectrum obtained by electron impact ionisation ($[\text{M}]^+$ ion at m/z 198) is consistent with molecular mass of Cymoxanil.	Acceptable	Betteley 1995a, (OXN 57/950183)

Study	Method	Material / Purity	GLP	Results	Conclusion/Comment	Reference
B.2.1.11 Spectra of relevant impurities (IIA 2.5.2)	IR, NMR, MS	---	N	(A): The technical material contains no toxicological and/or ecotoxicological relevant impurities. (B): The technical material contains no toxicological and/or ecotoxicological relevant impurities.	Acceptable	Curl, 2004, (Tier II summaries, CYMOA2S1 T2 2004)
B.2.1.12 Solubility in water (IIA 2.6)	EPA 63-8, (flask stirring method) OPPTS 830.7840 OECD 105, EEC A6 EEC A6 Calculation (ACD/log D Database	DPX-T3217-101, 99.9% DPX-T3217-151, 99.6% Lot 817, 99.1% PAI ---	Y Y N N	(A): Solubility [ppm]: 700 (pH 5, 10° C), 620 (pH 7, 10° C) 890 (pH 5, 20° C), 780 (pH 7, 20° C) 1200 (pH 5, 30° C), 1000 (pH 7, 30° C) (A): 782 (pH 5.68, unbuffered, 20° C) (B): Solubility [mg/L]: 783 (pH 6.8-7.1, 20° C) (A): Solubility of Metabolites in water at 25° C: IN-W3595: 1.27 x 10 ⁻⁵ mg/L (neutral conditions) IN-U3204: 2.063 x 10 ⁻⁴ mg/L (neutral conditions)	Acceptable. Not determined at pH 9, due to rapid hydrolysis Acceptable Acceptable Acceptable Acceptable Acceptable	Moore, 1993 (DuPont AMR 2526-92) Hansen, 2000 (DuPont 3711) Betteley, 1995a (OXN 57/950183) Schmuckler, 2001 (DuPont 6450) Schmuckler, 2001 (DuPont 6449)

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Study	Method	Material / Purity	GLP	Results	Conclusion/Comment	Reference
B.2.1.13 Solubility in organic solvents (IIA 2.7)	EPA 63-8, CIPAC MT 157	DPX-IN T3217-134, 97.4%	Y	(A): Solubility in g/L at 20 ° C: n-Hexane: 0.037 Toluene: 5.29 Acetonitrile: 57.0 Ethyl acetate 27.9 1-Octanol: 1.43 Methanol 22.9 Acetone: 62.4 Dichloromethane: 133.2 (B): Solubility in g/L at 20 ° C: n-Heptane: 0.0166 Xylene: 7.6 Ethyl acetate 28.8 Methanol 29.0 Acetone: 68.2 Methylene chloride: 58.4	Acceptable	Anderson 1993, (DuPont AMR 2541-92)
B.2.1.14 Partition coefficient n-octanol/water (IIA 2.8)	EPA 63-11, OECD 107 EEC A8 (Flask shaking method) Calculation (KOWWIN, ClogP Program)	DPX-T3217-101, 99.9% Lot 817, 99.1% PAI ---	Y Y N	(A): K _{ow} (pH 5.0): 3.89 (log K _{ow} = 0.59) K _{ow} (pH 7.0): 4.66 (log K _{ow} = 0.67) (B): K _{ow} (unbuffered): 4.37 (log K _{ow} = 0.64) (A): <u>Metabolites</u> : IN-KQ960: log K _{ow} : -1.64; BCF: 0.001 IN- T4226: log K _{ow} : 0.16; BCF: 0.07 IN- U3204: log K _{ow} : 0.39; BCF: 0.12 IN- W3595: log K _{ow} : 0.98; BCF: 0.46 (ClogP)	Acceptable Acceptable Acceptable	Santos 1993, (DuPont AMR 2581-92) Betteley 1995a, (OXN 57/950183) Schmuckler 2001 (Dupont 4620, 4622, 4621, 4623)

Study	Method	Material / Purity	GLP	Results	Conclusion/Comment	Reference
B.2.1.15 Hydrolysis rate (IIA 2.9.1)	EPA N161-1	¹⁴ C radiolabeled lot 376, >97 %, ¹³ C radio-labeled lot 455, >97%	Y	(A): DT ₅₀ (25 ° C): pH 5: 148 d pH 7: 1.1 d pH 9: 0.02 d <u>Degradation products:</u> At pH 5, no metabolites were observed above 10% AR. At pH 7, metabolites found above 10% AR were IN-KP533, IN-U3204, IN-W3595 and IN-R3273. At pH 9, metabolites found above 10% AR were IN-U3204, IN-W3595, IN-KP533, IN-KQ960, IN-T4226 and polars (oxamic acid, oxalic acid and unknowns). Minor metabolites (< 10% AR) observed at pH 7 and 9 were IN-JX915, IN-18474, IN-T4226 (pH 7), polars (pH 7) and IN-R3273 (pH 9).	Acceptable For details see B.8.4 fate and behaviour	Lawler 1996, (DuPont AMR 3677-95)
	Calculation	Lot 817, 99.1% PAI	Y	(B): DT ₅₀ (25 ° C): pH 4: between 1 day and 1 year pH 7: ≤ 1 day pH 9: < 1 day	Acceptable	Betteley 1995a, (OXN 57/950183)
	SETAC 1995	¹⁴ C radiolabeled lot 3304.265, >99 %, Oxon lot 89800028, 98.8%	Y	(B): DT ₅₀ (20 ° C): pH 4: > 1 y pH 7: 2.1 d pH 9: 0.04 d <u>Degradation products:</u> At pH 4, no individual metabolites were found above 10%. At pH 7, metabolites found above 10% AR were IN-W3595, IN-U3204 and IN-KP533. At pH 9, metabolites found above 10% AR were IN-U3204, IN-JX915, IN-KP533, IN-W3595 and IN-KQ960.	Acceptable after revision (metabolite identification) For details see B.8.4 fate and behaviour	Willems, Slangen, Hoitink, 2003 (Notox 308734) Goodyear, 2006 (TSGE 4-3-4.PP1)

Study	Method	Material / Purity	GLP	Results	Conclusion/Comment	Reference
B.2.1.16 Direct phototrans- formation (IIA 2.9.2)	USEPA 161-2	¹⁴ C radiolabeled lot 376, >97 %	Y	(A): DT ₅₀ (25 °C): pH 5 (xenon arc lamp): 1.7 d pH 7 (xenon arc lamp): 0.23 d pH 5 (dark conditions): 110 d pH 7 (dark conditions): 0.50 d <u>Degradation products:</u> In the sterile solution at pH 5, the major photo- degradation products were IN-R3273 and IN- JX915. IN-U3204, IN-KP533, oxamic acid (IN- 18474) and IN-T4226 were minor photolysis products.	Acceptable For details see B.8.4 fate and behaviour	Anderson 1993, (DuPont AMR 1990-91 incl. supplement No. 1)
	USEPA 161-2	Oxon ¹⁴ C Cymoxanil lot 3304.265 radiochemical purity > 99%	Y	(B): DT ₅₀ (25.4± 0.1 ° C): pH 5 (xenon lamp): 3.0 d (Equivalent to 12.1 days natural summer sunlight at 40°N.) <u>Degradation products:</u> The major degradation products (> 10 % of AR) were IN-JX915 and IN-R3273. Two minor, unidentified metabolite fractions were observed.	Acceptable after revision (metabolite identification) For details see B.8.4 fate and behaviour	Willems 2000 (Notox 257759, including attachment 1) Goodyear, 2006 (TSGE 4-3-4.PP1)
	Calculation using GCSOLAR	-	N	(A): The theoretical half-life of Cymoxanil in the top layer of an aqueous system integrated over a full day in summer at 40° N was 5.2 days.	Acceptable	Hatzenbeler Moore, 2004 (DuPont 12330)
	GC SOLAR		N	(B): The theoretical half-life of Cymoxanil in the top layer (near surface) of an aqueous system integrated over a full day in summer at 40°N was 17.3 days.	Acceptable	Willems 2003 (Notox 397439)

Study	Method	Material / Purity	GLP	Results	Conclusion/Comment	Reference
B.2.1.17 Quantum yield (IIA 2.9.3)	USEPA 161-2, Calculation	-	Y	(A): Quantum yield: $\Phi = 5.2 \times 10^{-3}$ (B): Quantum yield: $\Phi = 5.8 \times 10^{-4}$	Acceptable Acceptable	Anderson 1993, (DuPont AMR 1990-91 incl. supplement No. 1) Willems 2000 (Notox 257759)
B.2.1.18 Dissociation constant (pKa) (IIA 2.9.4)	EPA 63-10, OECD 112	DPX-T3217-101, 99.9% Lot 817, 99.1% PAI	Y Y	(A): pKa: 9.7 ± 0.2 (20° C) (B): pKa: 9.00 (20± 0.5° C)	Acceptable Acceptable	Schmuckler and Moore, 1993 (DuPont AMR 2598-92) Betteley 1995a, (OXN 57/950183), Serri 2002 (CYM001-02)
	Calculation (ACD/pKa Database v. 3.2)	---	N	(A): pKa of Metabolite IN-U3204 at 25° C: pKa: 5.83 ± 0.40 (environmental conditions)	Acceptable	Schmuckler, 2001 (DuPont 6448)
B.2.1.19 Stability in air, photochemical oxidative degradation (IIA 2.10)	Calculation with Atmospheric Oxidation Program (based on Atkinson method, version 1.83) Calculation	- Lot 817, 99.1% PAI	N Y	(A): $DT_{50} = 21.317$ hr or 1.776 d (using a 12 hr day with global OH-concentration of 1.5×10^6 OH radicals/cm ³); overall OH rate constant = 6.021212×10^{-12} cm ³ /molecules.sec Hydrogen Abstraction total: 4.0212×10^{-12} cm ³ /molecules.sec (B): $DT_{50} = 4.698$ hr (using an OH - concentration of 1.5×10^6 OH radicals/cm ³); overall OH rate constant = 27.3313×10^{-12} cm ³ /molecules.sec	Acceptable. No estimation of ozone reaction performed, since Cymoxanil is neither an olefin nor an acetylene Acceptable	Kleier 1997 (DuPont CYMO/PRO 5) Betteley 1995a, (OXN 57/950183)
B.2.1.20 Flammability (IIA 2.11)	EEC A10 EEC A10	DPX-T3217-113, 97.8%, TGAI Lot 805, 98.8% TGAI	Y Y	(A): Compound is not considered as highly flammable under the test conditions. (B): Compound is not considered as highly flammable under the test conditions.	Acceptable Acceptable	Gravell 1996 (DuPont AMR 3510-95) Betteley 1995b, (OXN 58/950197)

Study	Method	Material / Purity	GLP	Results	Conclusion/Comment	Reference
B.2.1.21 Auto- flammability (IIA 2.11.2)	UN-Bowes Cameron-Cage test (modified)	DPX-T3217-113, 97.8%, TGAI	Y	(A): Negative; the temperature of Cymoxanil reached 140 °C in a 100 mm cubic container with no changes during the 24-hour test. The compound is not considered as autoflammable under the test conditions.	Acceptable	Gravell 1996 (DuPont AMR 3510-95)
B.2.1.22 Flash point (IIA 2.12)	EEC A16	Lot 805, 98.8% TGAI	Y	(B): Cymoxanil does not self ignite at temperatures up to 450° C.	Acceptable	Betteley 1995b, (OXN 58/950197)
B.2.1.23 Explosive properties (IIA 2.13)	–	–	–	Not applicable. Cymoxanil is not a liquid.	–	–
B.2.1.23 Explosive properties (IIA 2.13)	EEC A.14 (thermal sensitivity) ASTM Standard E- 680-79 (mechanical sensitivity) EEC A.14 (mechanical friction)	DPX-T3217-113, 97.8%, TGAI	Y	(A): <u>Thermal sensitivity:</u> No explosions were observed for Cymoxanil with either the 6 mm or 2 mm orifice plates. <u>Mechanical sensitivity:</u> No positive results were obtained for Cymoxanil in 21 successive drop impact tests conducted at 49 Joules (3.5 kg at 1.40 m). <u>Mechanical friction:</u> No positive results were observed for Cymoxanil in six trials conducted with a force of 360 Newton. All three tests indicate, that Cymoxanil is not considered explosive.	Acceptable	Gravell 1996 (DuPont AMR 3510-95)
	EEC A.14	Lot 805, 98.8% TGAI	Y	(B): <u>Thermal sensitivity:</u> No explosion or deformation to any of the tubes. <u>Mechanical sensitivity and friction:</u> No observable or audible reaction obtained in both tests. Cymoxanil does not possess explosive properties under test conditions.	Acceptable	Betteley 1995b, (OXN 58/950197)

Study	Method	Material / Purity	GLP	Results	Conclusion/Comment	Reference
B.2.1.24 Surface tension (IIA 2.14)	EEC 2.14, EEC A.5	Lot 805, 98.8% TGA	Y	$\sigma = 68.7 \text{ mN/m}$ at $19 \pm 0.5^\circ \text{ C}$ (90% of saturation concentration).	Acceptable	Betteley 1995b, (OXN 58/950197)

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Study	Method	Material / Purity	GLP	Results	Conclusion/Comment	Reference
B.2.1.25 Oxidizing properties (IIA 2.15)	EEC A.17	DPX-T3217-113, 97.8%, TGAI	Y	(A): Cymoxanil was found to be an oxidizer. The maximum burning rate measured for the cellulose/ sample was found to be greater than the maximum rate measured for the cellulose/barium nitrate reference mixture. However, the Cymoxanil molecule does not include a high proportion of electro-negative atoms in high oxidation states and so it is unlikely to be an oxidizer and the result was likely to be a false positive. The supplementary test to prove 'false positives', which uses Kieselgur in place of the cellulose, should have been conducted but was not. The test was therefore not conducted to completion and the conclusion was incorrect. The test results were therefore inconclusive.	Not acceptable, test procedure was not completed as required.	Gravell 1996 (DuPont AMR 3510-95)
	EEC A.17	Lot 805, 98.8% TGAI	Y	(B): The maximum burning rate measured for the cellulose/ sample was found to be greater than the maximum rate measured for the cellulose/barium nitrate reference mixture. However, the Cymoxanil molecule does not include a high proportion of electronegative atoms in high oxidation states and so it is unlikely to be an oxidizer and the result was likely to be a false positive. The test was repeated using Kieselgur in place of the cellulose. In the re-test the barium nitrate/kieselgur mixture (oxidizer) failed to burn in contrast to the test substance/ kieselgur mixtures which burned with different burning rates. These are indications that the test results can not be considered valid.	Not acceptable, due to inconclusive test results. Study should be repeated in inert atmosphere (oxygen content <2% v/v). Reliable and unambiguous test results are required (e.g. for classification purposes).	Betteley 1995b, (OXN 58/950197)

B.2.1.1 Summary and evaluation of physical and chemical properties of the active substance

Cymoxanil pure and technical active substance is a white to pale peach/pink solid. The melting point for the technical active substance is 161 °C - 162 °C. Cymoxanil is thermally stable. The relative density of Cymoxanil determined at 20 °C is ranging from 1.32 - 1.33 for the technical and pure active substance. The vapour pressure of the active substance is low, ranging from 1.50×10^{-4} Pa (20 °C) to 4.50×10^{-5} Pa (25 °C).

The Henry's law constant is calculated to be 3.3×10^{-5} Pa.m³.mol⁻¹ at pH 5 and 3.8×10^{-5} Pa.m³.mol⁻¹ at pH 7, respectively. The IR-, MS- and NMR spectra are in agreement with the chemical structure. There are no known impurities of Cymoxanil of toxicological, ecotoxicological, or environmental significance. Cymoxanil has a low solubility in water. The active substance is slightly to moderately soluble in most medium polarity organic solvents, but only slightly soluble in non-polar hydrocarbons and octanol. The partition coefficient of Cymoxanil is 3.89 at pH 5, 4.66 at pH 7 and 4.37 in an unbuffered solution. The pKa value for the pure active substance at 20° C is determined to be 9.7 ± 0.2 or 9.0, respectively. The surface tension of an aqueous solution is 68.7 mN/ at 19 ± 0.5 °C, indicating that Cymoxanil has no surface active properties. Cymoxanil is not highly flammable, auto-flammable or explosive. Nevertheless, unambiguous determination of the oxidizing properties of Cymoxanil is required.

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B.2.2 Physical, chemical and technical properties of the plant protection product (Annex IIIA 2)

B.2.2.1 DPX-KP481 50WG containing 250 g/kg Cymoxanil and 250 g/kg Famoxadone (DuPont)

Table B.2.2.1-1 Summary of the physical and chemical properties of the plant protection product

Study	Method	Material/Purity	GLP	Results	Conclusion/Comment	Reference
B.2.2.1 Appearance: physical state (IIIA 2.1)	Visual assessment	DPX-KP481-25 (25% Cymoxanil)	Y	DPX-KP481-25 is solid	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)
B.2.2.2 Appearance: colour (IIIA 2.1)	Visual assessment	DPX-KP481-25 (25% Cymoxanil)	Y	DPX-KP481-25 is brown	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)
B.2.2.3 Appearance: odour (IIIA 2.1)	Organoleptic	DPX-KP481-25 (25% Cymoxanil)	Y	DPX-KP481-25 has a sweet odour	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)
B.2.2.4 Explosive properties (IIIA 2.2.1)	EEC A14	DPX-KP481-25 (25% Cymoxanil)	Y	<u>Thermal sensitivity</u>: No explosions were observed for the test substance with either the 6 mm or 2 mm orifice plates. <u>Mechanical sensitivity</u>: No positive results were obtained for the test substance in 21 successive drop impact tests conducted at 49 Joules (3.5 kg at 1.40 m). <u>Mechanical friction</u>: No positive results were observed for the test substance in six trials conducted with a force of 360 Newton.	Acceptable. DPX-KP481-25 has no explosive properties under test conditions.	Gravell, 1996 (DuPont AMR 3876-96)

Study	Method	Material/Purity	GLP	Results	Conclusion/Comment	Reference
B.2.2.5 Oxidizing properties (IIIA 2.2.2)	EEC A17	DPX-KP481-25 (25% Cymoxanil)	Y	The test substance was not found to be an oxidizer	Acceptable	Gravell, 1996 (DuPont AMR 3876-96)
B.2.2.6 Flash point (IIIA 2.3)	EEC A9 (Abel-Pensky closed cup)	-	-	Not relevant for solid preparations	-	-
B.2.2.7 Flammability (IIIA 2.3)	EEC A10	DPX-KP481-25 (25% Cymoxanil)	Y	Not flammable under test conditions	Acceptable	Gravell, 1996 (DuPont AMR 3876-96)
B.2.2.8 Auto-flammability (IIIA 2.3)	UN-Bowes Cameron-Cage test (modified)	DPX-KP481-25 (25% Cymoxanil)	Y	The test substance is not considered as autoflammable under the test conditions. The sample tested in the 25 mm cube did not exceed the oven temperature of 140° C for the duration of the 24 hours.	Acceptable	Gravell, 1996 (DuPont AMR 3876-96)
B.2.2.9 Acidity or alkalinity and pH value (IIIA 2.4.1)	-	-	-	Not necessary due to the pH-value determination	-	-
B.2.2.10 pH of 1 % aqueous dilution, emulsion or dispersion (IIIA 2.4.2)	CIPAC MT 75	DPX-KP481-25 (25% Cymoxanil)	Y	5.8	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)
B.2.2.11 Viscosity (Kinematic, Dynamic III 2.5.2)	-	-	-	Not relevant for solid formulation	-	-

Study	Method	Material/Purity	GLP	Results	Conclusion/Comment	Reference
B.2.2.12 Surface tension (III 2.5)	-	-	-	Not relevant for solid formulation	-	-
B.2.2.13 Relative density (III 2.6.1)	-	-	-	Not relevant for solid formulation	-	-
B.2.2.14 Bulk or tap density (IIIA 2.6.2)	CIPAC MT 169	DPX-KP481-25 (25% Cymoxanil)	Y	0.60 g/mL (Tap)	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)
B.2.2.15 Stability after storage for 14 days at 54° C (IIIA 2.7.1)	NAMB 95/02, Appearance, CIPAC MT 75, CIPAC MT 168, CIPAC MT 174, CIPAC MT 167, CIPAC MT 171	DPX-KP481-25 (25% Cymoxanil)	Y	Test	Acceptable. No significant changes were observed. The contents of active ingredients and the relevant physical chemical properties remained stable, after storage for 14 days at 54° C.	Jourdainne, 1997 (DuPont AMR 3833-96)
				Initial		
				After 14 d, 54° C		
				Content Cymoxanil	26.6 ± 0.5%	
				Content Famoxadone	25.4 ± 0.6%	
				Appearance	Brown, sweet	
				pH (1%)	5.8	
				Suspensibility	Cymoxanil: 101.2% Famoxadone: 100.1%	
				Suspension stability	102%	
				Wet Sieve test	0.4%	
				Dust content	0%	
					101%	
					0.1%	
					0.001%	

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Study	Method	Material/Purity	GLP	Results	Conclusion/Comment	Reference																																				
B.2.2.16, Effect of low temperature on stability (IIIA 2.7.2)	-	-	-	Not relevant for solid formulation	-	-																																				
B.2.2.17 Shelf life (IIIA 2.7.3)	GIFAP No. 17 Internal (NAM 95/02) Internal (NAM 95/02) Visual control CIPAC MT 75 CIPAC MT 53.3 CIPAC MT 47 CIPAC MT 168 CIPAC MT 174 CIPAC MT 167 CIPAC MT 171 Visual control	DPX-KP481-25 (25% Cymoxanil)	Y	<table><tr><th>Test</th><th>Initial</th><th>After 2 years</th></tr><tr><td>Content Cymoxanil</td><td>26.6 %</td><td>25.7 %</td></tr><tr><td>Content Famoxadone</td><td>25.4 %</td><td>24.9%</td></tr><tr><td>Appearance</td><td>Brown, sweet</td><td>Brown, sweet</td></tr><tr><td>pH (1%)</td><td>5.8</td><td>5.81</td></tr><tr><td>Wettability</td><td>19 Seconds</td><td>2 Seconds</td></tr><tr><td>Persistent foam</td><td>15 mL</td><td>4 mL</td></tr><tr><td>Suspensibility</td><td>Cymoxanil: 101.2% Famoxadone: 100.1 %</td><td>Cymoxanil: 100% Famoxadone: 99%</td></tr><tr><td>Dispersibility</td><td>102%</td><td>101%</td></tr><tr><td>Wet Sieve test</td><td>0.4%</td><td>0.2%</td></tr><tr><td>Dust content</td><td>0%</td><td>0.00%</td></tr><tr><td>Suitability of packaging material</td><td>Intact packaging material</td><td>Packaging material remained intact.</td></tr></table>	Test	Initial	After 2 years	Content Cymoxanil	26.6 %	25.7 %	Content Famoxadone	25.4 %	24.9%	Appearance	Brown, sweet	Brown, sweet	pH (1%)	5.8	5.81	Wettability	19 Seconds	2 Seconds	Persistent foam	15 mL	4 mL	Suspensibility	Cymoxanil: 101.2% Famoxadone: 100.1 %	Cymoxanil: 100% Famoxadone: 99%	Dispersibility	102%	101%	Wet Sieve test	0.4%	0.2%	Dust content	0%	0.00%	Suitability of packaging material	Intact packaging material	Packaging material remained intact.	Acceptable. The contents of active ingredients and the relevant physical chemical properties remained stable, after storage for 2 years at ambient temperature in a HD-PE container.	Thuet 1998 (DuPont AMR 3835-96)
Test	Initial	After 2 years																																								
Content Cymoxanil	26.6 %	25.7 %																																								
Content Famoxadone	25.4 %	24.9%																																								
Appearance	Brown, sweet	Brown, sweet																																								
pH (1%)	5.8	5.81																																								
Wettability	19 Seconds	2 Seconds																																								
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Suspensibility	Cymoxanil: 101.2% Famoxadone: 100.1 %	Cymoxanil: 100% Famoxadone: 99%																																								
Dispersibility	102%	101%																																								
Wet Sieve test	0.4%	0.2%																																								
Dust content	0%	0.00%																																								
Suitability of packaging material	Intact packaging material	Packaging material remained intact.																																								
B.2.2.18 Wettability (IIIA 2.8.1)	CIPAC MT 53.3.1	DPX-KP481-25 (25% Cymoxanil)	Y	Wetting Time: 19 seconds	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)																																				

Study	Method	Material/Purity	GLP	Results	Conclusion/Comment	Reference
B.2.2.19 Persistent foaming (IIIA 2.8.2)	CIPAC MT 47	DPX-KP481-25 (25% Cymoxanil)	Y	15 mL foam after 1 min. (Dilution of preparation with CIPAC water D to a conc. of 0.2 g/ 100 mL).	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)
B.2.2.20 Suspensibility (IIIA 2.8.3)	CIPAC MT 168	DPX-KP481-25 (25% Cymoxanil)	Y	Cymoxanil: 101.2% (30 min, 30° C, CIPAC water C) Famoxadone: 100.1% (30 min, 30° C, CIPAC water C); tested concentration: 0.5 g / 250 mL	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)
B.2.2.21, Suspension stability (Dispersibility) (IIIA 2.8.3)	CIPAC MT 174	DPX-KP481-25 (25% Cymoxanil)	Y	Initial: Cymoxanil: 102% (CIPAC water D, 20 ± 1 ° C, 9 g/L) Aged sample: Cymoxanil: 101%	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)
B.2.2.22 Dilution stability (IIIA 2.8.4)	-	-	-	Not relevant for water dispersible granules	-	-
B.2.2.23 Dry sieve test (IIIA 2.8.5)	-	-	-	Not relevant (preparation is not a dustable powder product)	-	-
B.2.2.24 Wet sieve test (IIIA 2.8.5)	CIPAC 167	DPX-KP481-25 (25% Cymoxanil)	Y	0.4% residue on a 75µm sieve	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)

Study	Method	Material/Purity	GLP	Results	Conclusion/Comment	Reference
B.2.2.25 Size distribution of particles - Nominal size range of granules (IIIA 2.8.6.1)	CIPAC MT 170 (modified)	DPX-KP481-25 (25% Cymoxanil)	Y	≥ 90% of product retained on a 75µm sieve ≤ 10% of product retained on a 500 µm sieve. The test was conducted using sieves of 710 µm, 500 µm, 250 µm, 150 µm, 125 µm, 75 µm and 63 µm. The amounts of material retained on each sieve is as follows: 1.3 g (710 µm) 1.8% 0.8 g (500 µm) 2.9% 22.9 g (250 µm) 34.7% 36.8 g (150 µm) 85.8% 6.6 g (75 µm) 95.0% 0.2 g (63 µm) 95.3%	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)
B.2.2.26 Dust content/ particle size (IIIA 2.8.6.2)	CIPAC MT 171	DPX-KP481-25 (25% Cymoxanil)	Y	Dust: 0 mg (0%)	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)
B.2.2.27 Attrition resistance and friability (IIIA 2.8.6.3)	CIPAC MT 178	DPX-KP481-40 (25% Cymoxanil)	N	Attrition resistance: 96.6% (125 µm), 0.06% (44µm)	Acceptable	Bloemer, 2000 (DuPont 4188)
B.2.2.28 Emulsifiability, re-emulsifiability and emulsion stability (IIIA 2.8.7.1)	-	-	-	Not relevant (preparation does not form emulsions)	-	-
B.2.2.29 Stability of dilute emulsions (IIIA 2.8.7.2)	-	-	-	Not relevant (preparation does not form emulsions)	-	-

Study	Method	Material/Purity	GLP	Results	Conclusion/Comment	Reference
B.2.2.30 Flowability (IIIA 2.8.8.1)	CIPAC MT 172	DPX-KP481-25 (25% Cymoxanil)	Y	100% (through a 4.75 mm sieve)	Acceptable	Jourdainne, 1997 (DuPont AMR 3833-96)
B.2.2.31 Pourability (rinsability) (IIIA 2.8.8.2)	-	-	-	Not relevant (preparation is not a suspension)	-	-
B.2.2.32 Dustability (IIIA 2.8.8.3)	-	-	-	Not relevant (preparation is not a DP)	-	-
B.2.2.33 Physical and chemical compatibility of tank mixes (IIIA 2.9)	pH measurement Internal method	DPX-KP 481-27, 50% (25% DPX-JE874, 25% DPX-T3217)	N	Chemical compatability: DPX-KP481-27 (WG) was tested with various potential tank mix partners (8 insecticides: Decis, Karate Vert, Karate K, Klartan, Sumi Alpha, Tralate, Decis B, Technoate and 3 fungicides: Dorimat, Shirian, Brestan 10 WP). The pH of the mixtures was measured. DPX-KP481-27 is chemically compatible with all the tank-mix partners. Physical compatability: DPX-KP481-27 (WG) was physically compatible with the above mentioned tank-mix partners.	Acceptable. DPX-KP481-27 (WG) contained the active substances DPX-JE874 (famoxadone) and DPX-T3217 (cymoxanil) in a 1:1 ratio.	Thuet 1997 (DuPont AMR 4255-96)
B.2.2.34 Adherence and distribution to seeds (IIIA 2.10)	-	-	-	Not relevant (preparation is not intended for seed treatment)	-	-

B.2.2.2 Cymoxanil 50 WP containing 500 g/kg Cymoxanil (Oxon)

Table B.2.2.2-1 Summary of the physical and chemical properties of the plant protection product

Study	Method	Material/Purity	GLP	Results	Conclusion/Comment	Reference
B.2.2.1 Appearance: physical state (IIIA 2.1)	Visual assessment (inhouse)	Cymoxanil 50% WP, batch BPL084 (50% Cymoxanil)	Y	Homogenous powder	Acceptable	Fraschini, 1999 (Study No. 004/99)
B.2.2.2 Appearance: colour (IIIA 2.1)	Visual assessment (inhouse)	Cymoxanil 50% WP, batch BPL084 (50% Cymoxanil)	Y	Clear, ivory	Acceptable	Fraschini, 1999 (Study No. 004/99)
B.2.2.3 Appearance: odour (IIIA 2.1)	Organoleptic (inhouse)	Cymoxanil 50% WP, batch BPL084 (50% Cymoxanil)	Y	Characteristic	Acceptable	Fraschini, 1999 (Study No. 004/99)
B.2.2.4 Explosive properties (IIIA 2.2.1)	92/69 EEC, A14	Cymoxanil 50%WP, batch BPL120 (50% Cymoxanil)	Y	Not explosive. Shock sensitivity: not sensitive Attrition sensitivity: not sensitive Thermal sensitivity: not sensitive	Acceptable	D'Olimpio, 2000 (Study 020/00)
B.2.2.5 Oxidising properties (IIIA 2.2.2)	92/69 EEC, A17	Cymoxanil 50%WP, batch BPL120 (50% Cymoxanil)	Y	Not oxidizing Max. burning rate (mm/s): 0.89 Reference substance (mm/s): 1.47	Acceptable	D'Olimpio, 2000 (Study 020/00)
B.2.2.6 Flash point (IIIA 2.3)	92/69 EEC, A9	Cymoxanil 50%WP, batch BPL120 (50% Cymoxanil)	Y	178 °C ± 2 °C	Acceptable	D'Olimpio, 2000 (Study 020/00)
B.2.2.7 Flammability (IIIA 2.3)	92/69 EEC, A10	Cymoxanil 50%WP, batch BPL120 (50% Cymoxanil)	Y	Not highly flammable	Acceptable	D'Olimpio, 2000 (Study 020/00)

Study	Method	Material/Purity	GLP	Results	Conclusion/Comment	Reference
B.2.2.8 Auto-flammability (IIIA 2.3)	92/69 EEC, A16	Cymoxanil 50%WP, batch BPL120 (50% Cymoxanil)	Y	Not autoflammable	Acceptable	D'Olimpio, 2000 (Study 020/00)
B.2.2.9 Acidity or alkalinity and pH value (IIIA 2.4.1)	-	-	-	Not necessary due to the pH-value determination	-	-
B.2.2.10 pH of 1 % aqueous dilution, emulsion or dispersion (IIIA 2.4.2)	CIPAC MT 75.1	Cymoxanil 50% WP, batch BPL084 (50% Cymoxanil)	Y	6.80	Acceptable	Fraschini, 1999 (Study No. 004/99)
B.2.2.11 Viscosity (Kinematic, Dynamic III 2.5.2)	-	-	-	Not relevant for solid formulations	-	-
B.2.2.12 Surface tension (III 2.5)	92/69 EEC, A5 Ring method	Cymoxanil 50%WP, batch BPL120 (50% Cymoxanil)	Y	$\sigma = 36.51 \pm 1.80$ mN/m at 25 °C. A saturated solution (10 g/L) after filtration was measured.	Acceptable Considered as additional information as it is required for liquids only.	D'Olimpio, 2000 (Study 020/00)
B.2.2.13 Relative density (III 2.6.1)	-	-	-	Not relevant for solid formulations	-	-
B.2.2.14 Bulk or tap density (IIIA 2.6.2)	CIPAC MT 33	Cymoxanil 50% WP, batch BPL084 (50% Cymoxanil)	Y	0.364 g/mL (tap density)	Acceptable	Fraschini, 1999 (Study No. 004/99)

Study	Method	Material/Purity	GLP	Results	After 14 d, 54 °C		Conclusion/Comment	Reference
B.2.2.15 Stability after storage for 14 days at 54° C (IIIA 2.7.1)	Internal method	Cymoxanil 50% WP, batch BPL084 (50% Cymoxanil)	Y	Test	Initial		Acceptable. No significant changes were observed. The content of active ingredient and the relevant physical chemical properties remained stable, after storage for 14 days at 54° C.	Fraschini, 1999 (Study No. 004/99)
	Visual control			Content Cymoxanil	49.95%	49.84%		
				Appearance	Homogenous powder	Nearly unaltered, slightly compacting		
	CIPAC MT 75.1			pH (1%)	6.80	6.75		
	CIPAC MT 53.3.1			Wettability (static, dynamic)	7 Sec. 5 Sec.	9 Sec. 5 Sec.		
	CIPAC MT 53.3.2			Persistent foaming	11mL after 1min.	10mL after 1min.		
	CIPAC MT 47.1			Suspensibility (0.2% water C, 1% water C)	83% 70%	82% 68%		
B.2.2.16 Effect of low temperature on stability (IIIA 2.7.2)	-	-	-	Wet Sieve test 100 mesh	<0.01%	<0.01%	-	-
				325 mesh	0.16%	0.46%		
B.2.2.17 Shelf life (IIIA 2.7.3)	Cymoxanil content (internal method) Appearance (Visual control) pH CIPAC MT 75.1)	Cymoxanil 50% WP, batch BPL084 (50% Cymoxanil)	Y	Test	Initial	After 24 months at room temp.	Acceptable No significant changes were observed. The content of active	Freschi 2000 (Sipcam Report No. 005/99)
				Content Cymoxanil	49.95 ± 0.11%	51.09 ± 0.15%		

Study	Method	Material/Purity	GLP	Results	Conclusion/Comment		Reference
	Wettability (CIPAC MT 53.3.1, 53.3.2) Persistent Foaming (CIPAC MT 47.1) Suspensibility (CIPAC MT 15.1) Wet Sive Test (CIPAC MT 59.3) Particle size distribution (OECD 110) Dissolution of water soluble bag (CIPAC MT 176)			Appearance	Homogenous powder, clear, ivory colour, characteristic odour	Unaltered	ingredient and the relevant physical chemical properties remained stable, after storage for 2 years at room temperature in a water soluble bag.
				Appearance of container	Regular	Outer bag: un-altered, inner bag: slightly stiffed	
				pH (1%)	6.80	6.62	
				Wettability (static, dynamic)	7 sec. 5 sec.	9 sec. 4 sec.	
				Persistent foaming	14mL after 1min.	18mL after 1 min.	
				Suspensibility (0.2% water, 1% water C)	83% 70%	81% 70% (+ sediment)	
				Wet Sieve 100 mesh	<0.01%	<0.01%	
				325 mesh	0.16 %	0.20%	
				Particle distribution	Mean diameter: 6.9 µm	Mean diameter: 6.6 µm	

Study	Method	Material/Purity	GLP	Results			Conclusion/Comment	Reference
				Dissolution rate of water soluble bag	No initial data but CIPAC test passed after 6 months (6 Seconds)	CIPAC test passed (7 Seconds)		
B.2.2.18 Wettability (IIIA 2.8.1)	CIPAC MT 53.3.1, 53.3.2	Cymoxanil 50% WP, batch BPL084 (50% Cymoxanil)	Y	7 sec. (static) 5 sec. (dynamic)			Acceptable	Fraschini, 1999 (Study No. 004/99)
B.2.2.19 Persistent foaming (IIIA 2.8.2)	CIPAC MT 47.1, CIPAC MT 47.2	Cymoxanil 50% WP, batch BPL084 (50% Cymoxanil) Cymoxanil 50% WP batch BPL180	Y Y	11 mL after 1 min. (1 g in 100 mL water D) 39 mL after 1 min. (1% dispersion in CIPAC water D) 41 mL after 1 min. (1% dispersion in CIPAC water D with water soluble bag material)			Acceptable Acceptable (Comparison of WP, WSP)	Fraschini, 1999 (Study No. 004/99) Freschi 2004 (Study 023/2004)
B.2.2.20 Suspensibility (IIIA 2.8.3)	CIPAC MT 15.1	Cymoxanil 50% WP, batch BPL084 (50% Cymoxanil) Cymoxanil 50% WP batch BPL180	Y Y	83% (0.2% CIPAC water C with water soluble bag) 70% (1% CIPAC water C with water soluble bag) 83% (0.2% CIPAC water C) 83% (0.2% CIPAC water C, with water soluble bag) 75% (1% CIPAC water C) 70% (1% CIPAC water C with water soluble bag)			Acceptable Acceptable (Comparison of WP, WSP)	Fraschini, 1999 (Study No. 004/99) Freschi 2004 (Study 023/2004)

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Study	Method	Material/Purity	GLP	Results	Conclusion/Comment	Reference
B.2.2.21 Spontaneity of dispersion (IIIA 2.8.3)	-	-	-	Not relevant for WP	-	-
B.2.2.22 Dilution stability (IIIA 2.8.4)	-	-	-	Not relevant for WP	-	-
B.2.2.23 Dry sieve test (IIIA 2.8.5)	-	-	-	Not relevant for WP	-	-
B.2.2.24 Wet sieve test (IIIA 2.8.5)	CIPAC MT 59.3	Cymoxanil 50% WP, batch BPL084 (50% Cymoxanil) Cymoxanil 50% WP batch BPL180	Y	< 0.01% residue on a 100 mesh sieve (150 µm) 0.16% residue on a 325 mesh sieve (45 µm) < 0.01% residue on a 100 mesh (150µm) 0.01% residue on a 200 mesh (75µm) 0.04% residue on a 325 mesh (45µm) <u>Test in presence of water soluble bag material:</u> < 0.01% residue on a 100 mesh (150µm) <0.01% residue on a 200 mesh (75µm) 0.08% residue on a 325 mesh (45µm) Dissolution rate of the water soluble bag: 7 seconds	Acceptable Acceptable (Comparison of WP, WSP)	Fraschini, 1999 (Report No. 004/99) Freschi 2004 (Report 023/2004)
B.2.2.25 Size distribution of particles (IIIA 2.8.6.1)	OECD 110 (Laser Diffraction)	Cymoxanil 50% WP, batch BPL084 (50% Cymoxanil)	Y	Median diameter: 6.9 µm % < 6 µm: 43.55 % < 12 µm: 76.65 % < 16 µm: 86.95	Acceptable	Fraschini, 1999 (Report No. 004/99)

Cymoxanil – Volume 3, Annex B.2 Physical and chemical properties

Study	Method	Material/Purity	GLP	Results	Conclusion/Comment	Reference
B.2.2.26 Dust content/ particle size (IIIA 2.8.6.2)	-	-	-	Not relevant for WP	-	-
B.2.2.27 Attrition resistance and friability (IIIA 2.8.6.3)	-	-	-	Not relevant for WP	-	-
B.2.2.28 Emulsifiability, re- emulsifiability and emulsion stability (IIIA 2.8.7.1)	-	-	-	Not relevant (preparation does not form emulsions)	-	-
B.2.2.29 Stability of dilute emulsions (IIIA 2.8.7.2)	-	-	-	Not relevant (preparation does not form emulsions)	-	-
B.2.2.30 Flowability (IIIA 2.8.8.1)	-	-	-	Not relevant for WP	-	-
B.2.2.31 Pourability (rinsability) (IIIA 2.8.8.2)	-	-	-	Not relevant (preparation is not a suspension)	-	-
B.2.2.32 Dustability (IIIA 2.8.8.3)	-	-	-	Not relevant (preparation is not a DP)	-	-

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Cymoxanil – Volume 3, Annex B.2 Physical and chemical properties

Study	Method	Material/Purity	GLP	Results	Conclusion/Comment	Reference
B.2.2.33 Physical and chemical compatibility of tank mixes (IIIA 2.9)	Static laboratory test Internal method (inhouse)	Cymoxanil 50%WP (Lot F04/11829/0201, int. Agrisearch Lot No.) Cymoxanil 50%WP, batch DC1803	N	Physical compatibility: Cymoxanil 50%WP is physically compatible with fluazinam and two mancozeb containing products. Chemical compatibility: Cymoxanil 50%WP is chemically compatible with mancozeb and fluazinam containing products. The content of Cymoxanil remained stable over 24 hours at room temperature in presence of both products.	Acceptable	Hale 2001a, 2001b, 2001c (Agrisearch Reports AC/5609/SP-1, AC/5609/SP-2 and AC/5609/SP-3) Chiesa, 2003 (Sipcam Report 002/03)
B.2.2.34 Adherence and distribution to seeds (IIIA 2.10)	-	-	-	Not relevant (preparation is not intended for seed treatment)	-	-

B.2.2.3 Summary and evaluation of physical and chemical properties of the plant protection products

B.2.2.3.1 DPX-KP481 50WG (DuPont):

DPX-KP481 50WG is a solid brown water-dispersible granule with a sweet odour, containing the two active ingredients Cymoxanil and Famoxadone. DPX-KP481 50WG is not explosive nor an oxidizer. The preparation DPX-KP481 50WG is not considered flammable. The pH of an aqueous suspension of DPX-KP481 50WG is 5.8 at room temperature. The bulk density is 0.60 g/mL. The preparation was tested for dustiness and found to be nearly dust-free. From these properties no particular problems are expected, when the product is used as recommended.

DPX-KP481 50WG is stable under accelerated storage conditions (14 days, 54 ° C) and over a period of two years at room temperature, since no decrease of Cymoxanil concentration or significant changes of technical properties was observed during storage.

The relevant technical properties of the product (wettability, persistence of foaming, suspensibility, flowability, attrition resistance, etc.) show acceptable technical performance when using the product as recommended. DPX-KP481 50WG is chemically and physically compatible with a lot of commonly used insecticides and fungicides.

B. 2.2.3.2 Cymoxanil 50% WP (Oxon):

Cymoxanil 50%WP is a homogeneous powder with a clear ivory colour, having a characteristic odour. The product is not explosive and not oxidizing. It has a flash point of 178 ± 2 °C and is not highly flammable. The product is not autoflammable. The pH of an aqueous suspension of Cymoxanil 50%WP is 6.8 at room temperature. The bulk density is 0.364 g/mL. From these properties no particular problems are expected, when the product is used as recommended.

Cymoxanil 50%WP is stable under accelerated storage conditions (14 days, 54° C) and over a period of two years at room temperature, since no decrease of Cymoxanil concentration or significant changes of technical properties was observed during storage.

The relevant technical properties of the product (wettability, persistence of foaming and suspensibility) show acceptable technical performance. No differences in technical properties are observed when using the formulated product with and without water soluble bag. Particle size analysis shows a median diameter of 6.9 µm. Cymoxanil 50%WP is physically and chemically compatible with mancozeb and fluazinam containing products.

B.2.3 References relied on

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner*)
Annex II					
IIA, 2.1.1./01	Huntley, K.	2000	Determination of the melting point/melting range for cymoxanil (DPX-T3217) ABC Laboratories, Inc. (Missouri) DuPont-4286 GLP: Yes Published: No	Y	DuPont
IIA, 2.1.1./02	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.1.1./03	Van der Baan-Treur, J.	2003	Determination of the melting and boiling temperature of cymoxanil technical by differential scanning calorimetry NOTOX BV, 's-Hertogenbosch, The Netherlands 374939 GLP: Yes Published: No	Y	Oxon
IIA, 2.1.3./01	Schmuckler, M.E., Lesieur, L.B.	1993	Thermal stability of cymoxanil DuPont Experimental Station AMR 2620-93 GLP: Yes Published: No	N	DuPont
IIA, 2.1.3./02	Van der Baan-Treur, J.	2003	Determination of the melting and boiling temperature of cymoxanil technical by differential scanning calorimetry NOTOX BV, 's-Hertogenbosch, The Netherlands 374939 GLP: Yes Published: No	Y	Oxon
IIA, 2.2./01	Huntley, K., Lowe, S.J.	2000	Determination of relative density for cymoxanil (DPX-T3217), ABC Laboratories, Inc. (Missouri) DuPont-3821 GLP: Yes Published: No	Y	DuPont

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner*)
IIA, 2.2./02	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.3.1./01	Schmuckler, M.E., Cooke, L.A.	1993	Vapor pressure determination of cymoxanil at 20° C, DuPont Experimental Station AMR 2537-92 GLP: Yes Published: No	N	DuPont
IIA, 2.3.1./02	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.3.2./01	Schmuckler, M.E.	1993	Volatility of cymoxanil DuPont Experimental Station AMR 2726-93 GLP: No Published: No	N	DuPont
IIA, 2.3.2./02	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.4.1/01	Moore, L.A.	2003	Cymoxanil (DPX-T3217): Appearance (color, odor, and physical state) DuPont Stine-Haskell Research Center DuPont-11983 GLP: No Published: No	Y	DuPont
IIA, 2.4.1/02	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.4.1/03	Betteley, J.M.T.	1995b	Cymoxanil (technical): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 58/950197 GLP: Yes Published: No	N	Oxon

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IIA, 2.4.2/01	Moore, L.A.	2003	Cymoxanil (DPX-T3217): Appearance (color, odor, and physical state) DuPont Stine-Haskell Research Center DuPont-11983 GLP: No Published: No	Y	DuPont
IIA, 2.4.2/02	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.4.2/03	Betteley, J.M.T.	1995b	Cymoxanil (technical): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 58/950197 GLP: Yes Published: No	N	Oxon
IIA, 2.5.1./01	Moore, L.A.	1998	UV/visible absorption of cymoxanil DuPont Experimental Station AMR 4865-98 GLP: No Published: No	N	DuPont
IIA, 2.5.1./02	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.5.1./03	Schmuckler, M.E.	1998	Spectra of cymoxanil DuPont Experimental Station CYMO/PRO 6 GLP: No Published: No	N	DuPont
IIA, 2.5.1./04	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.5.1./05	Curl, M.G.	2004	Tier II summaries, CYMOA2S1 T2 2004 GLP: No Published: No	N	DuPont

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner*)
IIA, 2.6./01	Moore, L.A.	1993	Solubility of cymoxanil in pH 5, 7, and 9 aqueous buffers DuPont Experimental Station AMR 2526-92 GLP: Yes Published: No	N	DuPont
IIA, 2.6./02	Hansen, S.W.	2000	Solubility of cymoxanil in water DuPont Experimental Station DuPont-3711 GLP: Yes Published: No	Y	DuPont
IIA, 2.6./03	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.6./04	Schmuckler, M.E.	2001	The calculated solubility in water at 25° C of IN-W3595 DuPont Stine-Haskell Research Center DuPont-6450 GLP: No Published: No	Y	DuPont
IIA, 2.6./05	Schmuckler, M.E.	2001	The calculated solubility in water at 25° C of IN-U3204 DuPont Stine-Haskell Research Center DuPont-6449 GLP: No Published: No	Y	DuPont
IIA, 2.7./01	Anderson, L.N.	1993	Solubility of cymoxanil in organic solvents DuPont Experimental Station AMR 2541-92 GLP: Yes Published: No	N	DuPont
IIA, 2.7./02	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.8./01	Santos, L.M.	1993	Octanol water partition coefficient of cymoxanil DuPont Experimental Station AMR 2581-92 GLP: Yes Published: No	N	DuPont

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner*)
IIA, 2.8./02	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.8./03	Schmuckler, M.E.	2001	The calculated octanol water partition coefficient (Log Kow) and bioconcentration factor (BCF) of cymoxanil metabolite, IN- W3595 DuPont Stine-Haskell Research Center DuPont-4623 GLP: No Published: No	Y	DuPont
IIA, 2.8./04	Schmuckler, M.E.	2001	The calculated octanol water partition coefficient (Log Kow) and bioconcentration factor (BCF) of cymoxanil metabolite, IN- U3204 DuPont Stine-Haskell Research Center DuPont-4621 GLP: No Published: No	Y	DuPont
IIA, 2.8./05	Schmuckler, M.E.	2001	The calculated octanol water partition coefficient (Log Kow) and bioconcentration factor (BCF) of cymoxanil metabolite, IN- T4226 DuPont Stine-Haskell Research Center DuPont-4622 GLP: No Published: No	Y	DuPont
IIA, 2.8./06	Schmuckler, M.E.	2001	The calculated octanol water partition coefficient (Log Kow) and bioconcentration factor (BCF) of cymoxanil metabolite, IN- KQ960 DuPont Stine-Haskell Research Center DuPont-4620 GLP: No Published: No	Y	DuPont
IIA, 2.9.1./01	Lawler, S.M.	1996	Hydrolysis of cymoxanil (DPX-T3217) in buffer solutions of pH 5, 7, and 9 DuPont Experimental Station AMR 3677-95 GLP: Yes Published: No	N	DuPont

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IIA, 2.9.1./02	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.9.1/03	Willems, H., Slangen, P.J., Hoitink, M.	2003	Aqueous Hydrolysis of Cymoxanil NOTOX B.V., 's-Hertogenbosch, The Netherlands 308734 GLP: Yes Published: No	Y	Oxon
IIA, 2.9.1/04	Goodyear, A.	2006	Cymoxanil Position Paper Identification of Cymoxanil Aquatic Degradation Products Report No. TSGE 4-3-4.PP1 GLP: No Published: No	Y	DuPont Oxon
IIA, 2.9.2./01	Anderson, J.J., Horne, P., Lawler, S.M., Swain, R.S.	1993	Photodegradation of [2-14C]DPX-T3217 (cymoxanil) in pond water and sterile buffer pH 5, DuPont Experimental Station AMR 1990-91 GLP: Yes Published: No	N	DuPont
IIA, 2.9.2/02	Willems, H.	2000	Photodegradation of Cymoxanil in Water NOTOX B.V., 's-Hertogenbosch, The Netherlands 257759 GLP: Yes Published: No	Y	Oxon
IIA, 2.9.2/03	Goodyear, A.	2006	Cymoxanil Position Paper Identification of Cymoxanil Aquatic Degradation Products Report No. TSGE 4-3-4.PP1 GLP: No Published: No	Y	DuPont Oxon
IIA, 2.9.2/03	Hatzenbeler, C.J., Moore, L.A.	2004	Calculated Theoretical Lifetime for Cymoxanil in the Top Layer of Aqueous Systems DuPont Stine-Haskell Research Center DuPont-12330 GLP: No Published: No	Y	DuPont

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IIA, 2.9.2/04	Willems, H.	2003	Aquatic Photolysis of Cymoxanil Estimation of Lifetime in the Top Layer of Aqueous Systems (GC Solar Calculations) NOTOX B.V., 's-Hertogenbosch, The Netherlands 397439 GLP: No Published: No	Y	Oxon
IIA, 2.9.3/01	Anderson, J.J., Lawler, S.M., Swain, R.S.	1993	Quantum yield determination of DPX-T3217 (cymoxanil) and LC/MS confirmation of unknown degradates in sterile buffer pH 5 DuPont Experimental Station AMR 1990-91, Supplement No. 1 GLP: Yes Published: No	N	DuPont
IIA, 2.9.3/02	Willems, H.	2000	Photodegradation of Cymoxanil in Water NOTOX B.V., 's-Hertogenbosch, The Netherlands 257759 GLP: Yes Published: No	Y	Oxon
IIA, 2.9.4/01	Schmuckler, M.E., Moore, L.A.	1993	Dissociation constant of cymoxanil DuPont Experimental Station AMR 2589-92 GLP: Yes Published: No	N	DuPont
IIA, 2.9.4/02	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: No Published: No	N	Oxon
IIA, 2.9.4/03	Serri, A.	2002	Hypothesis on identity of dissociation products Oxon Italia S.p.A. CYM001-02 GLP: No Published: No	Y	Oxon
IIA, 2.9./05	Schmuckler, M.E.	2001	The calculated pKa of IN-U3204 DuPont Stine-Haskell Research Center DuPont-6448 GLP: No Published: No	Y	DuPont

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Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner*)
IIA, 2.10./01	Kleier, D.A.	1997	Atmospheric oxidation rates for cymoxanil DuPont Stine Research Center CYMO/PRO 5 GLP: No Published: No	N	DuPont
IIA, 2.10./02	Betteley, J.M.T.	1995a	Cymoxanil (pure): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 57/950183 GLP: Yes Published: No	N	Oxon
IIA, 2.11.1/01	Gravell, R.L.	1996	Auto-flammability, flammability, explosive and oxidizing properties of cymoxanil DuPont Experimental Station AMR 3510-95 GLP: Yes Published: No	N	DuPont
IIA, 2.11.1/02	Betteley, J.M.T.	1995b	Cymoxanil (technical): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 58/950197 GLP: Yes Published: No	N	Oxon
IIA, 2.11.2/01	Gravell, R.L.	1996	Auto-flammability, flammability, explosive and oxidizing properties of cymoxanil DuPont Experimental Station AMR 3510-95 GLP: Yes Published: No	N	DuPont
IIA, 2.11.2/02	Betteley, J.M.T.	1995b	Cymoxanil (technical): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 58/950197 GLP: Yes Published: No	N	Oxon
IIA, 2.13./01	Gravell, R.L.	1996	Auto-flammability, flammability, explosive and oxidizing properties of cymoxanil DuPont Experimental Station AMR 3510-95 GLP: Yes Published: No	N	DuPont

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner*)
IIA, 2.13./02	Betteley, J.M.T.	1995b	Cymoxanil (technical): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 58/950197 GLP: Yes Published: No	N	Oxon
IIA, 2.14./01	Betteley, J.M.T.	1995b	Cymoxanil (technical): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 58/950197 GLP: Yes Published: No	N	Oxon
IIA, 2.15./01	Gravell, R.L.	1996	Auto-flammability, flammability, explosive and oxidizing properties of cymoxanil DuPont Experimental Station AMR 3510-95 GLP: Yes Published: No	N	DuPont
IIA, 2.15./02	Betteley, J.M.T.	1995b	Cymoxanil (technical): physicochemical properties Huntingdon Research Centre Ltd, UK OXN 58/950197 GLP: Yes Published: No	N	Oxon
Annex III Data and Information					
IIIA, 2.1./01	Jourdainne, C.	1997	Physical, chemical and technical properties of DPX-KP481 water-dispersible granular fungicide formulation (WG) DuPont European Research and Development Centre (ERDC) AMR 3833-96 GLP: Yes Published: No	N	DuPont
IIIA, 2.2.1/01	Gravell, R.L.	1996	Explosive and oxidizing properties, flammability of solids and spontaneous ignition of DPX-KP481 50% water-dispersible granular fungicide formulation DuPont Experimental Station AMR 3876-96 GLP: Yes Published: No	N	DuPont

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner*)
IIIA, 2.2.2/01	Gravell, R.L.	1996	Explosive and oxidizing properties, flammability of solids and spontaneous ignition of DPX-KP481 50% water-dispersible granular fungicide formulation DuPont Experimental Station AMR 3876-96 GLP: Yes Published: No	N	DuPont
IIIA, 2.3/01	Gravell, R.L.	1996	Explosive and oxidizing properties, flammability of solids and spontaneous ignition of DPX-KP481 50% water-dispersible granular fungicide formulation DuPont Experimental Station AMR 3876-96 GLP: Yes Published: No	N	DuPont
IIIA, 2.4.2/01	Jourdainne, C.	1997	Physical, chemical and technical properties of DPX-KP481 water-dispersible granular fungicide formulation (WG) DuPont European Research and Development Centre (ERDC) AMR 3833-96 GLP: Yes Published: No	N	DuPont
IIIA, 2.6.2/01	Jourdainne, C.	1997	Physical, chemical and technical properties of DPX-KP481 water-dispersible granular fungicide formulation (WG) DuPont European Research and Development Centre (ERDC) AMR 3833-96 GLP: Yes Published: No	N	DuPont
IIIA, 2.7.1/01	Jourdainne, C.	1997	Physical, chemical and technical properties of DPX-KP481 water-dispersible granular fungicide formulation (WG) DuPont European Research and Development Centre (ERDC) AMR 3833-96 GLP: Yes Published: No	N	DuPont

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner*)
IIIA, 2.7.3/01	Thuet, E.	1998	Shelf life stability of DPX-KP481 water-dispersible granular fungicide formulation (WG) in a high density polyethylene container DuPont European Research and Development Centre (ERDC) AMR 3835-96 GLP: No Published: No	N	DuPont
IIIA, 2.8.1/01	Jourdainne, C.	1997	Physical, chemical and technical properties of DPX-KP481 water-dispersible granular fungicide formulation (WG) DuPont European Research and Development Centre (ERDC) AMR 3833-96 GLP: Yes Published: No	N	DuPont
IIIA, 2.8.2/01	Jourdainne, C.	1997	Physical, chemical and technical properties of DPX-KP481 water-dispersible granular fungicide formulation (WG) DuPont European Research and Development Centre (ERDC) AMR 3833-96 GLP: Yes Published: No	N	DuPont
IIIA, 2.8.3/01	Jourdainne, C.	1997	Physical, chemical and technical properties of DPX-KP481 water-dispersible granular fungicide formulation (WG) DuPont European Research and Development Centre (ERDC) AMR 3833-96 GLP: Yes Published: No	N	DuPont
IIIA, 2.8.5/01	Jourdainne, C.	1997	Physical, chemical and technical properties of DPX-KP481 water-dispersible granular fungicide formulation (WG) DuPont European Research and Development Centre (ERDC) AMR 3833-96 GLP: Yes Published: No	N	DuPont

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner*)
IIIA, 2.8.6.1/01	Jourdainne, C.	1997	Physical, chemical and technical properties of DPX-KP481 water-dispersible granular fungicide formulation (WG) DuPont European Research and Development Centre (ERDC) AMR 3833-96 GLP: Yes Published: No	N	DuPont
IIIA, 2.8.6.2/01	Jourdainne, C.	1997	Physical, chemical and technical properties of DPX-KP481 water-dispersible granular fungicide formulation (WG) DuPont European Research and Development Centre (ERDC) AMR 3833-96 GLP: Yes Published: No	N	DuPont
IIIA, 2.8.6.3/01	Bloemer, D.S.	2000	Attrition resistance of famoxadone/cymoxanil (25% active ingredient ratio) water-dispersible granular fungicide formulation DuPont Experimental Station DuPont-4188 GLP: No Published: No	N	DuPont
IIIA, 2.8.8.1/01	Jourdainne, C.	1997	Physical, chemical and technical properties of DPX-KP481 water-dispersible granular fungicide formulation (WG) DuPont European Research and Development Centre (ERDC) AMR 3833-96 GLP: Yes Published: No	N	DuPont
IIIA, 2.9/01	Thuet, E.	1997	Physical and chemical compatibility of DPX-KP481 water dispersible granular (WG) fungicide formulation with tank mixtures, DuPont European Research and Development Centre (ERDC) AMR 4255-96 GLP: No Published: No	N	DuPont
IIIA 2.1	Fraschini, C.	1999	Cymoxanil 50 % WP (Physical, chemical and technical properties). SIPCAM S.p.A., Italy, Report 004/99 GLP: Yes Published: No	Y	Oxon Italia S.p.A.

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Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner*)
IIIA 2.2	D'Olimpo, P.	2000	Physical and chemical characterization of Cymoxanil 50 % WP EniChem S.p.A., Italy, Report 020/00 GLP: Yes Published: No	Y	Oxon Italia S.p.A.
IIIA 2.3	D'Olimpo, P.	2000	Physical and chemical characterization of Cymoxanil 50 % WP EniChem S.p.A., Italy, Report 020/00 GLP: Yes Published: No	Y	Oxon Italia S.p.A.
IIIA 2.4.2	Fraschini, C.	1999	Cymoxanil 50 % WP (Physical, chemical and technical properties). SIPCAM S.p.A., Italy, Report 004/99 GLP: Yes Published: No	Y	Oxon Italia S.p.A.
IIIA 2.5	D'Olimpo, P.	2000	Physical and chemical characterization of Cymoxanil 50 % WP EniChem S.p.A., Italy, Report 020/00 GLP: Yes Published: No	Y	Oxon Italia S.p.A.
IIIA 2.6	Fraschini, C.	1999	Cymoxanil 50 % WP (Physical, chemical and technical properties). SIPCAM S.p.A., Italy, Report 004/99 GLP: Yes Published: No	Y	Oxon Italia S.p.A.
IIIA 2.7.1	Fraschini, C.	1999	Cymoxanil 50 % WP (Physical, chemical and technical properties). SIPCAM S.p.A., Italy, Report 004/99 GLP: Yes Published: No	Y	Oxon Italia S.p.A.
IIIA 2.7.3	Freschi, G.	2000	Cymoxanil 50 WP: shelf life at ambient temperature SIPCAM S.p.A., Italy, Report 005/99 GLP: Yes Published: No	Y	Oxon Italia S.p.A.
IIIA 2.8/01	Fraschini, C.	1999	Cymoxanil 50 % WP (Physical, chemical and technical properties). SIPCAM S.p.A., Italy, Report 004/99 GLP: Yes Published: No	Y	Oxon Italia S.p.A.

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner*)
IIIA 2.8/02	Freschi, G.	2004	Comparison of Persistent foaming, Suspensibility, and Wet Sieve test on CYMOXANIL 50% WP with and without Water Soluble Bag (WSB) SIPCAM S.p.A., Italy, Report 023/2004 GLP: Yes Published: No	Y	Oxon Italia S.p.A.
IIIA 2.9.1/01	Hale, S.	2001a	Physical compatibility of tank mixes (fluazinam). Agriseach UK Ltd., UK, Report AC/5609/SP-1 GLP: No Published: No	Y	Oxon Italia S.p.A.
IIIA 2.9.1/02	Hale, S.	2001b	Physical compatibility of tank mixes (mancozeb) Agriseach UK Ltd., UK, Report AC/5609/SP-2 GLP: No Published: No	Y	Oxon Italia S.p.A.
IIIA 2.9.1/03	Hale, S.	2001c	Physical compatibility of tank mixes (mancozeb) Agriseach UK Ltd., UK, Report AC/5609/SP-3 GLP: No Published: No	Y	Oxon Italia S.p.A.
IIIA 2.9.2	Chiesa, I.	2003	Cymoxanil 50WP (Chemical compatibility with mancozeb and fluazinam based products). SIPCAM S.p.A., Italy, Report 002/03 GLP: No Published: No	Y	Oxon Italia S.p.A.

*) Owner of Annex II original reports as written in the column but all Annex II data are shared between DuPont and Oxon.

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Annex B

Cymoxanil

B.3 Data on application and further information

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

B.3 Data on application and further information

B.3.1 Data on application relevant to the active substance (Annex IIA 3.1 - 3.6)

B.3.1.1 Function (Annex IIA 3.1)

Fungicide

B.3.1.2 Effects on harmful organisms (Annex IIA 3.2)

B.3.1.2.1 Nature of the effects on harmful organisms (Annex IIA 3.2.1)

Cymoxanil prevents spore germination, haustorial formation and mycelial growth of the target pathogens.

B.3.1.2.2 Translocation in plants (Annex IIA 3.2.2)

Cymoxanil has local systemic activity with translaminar action, i.e. Cymoxanil applied to the upper leaf surface penetrates the leaf and controls fungal infections of the lower leaf surface (e.g., *Plasmopara viticola*). The compound will redistribute within the treated leaf but movement to new growth is limited. There is no significant movement downwards in the plant or translocation to untreated leaves. However, applications to the roots or stems will translocate to the leaves.

B.3.1.3 Field of use (Annex IIA 3.3)

Agriculture and horticulture.

B.3.1.4 Harmful organisms controlled and crops or products protected or treated (Annex IIA 3.4)

B.3.1.4.1 Details of existing and intended uses

Representative uses supported in this monograph are potatoes and lettuce. Cymoxanil is used in a wide range of crops with a wide range of mixture partners. The main crops are grapes, potatoes, tomatoes and lettuce.

B.3.1.4.2 Details of harmful organisms against which protection is afforded

Cymoxanil provides effective control of economically important fungal plant pathogens belonging to the order Peronosporales, namely *Phytophthora*, *Plasmopara*, and *Peronospora* spp., which cause downy mildew and blight in a wide range of crops. Specific examples are *Plasmopara viticola* (downy mildew in grape) and *Phytophthora infestans* (late blight in potato/tomato).

B.3.1.4.3 Effects achieved

Cymoxanil exhibits both preventative and curative action, for example, against *Plasmopara viticola* in grape and *Phytophthora infestans* in potato and tomato. This inhibits growth of the pathogen in treated leaves, damaging and preventing the development of fungal hyphae. It also initiates host responses, such as discoloration of infected cells and collapse of adjacent

cells, which confine the pathogen to the initial infection site. Sporulation of the pathogen is prevented. These actions effectively inhibit further development of the disease.

B.3.1.5 Mode of action (Annex IIA 3.5)

B.3.1.5.1 Statement of the mode of action of the active substance

Biochemical mechanism: Cymoxanil has an unique fungicidal action. Studies suggest that it inhibits multiple cellular processes such as DNA and RNA synthesis¹, amino acid synthesis², mycelial respiration, protein synthesis, uridine metabolism and membrane permeability³. These actions are due to the activation or metabolism of Cymoxanil by sensitive fungi to form toxic metabolites^{2,4,5}. These fungicidal actions September be secondary metabolic effects due to an, as yet, undetermined mechanism.

Physiological mechanism: Cymoxanil inhibits growth of the pathogen in treated leaves, damages and prevents the development of haustoria and initiates host responses, such as discoloration of infected cells and collapse of adjacent cells, to confine the pathogen to the initial infection site⁶.

B.3.1.5.2 Details of active metabolites and degradation products (Annex IIA 3.5)

All data indicate that Cymoxanil is the active substance and that no metabolism or degradation is required for fungicidal activity.

B.3.1.6 Information on possible occurrence of the development of resistance (Annex IIA 3.6)

To date, there are no records of the development of resistance of fungal pathogens to Cymoxanil. The potential for resistance to Cymoxanil is considered to be very low for the following reasons:

- The short residual life of Cymoxanil in plants reduces selection pressure.
- Cymoxanil is recommended for use in mixture with other fungicides which have different modes of action.
- Laboratory attempts by P. Leroux at INRA, Versailles (personal communication, M. G. Curl, September 2005, Tier II summary of DuPont and Oxon) to generate mutants of *Phytophthora* species that are resistant to Cymoxanil have not been successful.

¹ Ziogas, B.N. and Davidse, L.C. (1987). Studies on the mechanism of action of Cymoxanil in *Phytophthora infestans*. *J. Pestic. Biochem. and Physiol.* 29, 89 - 96.

² Leroux, P., Fritz, R. and Despreaux, D. (1987). The mode of action of Cymoxanil in *Botrytis cinerea*. *Pestic. Sci. and Biotechnol., Proc. 6th Int. Congr. Pestic. Chem.* (ed. R. Greenhalgh and T.R. Roberts), pp. 191 - 196. Blackwell Scientific Publications.

³ Despreaux, D., Fritz, R. and Leroux, P. (1981). Mode d'action biochimique du Cymoxanil. *Phytiatr. Phytopharm.*, 30, 245 - 255.

⁴ Cherton, J.-C., Chevassus-Clement, M.-T., Lange, C., Convert, O., Fritz, R. and Leroux, P. (1991). Behaviour studies of the fungicide Cymoxanil in two strains of the fungus *Botrytis cinerea* and in hemolymph of locust or lobster. I. *In situ* monitoring by ISRP-HPLC. *J. Chromatogr.* 566, 499 - 506.

⁵ Cherton, J.-C., Convert, O., Fritz, R., Leroux, P. and Cassier, P., 1993, Study on the metabolism of the fungicide Cymoxanil in two strains of the fungus *Botrytis cinerea* and in locust *Locusta migratoria* or lobster *Homarus americanus*. III. *In situ* monitoring by H-NMR. *Spectroscopy* 11, 21 - 35.

⁶ Howard, R.J., Ferrari, M.A., Bourett, T.M., Stidham, M.D., Shillingford, C., Power, R.J. and Hamlen, R.A., 1996a, Biology of Curzate 50 WP action against *Plasmopara viticola* on *Vitis*: A cytological analysis. Curzate Symposium, Rome, January 16, 1996.

- No shift in sensitivity has been observed in *P. infestans* (strains from A1 and A2 mating types) after more than 15 years of extensive and intensive exposure to Cymoxanil^{7, 8}.
- Cymoxanil is equally active against phenylamide sensitive and resistant strains^{9, 3} and it is not cross-resistant with other fungicides.

B.3.2 Data on application relevant to the plant protection product (Annex IIIA 3)

B.3.2.1 Field of use (Annex IIIA 3.1)

Agriculture and horticulture.

B.3.2.2 Effects on harmful organisms (Annex IIIA 3.2)

Fungicide (contact, protective) for the control of *Phytophthora infestans* in potatoes and *Bremia lactucae* in lettuce.

⁷ Power, R.J., Hamlen, R.A. and Morehart, A.L. (1995). Variation in sensitivity of *Phytophthora infestans* field isolates to Cymoxanil, chlorothalonil and metalaxyl. *Proc. EAPR, Phytophthora* - 150 Conference. Ed Dowleg, L.J., Bannon, E., Cooke, L.R., Keane, T. and O'Sullivan, E., Dublin, Ireland, pp. 154 - 159.

⁸ Sujkowski, L.S., Fry, B.A., Power, R.J., Goodwin, S.B., Peever, T.L., Hamlen, R.A. and Fry, W.E. (1995). Sensitivities of Mexican populations of *Phytophthora infestans* to chlorothalonil, Cymoxanil and metalaxyl, *Plant Disease* 79, 1117 - 1120.

⁹ Schober-Butin, B. (1995). Pathotypen, Paarungstypen und Fungizidresistenz von *Phytophthora infestans* (Mont.) de Bary. *Jahresbericht 1994, Bundesministerium für Ernährung, Landwirtschaft und Forsten*, BBA, p. 61.

B.3.2.3 Details of representative uses (Annex IIIA 3.3)**Table 3.2.3-1 Summary of representative uses evaluated (Cymoxanil) (Annex IIA 3.4)**

Crop and/or situation	Member state or Country (a)	Product Name (b)	F G or I (c)	Pests or Groups of pests controlled	Formulation		Application				Application rate per treatment			PHI (days)	Remarks (e)
					Type	Conc. of as	method kind	growth stage (d)	Number min max	Interval between application	kg as/ha min max	water l/ha min max	kg as/ha min max		
Lettuce	South	CYM 50	F	<i>Bremia lactucae</i>	WP	500 g/kg	Spray	40-49	3-4	7	0.03-0.048	500-800	0.240	10	Oxon
Potato	North	CYM 50	F	<i>Phytophthora infestans</i>	WP	500 g/kg	Spray	21-95	4	7-10	0.026-0.060-	200-450	0.120	7	Oxon
	South	CYM 50			WP	500 g/kg	Spray	21-95	5	7	0.012-0.024	500-1000	0.120	7	Oxon
	North	Tanos	F	<i>Phytophthora infestans</i>	WG	250g/kg	Spray	21-95	6-8	7-10	0.029-0.058	300-600	0.175	14	DuPont
	South														
(a) Southern Europe (South) Northern Europe (North).															
(b) CYM 50 = Cymoxanil 50 %WP; Tanos = Cymoxanil/Famoxadone 250:250g/kg.															
(c) Outdoor or field use (F), glasshouse application (G) or indoor application (I).															
(d) Growth stage at the first application according to BBCH system for a uniform coding of phenologically similar growth stages of all mono- and dicotyledonous plant species.															
(e) GAP for products supported by Oxon or DuPont.															

B.3.2.4 Application rate (Annex IIIA 3.4)

See Table B.3.2.3-1

B.3.2.5 Concentration of active substance in material used (Annex IIIA 3.5)

See Table B.3.2.3-1

B.3.2.6 Method of application (Annex IIIA 3.6)

Applicant A (DuPont):

DPX-KP481 50WG:

DPX-KP481 50WG is diluted in water and applied to potatoes using tractor-mounted hydraulic field sprayers with ground-directed booms.

Applicant B (Oxon):

Cymoxanil 50%WP:

Spraying by using standard equipment for field crop like tractor mounted sprayers. Dilution in water: 600-800 L/ha (lettuce) or 200 to 450 L/ha (potato, Northern Europe) and 500 to 1000 L/ha (potato, Southern Europe).

B.3.2.7 Number and timing of application (Annex IIIA 3.7)

Applicant A (DuPont):

DPX-KP481 50WG:

The GAP supported by this dossier for the EU re-registration of cymoxanil is for a maximum of 8 applications and a minimum spray interval of 7 days with a 14-day PHI. In practice, fewer applications of DPX-KP481 50WG are used for resistance management reasons relating to the mixture partner (famoxadone), which is a member of the QOI group of fungicides.

Applicant B (Oxon):

Cymoxanil 50%WP:

Potato: first spray should be applied before the haulm meets across the rows or as soon as a blight warning is received, whichever occurs first. Spraying should be repeated every 10 days.

A 7 day period might be used under exceptional circumstances where for instance, blight risk is already high and rain is forecast at the time the next spray is due. A maximum of 4 applications (Northern Europe) or 5 applications (Southern Europe) might be applied.

Lettuce: preventive treatment should be started as soon as there are conditions favourable for

infection by Peronosporales, carrying on during the whole season (max 4 applications; interval: 7 days). For curative action: 2 treatments with a short application interval, using the maximum dose. Duration of protection afforded by each application: as indicated by the interval between applications.

Duration of protection afforded by the maximum number of applications: In normal weather condition protection is granted for all crop vegetative cycle sensitive to disease attack.

B.3.2.8 Necessary waiting periods or other precautions to avoid phytotoxic effects on succeeding crops (Annex IIIA 3.8)

Applicant A (DuPont):

DPX-KP481 50WG:

Use of DPX-KP481 50WG according to the proposed GAP does not represent a hazard to rotational crops and does not justify a specific labelling. Cymoxanil is very rapidly degraded in soil and therefore, is not available for uptake into succeeding crops. Cymoxanil is not phytotoxic to plants in tests of vegetative vigour and seedling emergence.

Applicant B (Oxon):

Cymoxanil 50%WP:

Not relevant for Cymoxanil 50 %WP. Due to the fast degradation of the active substance in soil there are no restrictions regarding succeeding crops.

B.3.2.9 Proposed instructions for use (Annex IIIA 3.9)

Applicant A (DuPont):

DPX-KP481 50WG:

Product labels have been submitted.

Applicant B (Oxon):

Cymoxanil 50%WP:

Product labels have been submitted.

B.3.3 Summary of data on application

Cymoxanil acts as a fungicide with curative and protective activity against fungus from the class of *Oomycetes*, especially against the species *Phytophthora infestans* and *Bremia lactucae* in potatoes and lettuce. Cymoxanil needs to be applied before the disease attacks in a concentration of max. 240 g a.s./ha.

DPX-KP-481 50 WG and Cymoxanil 50% WP are registered in several European countries. A maximum number of 8 applications are recommended. The first treatment against the class of *Oomycetes* should take place when warning systems forecast indicates significant disease attacks using hydraulic filed sprayer. The typical spray volumes are between 500 to 800 L/ha for lettuce and 200 to 1000 L/ha for potato.

B.3.4 Further information on the active substance (Annex IIA 3.7 - 3.9)

B.3.4.1 Recommended methods and precautions concerning handling, storage, transport or fire (Annex IIA 3.7)

Applicant A (DuPont):

Handling:

Technical measures /precautions: Provide appropriate exhaust ventilation at places where dust is formed.

Safe handling advice: Keep away from heat and sources of ignition. Avoid dust formation in confined areas.

Storage:

Technical measures storage conditions: Keep containers tightly closed in a dry, cool and well-ventilated place. Store in a place accessible by authorized persons only.

Incompatible products: humid air and water.

Packaging material: No materials to be specially mentioned.

Further information: Keep out of reach of children.

Personal protection:

Respiratory protection:

Respirator with combination filter for vapour/particulate

Eye protection:

Safety glasses

Hand protection:

Rubber gloves

Skin and body protection:

Protective suit

Hygiene measures:

Keep away from food, drink and animal feeding stuff. Wash hands before breaks and immediately after handling the product. When using, do not eat, drink or smoke.

Transport:

Land transport ADR/RID:

ADR/RID-GGVSE Class: 9

Packaging group: III

UN-Number: 3077

Maritime transport IMDG:

IMDG Class: 9

Packaging group: III

UN-Number: 3077

Air transport ICAO-TI and IATA-DGR:

ICAO/IATA Class: 9

Packaging group: III

UN-Number: 3077

Fire:

Suitable extinguishing media: water, spray, foam, dry powder, carbon dioxide (CO₂).

Extinguishing media which must not be used for safety reasons: high volume water jet (contamination risk).

Special protective equipment for fire-fighters: In the event of fire, wear self-contained breathing apparatus.

Specific methods: (on small fires). If area is heavily exposed to fire and if conditions permit, let fire burn itself out since water September increase the area contaminated. Cool containers /tanks with spray water.

Applicant B (Oxon):

Handling:

Information for safe handling: Prevent formation of dust. Provide suction extractors if dust is formed. Information about protection against explosions and fires: Have fire extinguishing equipment ready in case of nearby fire. Dust can combine with air to form an explosive mixture.

Storage:

Requirements to be met by storerooms and containers: Store only in unopened original containers. Information about storage in one common storage facility: Store away from foodstuffs.

Further information about storage conditions: Store in cool, dry conditions in well sealed containers. Store container in a well ventilated position.

Protect from humidity and keep away from water. Protect from heat and direct sunlight.

Personal protection:

General protective and hygienic measures: Do not inhale dust/ smoke/mist

Avoid contact with the eyes and skins.

Take off immediately all contaminated clothing.

Wash hands during breaks and at the end of the work.

Keep away from foodstuffs, beverage and food.

Breathing equipment: In case of brief exposure or low pollution use breathing filter apparatus.

In case of intensive or longer exposure use breathing apparatus that is independent of circulating air.

Protection of hand: synthetic gloves

Material of gloves: Butyl rubber, BR

Penetration time of glove material: Value for the permeation: level ≥ 6

For permanent contact in work areas without heightened risk of injury (e.g. laboratory) gloves made of the following material are suitable: Plastic gloves

Eye protection: Safety glasses recommended during refilling

Body protection: Light weight protective clothing, Boots.

Transport:

Land transport ADR/RID (cross-border): ADR/RID-GGVSE Class: 9 (M7)

Packaging group: III

UN-Number: 3077

Label: 9

Maritime transport IMDG: IMDG Class: 9

Packaging group: III

UN-Number: 3077

Label: 9

Air transport ICAO-TI and IATA-DGR: ICAO/IATA Class: 9

Packaging group: III

UN-Number: 3077

Label: 9

Fire: Suitable extinguishing agents: CO₂, extinguishing powder or water jet. Fight larger fires with water jet or alcohol-resistant foam. Special hazards caused by the material, its products of combustion or resulting gases: Formation of poisonous gases during heating or in fires.

Can be released in case of fire: Hydrogen cyanide (HCN), Carbon monoxide (CO), Nitrogen oxides (NO_x).

Protective equipment: Wear full protective suit. Do not inhale explosion gases or combustion gases. Put breathing apparatus.

B.3.4.2 Procedures for destruction or decontamination (Annex IIA 3.8)

Applicant A (DuPont):

Waste from residues /unused products: In accordance with local and national regulations. Must be incinerated in a suitable incineration plant holding a permit delivered by the competent authorities. Do not allow material to contaminate ground water systems. Contaminated packaging: Do not re-use empty containers. Do not contaminate ponds, waterways or ditches with chemical or used container.

Applicant B (Oxon):

Recommendation: Must not be disposed of together with household garbage. Do not allow product to reach sewage system.

Uncleaned packaging: Recommendation: Disposal must be made according to official regulations.

B.3.4.3 Emergency measures in case of accident (Annex IIA 3.9)

Applicant A (DuPont):

Inhalation:	Move to fresh air. Oxygen or artificial respiration, if needed. Consult a physician after significant exposure.
Skin contact:	Wash off immediately with soap and plenty of water.
Eye Contact:	Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. If eye irritation persists, consult a specialist.
Ingestion:	Drink 1 or 2 glasses of water. Do not induce vomiting without medical advice. Never give anything by mouth to an unconscious person. Call a physician immediately.

Applicant B (Oxon):

General information:	Take affected persons out of danger area and instruct to lie down. Keep warm, position comfortably and cover well.
Symptoms of poisoning	Symptoms even occur after several hours; therefore medical observation for at least 48 hours after the accident.
After inhalation:	Supply fresh air and call for doctor for safety reasons. In

	case of unconsciousness bring patient into stable side position for transport.
After skin contact:	Instantly wash with water and soap and rinse thoroughly. If skin irritation continues, consult a doctor.
After eye contact:	Rinse opened eye for several minutes under running water. Call a doctor immediately.
After swallowing:	Rinse out mouth and then drink plenty of water. Induce vomiting.

B.3.5 Further information on the plant protection product (Annex IIIA 4)

B.3.5.1 Packaging (type, materials, size, etc.), compatibility of the preparation with packaging materials (Annex IIIA 4.1)

B.3.5.1.1 Description and specification of packaging and materials used in packaging

Applicant A (DuPont):

DPX-KP481 50WG:

DPX-KP481 50WG will be packed in 400g, 2kg, and 3.5 kg pack sizes.

400 g pack size (1 Litre bottle):

10 bottles are grouped into a corrugated box.

Material: High density polyethylene (HDPE)

Shape/size: Rectangular based bottle

Approximated size: 141 (L) x 90 (W) x 163 (H) mm

Opening: 63 mm diameter

Closure: Screw cap with sealing disk

2 kg pack size (5 Litre bottle):

4 bottles are grouped into a corrugated box.

Material: High density polyethylene (HDPE)

Shape/size: Rectangular based bottle

Approximated size: 181 (L) x 151 (W) x 201 (H) mm

Opening: 63 mm diameter

Closure: Screw cap with sealing disk

3.5 kg pack size (7 Litre bottle):

4 bottles are grouped into a corrugated box.

Material: High density polyethylene (HDPE)

Shape/size: Rectangular based bottle

Approximated size: 240 (L) x 179 (W) x 300 (H) mm

Opening: 63 mm diameter

Closure: Screw cap with sealing disk

Applicant B (Oxon):

Cymoxanil 50%WP:

Cymoxanil 50 % WP will be packed into a normal packaging system or a water soluble packaging.

Normal packaging:

1, 5, 10 and 12 x 1 kg polyethylene laminate bag in cardboard carton boxes.

Water soluble packaging:

3 x 0.24 kg water soluble bag (PVA-EF210 35 µ) in a single waterproof envelope (180x440 mm) made with special three-layer film (PET+ aluminium +PE): 10 envelopes are then grouped in cardboard carton box (code 019508288).

B.3.5.1.2 Suitability of packaging

Applicant A (DuPont):

DPX-KP481 50WG:

The suitability of the packaging, including closures, in terms of its strength, leakproofness, and resistance to normal transport and handling has been determined and reported according to the RTMD/ADR/RID/OACI/IATA/OMI/IMDG and 94-N-359-1 requirements.

The packaging has been tested and approved according to the RTMD/ADR/RID/OACI/IATA/OMI/IMDG and 94-N-359-1 requirements. The packaging complies with ADR regulations having been tested using the ADR test methods appropriate to the pack type and material and classification of the contents and an appropriate UN certificate issued for:

10 x 400 g pack

4 x 2 kg pack

4 x 3.5 kg pack

Applicant B (Oxon):

Cymoxanil 50%WP:

Tri-layer polyethylene and water soluble films suitability has been tested by commercial supplier of the material. Moreover dissolution rate of the whole water soluble bags has been tested according to CIIPCA method MT 176 and it resulted to satisfy the criteria for a suitable dissolution. Cardboard containers have been certified by Italian competent authority (Ministero dei Trasporti e della Navigazione, Direzione Generale della Navigazione e del Traffico Marittimo) to be suitable for transport according to ADR, RID and IMDG - classes 3, 6.1 and 8, packing groups I, II and III. For water soluble bags container suitability tests were made by "Istituto Sperimentale Area Merci Pericolose-FS SpA" (Resolution of 11.12.92, cross reference Doc. KIII AIIIP4.1.2): granted homologation is confirmed by the ONU number 4G/Y11/S/Year/II/ISP2978392-SPC 465 10x1.

B.3.5.1.3 Resistance of packaging material to its contents

Applicant A (DuPont):

DPX-KP481 50WG:

The packaging is a standard DuPont packaging used for similar formulations of other compounds such as sulfonylureas for more than 10 years. DPX-KP481 50WG formulation has been sold in this packaging for several years. This long period of use has proved its suitability and resistance to leakage and normal transport and handling. In addition storage stability at ambient temperature over 2 years demonstrated resistance and compatibility of the formulation with the packaging system (see B.2.2.17).

Applicant B (Oxon):

Cymoxanil 50%WP:

The packaging material has been chosen taking the properties of the product into account. Cymoxanil 50%WP is a wettable powder, which is packed for several years in the described packaging material (B.3.5.1.1). Information regarding insufficient resistance of the material to its content has never been reported. The shelf life study comprising 2 years storage at room temperature showed that the water soluble bag did not change significantly under the storage conditions (see B.2.2.17).

B.3.5.2 Procedures for cleaning equipment (Annex IIIA 4.2)

Applicant A (DuPont):

References:

Cahill W R (1998). Laboratory cleanout of DPX-KP481 50% water dispersible granular fungicide formulation. DuPont Report AMR 4805-97

GLP: No

Published: No

DPX-KP481 50WG:

Application equipment should be rinsed thoroughly with water. Effectiveness of cleaning procedure was demonstrated using the following procedure:

The tank cleanout procedure was evaluated for effectiveness using an in-house DuPont Jar Test Protocol. 300-mL CIPAC Standard Water D was added to a 600-mL glass beaker equipped with a magnetic stir bar. To this, 0.2118 g DPX-KP481 50WG was added (corresponds to the most concentrated spray solution recommended on the label of ~800 g product/ha at 600 L/ha spray rate). After 2 minutes of stirring, 100-mL aliquots were poured into three 4-oz polyethylene bottles which were capped and allowed to stand at room temperature overnight.

Each polyethylene bottle was subjected to a standard cleanout: The bottle was inverted twice and the liquid was discarded. 10-mL tap water was added, the bottle was inverted twice, and the rinsate was discarded. Step 2 was repeated. 10-mL acetonitrile was added to extract any residual fungicide and the bottle was shaken well.

Results: The 1 ppm DPX-JE874 and 0.2 ppm Cymoxanil found in the acetonitrile after the cleanout corresponds to less than 0.07 % of the original DPX-JE874 content and 0.02% of the original Cymoxanil in the jar. The results indicate that the cleanout procedure prescribed is effective.

Applicant B (Oxon):

References:

Lucini, L. (2003). Cleaning efficiency in Cymoxanil residues removal from clothes.

CERZOO, Italy, Report CZ/03/013/OXON/CYMLAV

GLP: Yes

Published: No

Cymoxanil 50%WP:

Application equipment should be rinsed thoroughly with water.

Effectiveness of cleaning procedure: Cleaning procedures for the application equipment were studied by Sipcam S.p.A. In this study hand-held sprayer was filled with the plant protection product. After spraying, the apparatus was rinsed three times with water. Each rinse was analysed for residues of Cymoxanil. The analyses show that common agricultural practice (cleaning of application equipment with triple water rinsing) assures removal of almost all remainders of Cymoxanil from the spraying equipment (100 % rinse efficacy). Even one rinse was concluded to be sufficient to guarantee the efficacy of the cleaning (99.54 % of removal). The results indicate that the cleanout procedure prescribed is effective.

B.3.5.3 Re-entry periods, necessary waiting periods or other precautions to protect man, livestock and the environment (Annex IIIA 4.3)

Applicant A (DuPont):

DPX-KP481 50WG (DuPont):

Preharvest interval (in days) for each relevant crop:

Pre-harvest interval (PHI): The PHI for potatoes is 14 days.

Re-entry period (in days) for livestock, to areas to be grazed

Not relevant. Livestock are not expected to enter treated fields under normal circumstances.

Re-entry period (in hours or days) for man to crops, buildings or spaces treated:

Workers do not normally enter or handle treated potato crops before harvest. No waiting period between application and re-entry is required after the spray solution has dried on the plants.

Withholding period (in days) for animal feedingstuffs:

Livestock are not fed with treated crop.

Waiting period (in days) between application and handling treated products:

No additional period is required, due to fast degradation of the active substance.

Waiting period (in days) between last application and sowing or planting of succeeding crops:

Not required as Cymoxanil degrades very rapidly in soil. Therefore the active ingredient is not available for an uptake into succeeding crops.

Applicant A (DuPont):

Cymoxanil 50%WP (Oxon):

Preharvest interval (in days) for each relevant crop:

Pre-harvest interval is 7 days for potatoes and 10 days for lettuce.

Re-entry period (in days) for livestock, to areas to be grazed:

Not relevant. Livestock are not expected to enter treated fields under normal circumstances.

Re-entry period (in hours or days) for man to crops, buildings or spaces treated:

No waiting period between application and re-entry is required after the spray solution has dried on the plants.

Withholding period (in days) for animal feedingstuffs:

Livestock are not fed with treated crop.

Waiting period (in days) between application and handling treated products:

No additional period is required, due to fast degradation of the active substance.

Waiting period (in days) between last application and sowing or planting of succeeding crops:

Not required as Cymoxanil degrades very rapidly in soil. Therefore the active ingredient is not available for an uptake into succeeding crops.

B.3.5.4 Recommended methods and precautions concerning handling, storage, transport or fire (Annex IIIA 4.4)

Applicant A (DuPont):

DPX-KP481 50WG :

Handling and storage:

Advice on safe handling: Provide appropriate exhaust ventilation at places where dust is formed. Avoid dust formation in confined areas.

Advice on protection against fire and explosion: Keep away from heat and sources of ignition.

Other data: Stable under recommended storage conditions.

Stability: No decomposition if stored and applied as directed.

Conditions to avoid: Avoid temperatures above 190 °C.

Materials to avoid: Decomposes slowly on exposure to water.

Transport information:

In case of accident use personal protective equipment for clean up.

Do not flush into surface water or sanitary sewer system.

Clean up promptly by sweeping or vacuum. Shovel into suitable container for disposal or use approved industrial vacuum cleaner for removal.

Land transport ADR/RID (cross-border):

ADR Class: 9 (M7)

Packaging group: III

UN-Number: 3077

Label: 9

Maritime transport IMDG:

IMDG Class: 9

Packaging group: III

UN-Number: 3077

Label: 9

Marine pollutant:

Marine pollutant

Air transport ICAO-TI and IATA-DGR: ICAO/IATA Class: 9

Packaging group: III

UN-Number: 3077

Label: 9

Protective clothing and equipment proposed:

Gloves and overall for mixing, loading and application.

Fire-fighting measures:

Suitable extinguishing media: Water spray, foam, dry powder, carbon dioxide (CO₂).

Extinguishing media which must not be used for safety reasons: High volume water jet (contamination risk).

Special protective equipment for fire fighters: In the event of fire, wear self-contained breathing apparatus.

Specific methods (on small fires): If area is heavily exposed to fire and if conditions permit, let fire burn itself out since water may increase the area contaminated. Cool containers/tanks with spray water.

Information on combustion products likely to be generated in the event of a fire:

A specific study on the thermal decomposition has not been carried out. Current practice is to incinerate at a temperature greater than 900 °C with a residence time of 2-4 seconds in the chamber. Oxygen supply should be adjusted to generate <100 ppm carbon monoxide in the stack. As there are no halogens in Cymoxanil, there is no concern about dioxin formation. Hazardous decomposition products: carbon oxides, nitrogen oxides, hydrogen cyanide (hydrocyanic acid).

Procedures to minimise the generation of waste:

Only purchase and store quantities of product required in the short term. Do not open larger containers than is necessary for immediate use. Do not prepare spray mixture volumes greater than is necessary for immediate use.

Applicant B (Oxon):

Cymoxanil 50%WP:

Information on safe handling:

Ensure that suitable extractors are available on processing machines.
Wear protective equipment.
When handling, do not eat, drink or smoke.
Avoid contact with skin and eyes and avoid breathing dust.

Information about protection against explosion and fires:

The product is not explosive.

Information on storage:

Store the product closed in its original containers at temperature < 40°C in a cool and dry place, away from heat sources and direct sunlight.
Store, handle and transport away from food, beverages and feeding stuffs.
Requirements to be met by storerooms and containers:
Store only in the original container.

Information about storage in one common storage facility:

Store away from food stuffs.
Further information about storage conditions:
Store under cool, dry conditions in well sealed containers.

Transport information:

Land transport ADR/RID (cross-border):	ADR/RID-GGVSE Class: 9 (M7)
Maritime transport IMDG:	IMDG Class: 9
Air transport ICAO-TI and IATA-DGR:	ICAO/IATA Class: 9

Protective clothing and equipment proposed:

General protective and hygienic measures:

The usual precautionary measures should be adhered to general rules for handling chemicals.

Keep away from foodstuffs, beverages and feed.

Wash hands before breaks and at the end of work.

When handling do not eat, drink or smoke.

Breathing equipment: Breathing equipment recommended.

Protection of hands: Protective gloves.

Eye protection: Safety glasses.

Body protection: Protective work clothing.

Fire-fighting measures:

Suitable extinguishing agents: CO₂, extinguishing powder or water jet. Fight larger fires with water jet or alcohol-resistant foam.

Special hazards caused by the material, its products of combustion or resulting gases: formation of toxic gases is possible during heating or in case of fire. Nitrogen oxides (NO_x), Carbon monoxide (CO), Cyanide.

Protective equipment: Wear self-contained breathing apparatus. Protective clothes, gloves, boots and eye protection.

Additional information:

Cool endangered containers with water spray jet. Keep upwind.

Procedures to minimize the generation of waste:

No data available.

Information on combustion products likely to be generated in the event of fire:

Formation of toxic gases is possible during heating or in case of fire. Combustion products to be expected are Nitrogen oxides (NO_x), Carbon monoxide (CO) and Cyanides.

B.3.5.5 Emergency measures in case of an accident (Annex IIIA 4.5)

Applicant A (DuPont):

DPX-KP481 50WG:

Protection of emergency workers and bystanders:

Respiratory protection: Not required; except in case of aerosol formation. Half mask with a particle filter P2 (EN 143).

Hand protection: Material: Nitrile rubber
Glove thickness: 0.4-0.7 mm
Wearing time: 480 min.
Do not wear cotton or leather gloves. Take note of the information given by the producer concerning permeability and break thorough times, and of special workplace conditions (mechanical strain, duration of contact).

Eye protection: Safety glasses with side-shields.

Skin and body protection. Lightweight protective clothing.

Hygiene measures: Wash hands and face before breaks and immediately after handling the product. When using, do not eat, drink or smoke.
Wash contaminated clothing before re-use.

Protective measures: All chemical protective clothing should be visually inspected prior to use. Clothing and gloves should be replaced in case of chemical or physical damage or if contaminated.

First aid measures:

Inhalation: Move to fresh air. Oxygen or artificial respiration, if needed. Consult a physician after significant exposure.

Skin contact: Wash off immediately with soap and plenty of water.

Eye contact: Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. If eye irritation persists, consult a specialist.

Ingestion: Drink 1 or 2 glasses of water. Call a physician immediately. Never give anything by mouth to an unconscious person.

Applicant B (Oxon):

Cymoxanil 50%WP:

Person related safety precautions:

Wear protective clothing. Put on breathing apparatus.

Measures for environmental protection:

Do not allow product to reach sewage system or water bodies.

Keep dirty washing water for appropriate disposal.

Inform respective authorities in case product reaches water or sewage system.

Measures for cleaning/collecting:

Dispose of contaminated material, as waste according to official regulations.

Collect into hermetically sealed containers and dispose of according to local regulations.

Protection of emergency workers and bystanders:

Use the personal protective equipment proposed above.

First aid measures:

General information: Seek the advice of a poison control centre.

After inhalation: Supply fresh air or oxygen; call for doctor.

Seek immediate medical advice.

After skin contact: Immediately wash with water and soap and rinse thoroughly.

After eye contact: Rinse opened eye for several minutes under running water.

If symptoms persist, consult a doctor.

After swallowing: Do not induce vomiting. Instantly call for medical help.

B.3.5.6 Procedures for the destruction or decontamination of the plant protection product and its packaging (Annex IIIA 4.6)

Applicant A (DuPont):

DPX-KP481 50WG:

Neutralisation procedures:

Neutralisation by chemical reaction does not apply to DPX-KP481 50WG, which is in the neutral pH range.

Pyrolytic behaviour of the active substance under controlled conditions at 800°C and the content of polyhalogenated dibenzo-p-dioxins in the products of pyrolysis:

The requirement does not apply to Cymoxanil, which does not contain halogens.

Detailed instructions for safe disposal of the plant protection product and its packaging:

Package product wastes: Close and label the waste receptacles and, likewise, any uncleaned containers. Dispose of them at a suitable waste incineration plant and/or in accordance with the official local regulations. Where large quantities are concerned, consult the supplier.

Methods other than controlled incineration for disposal of the plant protection product, contaminated packaging and contaminated materials:

No other methods are currently available.

Applicant B (Oxon):

Cymoxanil 50%WP:

Neutralisation procedures: No procedures proposed.

Pyrolytic behaviour of the active substance under controlled conditions at 800 °C and the content of polyhalogenated dibenzo-p-dioxins in the products of pyrolysis:

Not applicable, as the product does not contain halogens.

Detailed instructions for safe disposal of the plant protection product and its packaging:

Product recommendation: Must be specially treated under adherence to official regulations.

Uncleaned packaging recommendation: Disposal must be made according to official regulations.

Methods other than controlled incineration for disposal of the plant protection product, contaminated packaging and contaminated materials:

No other methods are currently available.

B.3.6 References relied on

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Annex II					
IIA, 3.1-3.9	Curl, M.G.	2004	Tier II summaries, Document MII CYMOAS1T22004 GLP: No Published: No	N	DuPont/ Oxon
Annex III					
IIIA, 4.1-4.6	Vanderbroeck, V. Cosgrove T.	2006	Tier II summaries, MIII DuPont- 11710 EU, CYMOA3S1T2 2004 EuRev 8, May 2006 GLP: No Published: No	N	DuPont
IIIA, 4.1.3/01	Perrin, J.L.	1998	Packaging compatibility and suitability testing for water-dispersible granular formulation DPX-KP481 (Interim report) DuPont European Research and Development Centre (ERDC), AMR 4967-98 GLP: No Published: No	N	DuPont
IIIA,4.2	Cahill, W. R.	1998	Laboratory cleanout of DPX-KP481 50% water dispersible granular fungicide formulation. DuPont Report AMR 4805-97 GLP: No Published: No	N	DuPont
IIIA, 4.1-4.6	Ciocccotelli, M.	2006	Tier II summaries, MIII, Oxon AIIS1T2, May 2006 GLP: No Published: No	N	Oxon
IIIA 4.1.1	Anonymus	2002	Cymoxanil 50 % WP: water soluble complete packaging SIPCAM S.p.A., Italy, Report n.a. GLP: No Published: No	Y	Oxon

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Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
IIIA 4.1.2	Santarella, M.	1992	Certificato di omologazione di un imballaggio di tipo combinato cassa cartone 4G, destinato al trasporto di merci pericolose. Istituto Sperimentale Area Merci Pericolose, Italy, Report TC.I/S/082.510/29783 GLP: No Published: No	Y	Oxon
IIIA 4.2/01	Freschi, G.	2003	Cymoxanil 50%WP: Sprayability test and cleaning of the field sprayer equipment. SIPCAM S.p.A., Italy, Report 006/2003 GLP: Yes Published: No	Y	Oxon
IIA 4.2/02	Lucini, L.	2003	Cleaning efficiency in Cymoxanil residues removal from clothes. CERZOO, Italy, Report CZ/03/013/OXON/CYMLAV GLP: Yes Published: No	Y	Oxon

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Annex B

Cymoxanil

B.4 Proposal for classification and labelling

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

B.4 Proposals for classification and labelling

B.4.1 Proposals for the classification and labelling of the active substance (Annex IIA 10)

On the basis of the available data the following classification and labelling is proposed for cymoxanil according to Directive 67/548/EEC in combination with Directive 93/21/EEC:

Hazard symbols:		Black St. Andrew's Cross on orange square
		Dead fish, dead tree
Indication of danger:	Xn	Harmful
	Xi	Irritant
	N	Dangerous for the environment
Risk phrases:	R22	Harmful if swallowed
	R43	May cause sensitisation by skin contact
	R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed
	R63	Possible risk of harm to the unborn child
	R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Safety phrases:	S2	Keep out of the reach of children
	S13	Keep away from food, drink and animal feedingstuffs
	S20/21	When using do not eat, drink or smoke
	S24	Avoid contact with skin
	S36/37	Wear suitable protective clothing and gloves
	S46	If swallowed, seek medical advice immediately and show this container or label
	S56	Dispose of this material and its container to hazardous or special waste collection point.
	S57	Use appropriate container to avoid environmental contamination.
	S60	This material and its container must be disposed of as hazardous waste.
	S61	Avoid release to the environment. Refer to special instructions/safety data sheets.

Justification for the proposal with respect to health effects:

R22 ("harmful if swallowed"): The risk phrase is proposed because the active substance showed an LD₅₀ of 960 mg/kg bw in the rat.

R43 ("may cause sensitisation by skin contact"): With respect to skin sensitisation of cymoxanil, 3

Maximisation tests have been submitted. These studies have been conducted according to OECD Guideline 406 and meet the GLP criteria; regarding the study design, the studies are comparable and differ only in the vehicle used. The results of two studies indicate no skin sensitising property of cymoxanil. However, in the third study (*Allan, 1994*), in all test animals dermal reactions have been observed after challenge (slight to moderate erythema and slight to well defined oedema). In contrast to the notifier's opinion, that "the weight of evidence would suggest that cymoxanil is not a skin sensitizer", a possible skin sensitizing property of cymoxanil cannot be excluded. It should be mentioned that also in directive 2000/32/EC (26th ATP; 19 May 2000) cymoxanil has been classified and labelled with respect to its sensitizing properties.

R48/22 ("Harmful: danger of serious damage to health by prolonged exposure if swallowed"):

Based on the results of all subchronic toxicity studies, effects on testes/epididymides caused by cymoxanil technical is evident in rats and dogs as well:

- In the 28 days dietary study in rats (*Ramesh, 1999a*), animals of the two highest dose levels in rats showed changes in testes and epididymides weight, which might be linked to the reduction in body weight and body weight gain that occurred at the two higher dose groups. However, no histology has been performed in this study.
- In a 90 days dietary rat study (*Malek, 1992*), increase of testes weight of animals of the two highest dose levels had been accompanied by histological changes in testes and epididymides (spermatid degeneration, multinucleated spermatids, cell debris, hypospermia).
- Also in one out of two 90 days dog study (*Tompkins, 1993*), "small" testes, reduced epididymides weight as well as aspermatogenesis were reported at a dose level of 500 ppm. These effects could not be confirmed in the first 1 year dietary study. However, the highest dose administered (200 ppm) was much lower than the "effect dose" in the 90 days study.
- Nevertheless, in the second 1 year dog study (*Teunissen, 2003*), pathological examination exhibited finding in testes and epididymides at the high dose group (200 ppm): reduced size of testis as well as reduced size of epididymides and thickened epididymides: The histological findings comprised atrophic changes of testes and epididymides (seminiferous cell debris).
- In addition, it has to be mentioned that increased incidences of elongate spermatid degeneration and multinucleated spermatids were also observed in a chronic study on rats (see B.6.5.).

According to directive 2001/59/EC, substances have to be classified for their possible health effects by prolonged exposure, when morphological and functional changes after repeated exposure are evident (subchronic studies at and below a dose level of 50 mg/kg bw). The effects in testes mentioned have been observed in a 90 days toxicity study in rats at dose levels of 47.6 mg/kg bw (testes) as well as 102 and 224 mg/kg bw (testes and epididymides). However, findings in testes were also evident in the 90 days dog study at dose levels of 10.56 mg/kg bw and in the 1 year dog study at 5.6 mg/kg bw, too.

Although the respective findings were not seen consistently in all relevant studies, adverse effects on testes/epididymides are clearly evident in rats and dogs after subchronic administration of cymoxanil. Despite of no functional impairment of reproductive performance in multigeneration studies in rats indicative for testes effects, possible classification of cymoxanil with **Xn, R 48/22**

(**"Harmful: danger of serious damage to health by prolonged exposure if swallowed"**) should be considered based on these morphological changes.

R63 ("Possible risk of harm to the unborn child"): With respect to teratogenicity, cymoxanil should be classified into Repro Cat 3 considering the following reasons:

Taking into account the results of all developmental studies available, there is strong evidence that cymoxanil can impair fetal development producing also malformations (demonstrated in one out of two studies in rats and in three out of four studies in rabbits) and has to be classified into Repro Cat 3 (**Xn**,

R 63 "Possible risk of harm to the unborn child") considering the following reasons:

- In the first rat study (*Murray, 1993*) increased incidences of malformations (hemi vertebra, exencephalic head and fused ribs; findings above the range of historical control) were observed at maternal toxic dose levels.
- Also in the second rat study (*Veena; 1998*) increased incidences of variants and minor anomalies even at not maternal toxic dose levels indicate the potential of cymoxanil to disturb the development of foetuses.
- In one rabbit study (*Palmer et al., 1981*), there was a clear dose dependent increase of "vertebra and/or rib alterations", sometimes associated with scoliosis at maternal toxicity, without statistical significance but above the historical control data.
- In a further rabbit study (*Feussner et al., 1982*) increased incidences of malformations (hydrocephaly, cleft palates) occurred at the highest dose tested. Incidences were statistically significant increased and above historical background of these findings.
- Finally the incidence of dilation of heart ventricles of a third study in rabbits (*Ponnana, 1999*) was statistically significant increased in the high dose animals and was above the historical control data.

The safety phrases **S2**, **S13**, **S20/21** and **S46** follow a general precautionary approach. The safety phrase **S24** (Avoid contact with skin) is proposed because of the skin sensitising properties; **S36/37** (Wear suitable protective clothing and gloves) has to be applied caused by R43, R48/22 and R63.

Justification for the proposal with respect to environmental effects:

N follows from R50/53

R50/53 follows from the toxicity of the active substance to algae (*Pseudokirchneriella subcapitata*: E_rC_{50} (72 h) = 0.63 mg/L, Bell et al. (1996); *Anabaena flos-aquae*: E_rC_{50} (72 h) = 0.254 mg/L, Hughes et al. (1996a)) and from the results of a biodegradation study where it was shown that cymoxanil is not readily biodegradable (Luit, 2001).

S56, **S 57**, **S60** and **S61** follow from the toxicity to aquatic organisms and potential long-term adverse effects to the aquatic environment.

B.4.2 Proposals for the classification and labelling of preparations (Annex IIIA 12.3 and 12.4) **Formulation "Cymoxanil 50 % WP"**

On the basis of the available data the following classification and labelling is proposed according to Directive 67/548/EEC in combination with Directive 93/21/EEC:

Hazard symbols:		Black St. Andrew's Cross on orange square
		Dead fish, dead tree
Indication of danger:	Xn	Harmful
	N	Dangerous for the environment
Risk phrases:	R22	Harmful if swallowed
	R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed
	R63	Possible risk of harm to the unborn child
	R51/53	Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Safety phrases:	S2	Keep out of the reach of children
	S13	Keep away from food, drink and animal feedingstuffs
	S20/21	When using do not eat, drink or smoke
	S36/37	Wear suitable protective clothing and gloves
	S46	If swallowed, seek medical advice immediately and show this container or label
	S56	Dispose of this material and its container to hazardous or special waste collection point.
	S57	Use appropriate container to avoid environmental contamination.
	S60	This material and its container must be disposed of as hazardous waste.
	S61	Avoid release to the environment. Refer to special instructions/safety data sheets.

Justification for the proposal with respect to health effects:

R22: is proposed because the formulation showed an LD₅₀ of 1200 mg/kg bw in the rat.

Remark: R43 is not justified since a Maximizations test conducted with the preparation indicates no sensitising properties of the formulation "Cymoxanil 50 % WP".

R48/22 and **R63** are necessary because of proposed classification and labelling of the active ingredient cymoxanil (51.5 %).

The safety phrases **S2**, **S13**, **S20/21** and **S46** follow a general precautionary approach. The safety phrases **S36/37** have to be applied caused by R48/22 and R63 together with the risk assessment with respect to operator exposure. In these calculations, a safe use could only be identified if

appropriate personal protective equipment is considered.

Justification for the proposal with respect to environmental effects:

N follows from R51/53

R51/53 follows from the toxicity of the formulation Cymoxanil 50 % WP to algae

(*Pseudokirchneriella subcapitata*: E_rC_{50} (72 h) = 4.72 mg/L, Bogers (1999b)

and from the results of a biodegradation study where it was shown that the active substance is not readily biodegradable (Luit, 2001).

S56, S 57, S60 and S61 follow from the toxicity to aquatic organisms and potential long-term adverse effects to the aquatic environment.

Formulation "TANOS"

On the basis of the available data the following classification and labelling is proposed according to Directive 67/548/EEC in combination with Directive 93/21/EEC:

Hazard symbols:		Black St. Andrew's Cross on orange square
		Dead fish, dead tree
Indication of danger:	Xn	Harmful
	N	Dangerous for the environment
Risk phrases:	R22	Harmful if swallowed
	R43	May cause sensitisation by skin contact
	R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed
	R63	Possible risk of harm to the unborn child
	R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Safety phrases:	S2	Keep out of the reach of children
	S13	Keep away from food, drink and animal feedingstuffs
	S20/21	When using do not eat, drink or smoke
	S24	Avoid contact with skin
	S36/37	Wear suitable protective clothing and gloves
	S46	If swallowed, seek medical advice immediately and show this container or label
	S56	Dispose of this material and its container to hazardous or special waste collection point.
	S57	Use appropriate container to avoid environmental contamination.

Hazard symbols:		Black St. Andrew's Cross on orange square
		Dead fish, dead tree
	S60	This material and its container must be disposed of as hazardous waste.
	S61	Avoid release to the environment. Refer to special instructions/safety data sheets.

Justification for the proposal with respect to health effects:

R22: is proposed because the formulation showed an LD₅₀ of 1732 mg/kg bw in male rats and 566 mg/kg bw in female rats.

R43: With respect to possible skin sensitization properties of "TANOS", only a modified Buehler test showing the formulation to be non-sensitizing has been provided. Since the active substance is judged to be a possible skin sensitizer based on a Maximisation test, such a study would have been more appropriate to investigate the possible skin sensitization of the formulation "TANOS". In conclusion and as a precautionary principle, "TANOS" has to be classified and labelled with respect to its sensitisation by skin contact.

R48/22 and **R63** are necessary because of proposed classification and labelling of the active ingredient cymoxanil (51.5 %).

The safety phrases **S2**, **S13**, **S20/21** and **S46** follow a general precautionary approach. The safety phrase **S24** (Avoid contact with skin) is proposed because of the skin sensitising properties; **S36/37** (Wear suitable protective clothing and gloves) has to be applied caused by R43, R48/22 and R63. According to the second active ingredient (famoxadone), no additional classification and labelling of TANOS is considered necessary.

Justification for the proposal with respect to environmental effects:

N follows from R50/53

R50/53 follows from the toxicity of the formulation Tanos to fish (*Oncorhynchus mykiss*:

LC₅₀ (96 h) = 0.0287 mg/L, Brown, (1997a)), the toxicity to aquatic invertebrates (*Daphnia magna*: EC₅₀ (48 h) = 0.0555 mg/L, Brown (1997b)) and from the results of a biodegradation study where it was shown that the active substance cymoxanil is not readily biodegradable (Luit, 2001).

S56, **S 57**, **S60** and **S61** follow from the toxicity to aquatic organisms and potential long-term adverse effects to the aquatic environment.

B.4.3 References relied on

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Annex II Data and Information					
IIA, 5.2.1	Sarver, J. W.	1992	Acute oral toxicity study with DPX-T3217-113 (Cymoxanil) in male and female rats [REDACTED] [REDACTED] Report No. 63-92 GLP not published	N	DuPont
IIA, 5.2.6	Allan, S. A.	1994	Cymoxanil: skin sensitization in the guinea pig [REDACTED] Report No. OXN 44/940205/SS GLP not published	N	OXON
IIA, 5.3.1	Ramesh, E.	1999a	Cymoxanil technical: 28-day dietary range finding study in rats [REDACTED] Report No. 2140/96 GLP not published	Y	OXON
IIA, 5.3.2	Malek, D., E.	1992	Subchronic oral toxicity: 90-day study with DPX-T3217-107 (cymoxanil) feeding and neurotoxicity study in rats, revision no. 1 [REDACTED] [REDACTED] Report no. HLR 370-91 GLP not published	N	DuPont
IIA, 5.3.2	Teunissen, M. S.	2003	52 week oral dietary toxicity study with cymoxanil technical in male and female Beagle dogs [REDACTED] Report No. [REDACTED] Project 338335 GLP not published	Y	OXON
IIA, 5.3.2	Tompkins, E. C.	1993	Subchronic oral toxicity: 90-day study with DPX-T3217-113 (cymoxanil) feeding study in dogs [REDACTED] Report No. HLO 797-92 GLP not published	N	DuPont

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
IIA, 5.6.2	Feussner, E. L.; Christian, M. S.; Christian, G. D.	1982	Teratogenicity study of INT-3217 in New Zealand white rabbits (segment II evaluation) [REDACTED] Report No. HL 467-82 GLP (Quality assurance unit final report statement available) not published	N	DuPont
IIA, 5.6.2	Murray, S.	1993	Developmental toxicity study of DPX-T3217- 113 (cymoxanil) in rats [REDACTED] [REDACTED] Report No. HLR 744-92 GLP not published	N	DuPont
IIA, 5.6.2	Ponnana, D.	1999	Teratogenicity in rabbits with cymoxanil technical [REDACTED] Report No. 2151/96 GLP not published	Y	OXON
IIA, 5.6.2	Palmer, A. K.; James, P.; Cox, R.; Clark, R.	1981	Effect of H 12712 on pregnancy of the New Zealand white rabbit [REDACTED] [REDACTED] Report No. HLO-805-81 GLP not published	N	DuPont
IIA, 5.6.2	Veena, A. S.	1998	Teratogenicity in Wistar rats with cymoxanil technical [REDACTED] Report No. 2150/96 GLP not published	Y	OXON

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
IIA, 8.2.6	Bell, G.; Thirkettle, K.M.; Smith, B.	1996	Cymoxanil technical algal growth inhibition Huntingdon Life Sciences, Ltd OXN 107A(a)/950955 GLP not published	N	Oxon
IIA, 8.2.6	Hughes, J.S., Williams, T.L., Conder, L.A.	1996a	DPX-T3217-113 (cymoxanil): Influence on growth and reproduction of <i>Anabaena flos- aquae</i> Carolina Ecotox, Inc. AMR 4109-96 GLP not published	N	DuPont
IIA, 7.2.1.3	Luit, R. J.	2001	Determination of Ready Biodegradability: Carbon Dioxide (CO ₂) Evolution Test (Modified Sturm Test) with Cymoxanil Technical NOTOX B.V., 's-Hertogenbosch, The Netherlands 308778 GLP Not published	Y	Oxon
Annex III Data and Information					
CYMOXANIL 50 % WP					
IIIA, 7.1.1	McRea, L., A.	1995a	Cymoxanil 50 % WP: Acute oral toxicity study to the rat [REDACTED] [REDACTED] Report no. OXN 113a/950083/AC GLP not published	Y	OXON
IIIA 10.2.1	Bogers M.	1999b	Fresh water algal growth inhibition test with Cymoxanil 50 % WP NOTOX B.V., The Netherlands, Report 262441 GLP not published	Y	Oxon
TANOS (DPX-KP481-25 50WG)					
IIIA, 7.1.1	Finlay, C.	1997a	Acute oral toxicity study with DPX-KP481-25 50WG in male and female rats [REDACTED] [REDACTED] [REDACTED] Report no. HLR 1048-96 GLP not published	N	DuPont

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
IIIA, 7.1.6	Moore, G., E.	1996	Guinea pig dermal sensitization – modified Buehler method with DPX-KP481-25 50WG [REDACTED] Report no. HLO 628-96 GLP not published	N	DuPont
IIIA, 10.2.1	Brown, M.R.	1997a	DPX-KP481-25 50WG: Flow-through, acute, 96-hour LC ₅₀ to rainbow trout, <i>Oncorhynchus mykiss</i> [REDACTED] HL-1997-00440 GLP not published	N	DuPont
Brown, M.R.	IIIA, 10.2.1	1997b	DPX-KP481-25 50WG: Flow-through, acute, 48-hour EC50 to <i>Daphnia magna</i> DuPont Haskell Laboratory HL-1997-00437 GLP not published	N	DuPont

Annex B

Cymoxanil

B.5 Methods of analysis

WARNING: This document forms part of an EC evaluation data package and should not be read in isolation. No registration must not be granted on the basis of this document.

B.5 METHOD OF ANALYSIS

B.5.1 Analytical methods for technical active substance and formulation analysis (Annex IIA 4.1, Annex IIIA 5.1)

B.5.1.1 Methods for the analysis of pure active substance in the active substance as manufactured (Annex II 4.1.1 and 4.1.3)

Applicant A (DuPont):

References:

E.I. du Pont (1995). Method No. T3217.220.01.ES, Revision No.1. Determination of Cymoxanil in technical Cymoxanil. Reversed-phase liquid chromatographic (RPLC) assay method.

Guidelines: Not applicable

GLP: No.

Validity: The method is acceptable.

Principle of the method:

The method for assay of Cymoxanil involves dissolution by ultrasonication of Cymoxanil in a solution of acidified acetonitrile containing acetophenone. Analysis is performed by reversed-phase liquid chromatography and ultraviolet detection of the analyte at 240 nm. The column is a Zorbax® RX-C₈ with a mobile phase of 80% acetonitrile: 20% water at pH 2.8. The weight percentage of Cymoxanil in each sample is determined by comparing peak area ratios of Cymoxanil with a calibration curve of standard solutions using an internal standard method.

Findings:

The results of method validation for the active substance Cymoxanil are summarized in table B.5.1.1.-1.

Specificity:

Specificity of the method was shown by chromatograms, in which the retention time of technical Cymoxanil match with the reference standard. All known impurities are separated from the internal standard and from the active substance.

Linearity:

The linearity of the method was determined using three standard concentrations in duplicate, ranging from 25% below and 25% above the nominal assay level of 2.5 mg.mL⁻¹. The correlation coefficient is greater than 0.99, demonstrating the linearity of the method.

Repeatability:

Precision of the method was determined by measuring eight replicates within one lab on one day. Additional the reproducibility was shown by assaying replicate samples in two different labs.

Accuracy:

Accuracy was demonstrated by measuring the Cymoxanil content of representative samples of an analytical standard (DPX-3217-101, purity 99.9%) and calculation of the average percent recovery.

Table B.5.1.1.-1. Method validation data for technical Cymoxanil (lot DPX-T3217-142)

Active substance (HPLC)	Linearity (3 levels in duplicate)			Precision			Accuracy ^{#)}	Specificity
	mg/mL	Working conc. (%)	Corr. Coef-ficient	Repeat-ability	Reproducibility			
					Lab1	Lab2		
---	1.85-3.15	75 - 125	0.9997	98.33%	98.33%	98.43%	100.1%	No inter-ferences shown by chromatograms
n		6		8	8	5	4	
SD		-		0.35	0.35	0.19	0.12	
RSD		-		0.36%	0.36%	0.19%	0.12%	

^{#)} Analytical standard lot DPX-T3217-101

Conclusion:

The submitted method is acceptably validated and allows the determination of Cymoxanil in the technical material.

Applicability of existing CIPAC methods:

The CIPAC method 419/TC/M/3 can be used for determination of the active substance in technical Cymoxanil.

Applicant B (Oxon):

References:

Fraschini C. (1997). Cymoxanil techn. Analytical Profile of Oxon Production. Final study, Sipcam report No. 004/97

Guidelines: Not applicable

GLP: Yes.

Validity: The method is acceptable.

Freschi G. (2003). Cymoxanil techn. Analytical Profile of Oxon Production. Final study, Sipcam report No. 001/2003

Guidelines: Not applicable

GLP: Yes.

Validity: The method is acceptable.

Freschi G. (2001), Cymoxanil 50 WP, Shelf life at ambient temperature. Sipcam Report 005/99

Guidelines: Not applicable

GLP: Yes.

Validity: The study is acceptable.

Two studies of analytical methods for analysis of technical Cymoxanil are available by the applicant. A former study carried out by Frascini in 1997 (Sipcam report 004/97) by using technical material obtained from pilot plant and a more recent study performed by Freschi in 2003 with industrial scale lot of technical Cymoxanil (Sipcam report 001/2003). Basically the two studies use the same methodology for the determination of the pure active substance.

Principle of the method:

A HPLC method is used for quantitative analysis of technical Cymoxanil. A reversed phase column (RP₁₈, 200 x 4 mm, 5µm, Merck) is applied for the separation using a mobile phase consisting of 50% acetonitrile and 50% water. In the case of analysing technical Cymoxanil from industrial scale a C18 column (LiChrospher, 100 RP-18, 250 x 4 mm, 5µm, Merck) is used. The detection of the analyte is performed at 254 nm in both methods. Quantification of technical Cymoxanil in each sample is determined by comparing peak area of Cymoxanil with a calibration curve generated from the analysis of external standard solutions.

Findings: The results of method validation for the active substance Cymoxanil are summarized in table B.5.1.1.-2.

Specificity:

The specificity of the HPLC method for the determination of Cymoxanil was tested by comparison of analytical standards and retention times of active ingredient. No interferences were observed between retention time of active ingredient and analytical standards, demonstrating the specificity of the applied method.

Linearity:

Linearity was determined on a calibration curve using three Cymoxanil concentrations in the range between 49 and 149 mg/L which were analysed by duplicate injections. The correlation coefficient was >0.9999.

Precision:

The precision was determined by analysing two separate standard solutions containing 100 mg/L Cymoxanil. Relative standard deviation was calculated to be 0.39% for these standard solutions. Precision in the industrial scale study was determined by analysing five independently prepared standard solutions. Relative standard deviation was calculated to be 0.17%.

Accuracy:

Accuracy from the shelf life study (Sipcam report 005/99) was taken to show the accuracy of the method. In this study the accuracy was determined by analyzing four sample solutions of

a placebo-mixture containing 100 mg/L Cymoxanil. The recovery and relative standard deviation were shown to be 100.03 % and 0.12% RSD, respectively. Accuracy in the industrial scale study was determined by spiking a portion of sample solution using known amounts of reference standard. Four samples were analysed and the mean recovery (100.34%) and relative standard deviation (0.15%) was calculated.

Table B.5.1.1-2. Results of method validation of technical Cymoxanil

Active substance/ (Method)	Specificity	mg/L	Linearity		Precision		Accuracy		Reference
			Working conc. (%)	Corr. Coeff.	RSD (%)	n	Recovery (%)	RSD (%) (n)	
Cymoxanil (pilot plant) /HPLC	No interferences shown by chromatograms	49-149	50 - 150	1.0	0.39	13	100.03	0.12, (4)	Fraschini C. (1997), Sipcam report 004/97, Freschi G. (2001), Sipcam Report 005/99
Cymoxanil (industrial scale) /HPLC	No interferences shown by chromatograms	49.6-148.9	50-150	≥0.999	0.17	5	100.34	0.15, (4)	Freschi G. (2003), Sipcam report 001/2003
Cymoxanil (industrial scale) /CIPAC method 419/TC/M/3	No interferences shown by chromatograms	453.6-753.4	---	≥0.999	0.33	5	No data	No data	

Conclusion:

The submitted methods are acceptably validated and allow the determination of Cymoxanil in the technical material.

Applicability of existing CIPAC methods:

In addition, the CIPAC method 419/TC/M/3 is available for determination of the active substance in technical Cymoxanil. The published CIPAC method has been shown to be applicable for the determination of Cymoxanil (Freschi, G. 2003, Sipcam report 001/2003). Results from specificity, linearity and precision of the CIPAC method are shown in table B.5.1.1-2. A Student's t-test was applied to compare the precision results between the internal method from Oxon and the CIPAC method. The t- test revealed no significant differences in precision results obtained from both methods ($t = 0.564$, $\alpha = 0.05$, $n = 5$). The

obtained t-value is lower than t_{critical} with 2.776.

B.5.1.2 Methods for the determination of significant and/or relevant impurities and additives (e.g. stabiliser) in the active substance as manufactured (Annex IIA 4.1.2 and 4.1.3)

This confidential information is provided in Volume C (Annex 4) for both applicants.

B.5.1.3 Analytical methods for the determination of the active substance in plant protection products (Annex IIIA 5.1.1 and 5.1.3)

Applicant A (DuPont):

References:

Flament, C. (1999a). Validation of the analytical method to verify the certified limits of Cymoxanil (DPX-T3217) and Famoxadone (DPX-JE874) in: DuPont water-dispersible granular formulation DPX-KX007, containing 300 g/kg Cymoxanil and 225 g/kg Famoxadone; DuPont suspension concentration formulation DPX-KX007, containing 240 g/L Cymoxanil and 180 g/L Famoxadone; DuPont water-dispersible granular formulation DPX-KP481, containing 250 g/kg Cymoxanil and 250 g/kg Famoxadone, Method 2. DuPont Report No.1916

Guidelines: EPA, OPPTS 830.1800, EEC 91/414/ Annex III, 5.1

GLP: Yes

Validity: The method is acceptable.

Flament, C. (1999b); Validation of the analytical method to verify the certified limits of Cymoxanil (DPX-T3217) and famoxadone (DPX-JE874) in: DuPont water-dispersible granular formulation DPX-KX007, containing 300 g/kg Cymoxanil and 225 g/kg Famoxadone; DuPont suspension concentration formulation DPX-KX007, containing 240 g/L Cymoxanil and 180 g/L Famoxadone; DuPont water-dispersible granular formulation DPX-KP481, containing 250 g/kg Cymoxanil and 250 g/kg Famoxadone. DuPont Report No. 1659

Guidelines: EPA, OPPTS 830.1800, EEC 91/414/ Annex III, 5.1

GLP: Yes

Validity: The method is acceptable.

Vindevoghel, C. (1999). Validation of the analytical method to verify the certified limits of Cymoxanil (DPX-T3217) and Famoxadone (DPX-JE874) in: DuPont water-dispersible granular formulation DPX-KX007, containing 300 g/kg Cymoxanil and 225 g/kg Famoxadone; DuPont suspension concentration formulation DPX-KX007, containing 240 g/L Cymoxanil and 180 g/L Famoxadone; DuPont water-dispersible granular formulation DPX-KP481, containing 250 g/kg Cymoxanil and 250 g/kg Famoxadone, Method 3. DuPont Report No. 2731

Guidelines: EPA, OPPTS 830.1800, EEC 91/414/ Annex III, 5.1

GLP: Yes

Validity: The method is acceptable.

The applicant submitted four validated methods for determination of Cymoxanil in the plant protection product (3 RP-HPLC and 1 normal-phase-HPLC method). Since the normal-phase HPLC method was substituted by the RP-HPLC methods, only data from the RP-HPLC were used in the evaluation of the method validation. Basically all three RP-HPLC methods are using the same methodology. Minor modifications in the methods were made regarding the sample and solvent preparation (in method NAMB 95/02) and in the time schedule of the elution gradient (in method KP 481.220.01.NB).

Principle of the method:

The method for the assay of Cymoxanil and Famoxadone in manufactured preparation DPX-KP481 50WG involves dissolution by ultrasonification of the preparation in acetonitrile and water. A known amount of diphenylsulfone internal standard was added to each standard or sample. Analysis was done by reversed-phase liquid chromatography (RPLC) with a Zorbax® XDB-C8 column (250mm x 4.65 mm, 5µm) and a mobile phase consisting of acetonitrile and water adjusted to pH 2.8 with diluted phosphoric acid using a linear gradient. Cymoxanil, Famoxadone, and Diphenylsulfone were quantitated by ultraviolet absorbance detection at 230 nm. The weight percent of Cymoxanil and Famoxadone in each sample was determined by comparing the peak area ratios of Cymoxanil/Diphenylsulfone and Famoxadone/Diphenylsulfone with standard calibration curves.

Findings: The results of method validation for Cymoxanil in the plant protection product are summarized in table B.5.3.1.-1.

Specificity:

The methods were validated for interferences from manufacturing impurities and formulation inerts. None of the known impurities expected to be present in Cymoxanil and Famoxadone technical grade or formulation inerts coelute with Cymoxanil or Famoxadone or the internal standard. No interferences more than 3% to the total quantity determined are observed, therefore the criteria for specificity were met.

Linearity:

The correlation coefficients for three different concentrations analysed in duplicate of

Cymoxanil were ranging between >0.99 and 1.0 for all three studies, demonstrating the linearity of the applied methods.

Precision (Repeatability):

Precision of the assay method was determined by calculating the standard deviation of the average percent Cymoxanil obtained from the analysis by one analyst on one day using five replicates of the sample DPX-KP481 50WG. Each sample was injected in duplicate. The relative standard deviation for precision was ranging between 0.2 and 0.7% for Cymoxanil in all three studies. The maximum allowable relative standard deviation from the modified Horwitz equation was calculated for all three studies and the measured RSD fulfilled the acceptance criteria for repeatability. In addition, no outliers were observed during testing.

Accuracy:

Accuracy of the methods for analysis of DPX-KP481 50WG was performed by spiking placebo solutions with Cymoxanil and famoxadone to simulate a DPX-KP481 50WG formulation. Average percent recovery for Cymoxanil, using four spike levels, was ranging between 99.8% and 100.9% with a relative standard deviation of 0.06% to 1.23% . The accuracy of all methods met the acceptance criteria for formulations with active ingredient above 10% of 98 to 102% mean recovery.

Conclusion:

All three analytical methods are validated sufficiently and met the acceptance criteria for specificity, linearity, precision and accuracy. The methods are acceptable for the determination of Cymoxanil in the plant protection product.

Applicability of existing CIPAC methods:

In addition, the CIPAC method 419/WG/M/3 is available for the determination of Cymoxanil active substance in Cymoxanil water-dispersible granules.

Table B.5.3.1-1. Results of method validation of technical Cymoxanil in the plant protection product

Active substance (Method No.)	Specificity/ interferences	Linearity (3 levels in duplicate)		Accuracy (n=4)		Precision		n	Reference
		Conc. (mg/mL)	Corr. Coeff.	Fortification level (mg added)	Mean recovery (%)	RSD (%)	RSD (%)		
Cymoxanil (T3217.22 0.05 NNB, Method 2)	Demonstrated, no interferences	0.30-0.51	0.9999 3	31.35-39.44	100.9	1.23	0.69 (0.8)*	5	Flament, C. (1999a). DuPont Report No. 1916
Cymoxanil (NAMB 95/02, modified)	Demonstrated, no interferences	0.14-0.42	1.0	25.84-29.13	100	0.26	0.32 (1.6)*	5	Flament, C. (1999b). DuPont Report No. 1659
Cymoxanil (KP481.22 0.01. NB, Method 3)	Demonstrated, no interferences	0.30-0.50	0.9999 9	32.22-38.85	99.8	0.06	0.22 (1.6)*	5	Vindevoghel, C. (1999). DuPont Report No. 2731

* calculated RSD by Horwitz equation

WARNING: This document forms part of an EC evaluation data package and should not be used in isolation. Registration must not be granted on the basis of this document.

Applicant B (Oxon):

References:

Freschi G. (2001). Cymoxanil 50 WP, Shelf life at ambient temperature. Sipcam Report 005/99

Guidelines: none

GLP: Yes.

Validity: The study is acceptable.

Principle of the method:

A HPLC method is used for quantitative analysis of technical Cymoxanil in the formulated product. A reversed phase column (Lichrospher 100-RP₁₈, 250 x 4 mm, 5µm, Merck) is applied for the separation using a mobile phase consisting of 50% acetonitrile and 50% water under isocratic conditions. The flowrate is 1 mL.min⁻¹. The detection of the analyte is performed at 254 nm. Quantification of technical Cymoxanil is determined by comparing peak areas of Cymoxanil with a calibration curve generated from the analysis of external standard solutions.

Findings: The results of method validation for the active substance in the plant protection product are summarized in table B.5.3.1.-2.

Specificity:

The specificity of the HPLC method for the determination of Cymoxanil was tested by comparison of analytical standards and product retention times. No interferences were observed between retention time of product and analytical standards demonstrating the specificity of the applied method.

Linearity:

Linearity was determined based on a calibration curve using three different Cymoxanil concentrations in the range between 50 and 150 mg/L, analysed by duplicate injections. The correlation coefficient was ranging between 0.999994 and 1.0 for all analysed time points in the stability study (0, 6, 12, 18 and 24 months).

Precision:

The precision was determined by analysing five separate solutions in duplicate, containing approx. 200 mg/L sample (approx. 100 mg/L technical Cymoxanil) of the timepoints 12, 18 and 24 months of the stability study. For the time points 0 and 6 months, only two solutions were analysed in triplicates, each containing approx. 200 mg/L of sample. Relative standard deviation was calculated for each time point ranging between 0.14 and 0.28 %.

Accuracy:

The accuracy was determined by analyzing four sample solutions of a placebo-mixture containing approx. 100 mg/L technical Cymoxanil. The recovery and relative standard deviation were shown to be 100.03 % and 0.12% RSD, respectively.

Table B.5.3.1-2. Results of method validation of technical Cymoxanil in the plant protection product

Active substance	Specificity/interferences	Linearity (3 levels in duplicate)		Accuracy (n=4)		Precision		Reference
		Conc. (mg/L)	Corr. Coeff.	Fortification level (mg/L added)	Mean recovery (%)	RSD (%)	RSD (%) n = 42	
Cymoxanil (HPLC)	Demonstrated, no interferences shown by chromatograms	50.15–150.99	0.999994 -1.0	100	100.03	0.12	0.14–0.28	Freschi G. (2001), Report 005/99

+) Data from 0, 6, 12, 18 and 24 months time points

Conclusion:

The analytical method was sufficiently validated and met the acceptance criteria for specificity, linearity, precision and accuracy. The method is acceptable for the determination of Cymoxanil in the plant protection preparation.

Applicability of existing CIPAC methods:

The notifier stated that CIPAC method 419/WP/M/3 is considered to be applicable to a Cymoxanil 50 % WP preparation. This method has not been specifically proved for its applicability to Cymoxanil 50 WP formulation. Nevertheless considering that CIPAC method for the active ingredient in technical material was proved to be applicable to Cymoxanil technical material and that this methodology does not substantially differ from CIPAC method for WP formulation it can be reasonably assumed that CIPAC method for WP products is also applicable to Cymoxanil 50 % WP preparation.

B.5.1.4 Analytical methods for the determination of relevant impurities and formulants in plant protection products (Annex IIIA 5.1.2 and 5.1.3)

No relevant impurities are formed in both representative plant protection products, neither from the formulation process nor from storage.

B.5.2 Analytical methods (residue) for plants, plant products, foodstuffs of plant and animal origin, feedingstuffs (Annex IIA 4.2.1; Annex IIIA 5.2.1)

B.5.2.1 Plant material

Reference: Kretschmer, S., Class, T. (1999); Method assessment and validation of an analytical multi-residue enforcement method (DFG S19 modified) for the determination of residues of Cymoxanil in plant material (grape, potato, tomato, hops cones, post-cured tobacco). DuPont Report No.: DuPont-2158

Guidelines: EEC Directive 91/414/EEC.

GLP: Yes

Validity: The method is considered acceptable.

Principle of the method:

Cymoxanil is extracted from homogenized samples with water/acetone (1/2, v/v). Addition of NaCl and ethyl-acetate/cyclohexane (1/1, v/v) results in a phase separation and partition of Cymoxanil into the organic phase. The extract is concentrated and subjected to gel permeation chromatography (GPC). The GPC eluate is concentrated and fractionated on silica gel (SiO₂, 1.5 % water). Cymoxanil elutes mainly with toluene/acetone (80/20, v/v, fraction F4) and is determined by capillary gas chromatography and nitrogen phosphorus detection using non-polar (DB-1, 15 m, 0.32 mm i. d., 0.25 µm and DB-5, 15 m, 0.32 mm i. d., 0.25 µm) or medium-polar (BPX-35, 10 m, 0.32 mm i.d., 0.25 µm, for confirmatory analysis) stationary phases. Validation data for the representative use (potato) and additional matrices from plant materials are summarized in table B.5.2.1.-1.

Findings:

Specificity: Specificity was demonstrated by analysis of standards, blank controls and fortified samples for each crop. No background interferences were observed in gas chromatographic detection that affected the quantitative results for limit of quantification (LOQ) or 10 x LOQ fortifications for all crops. DB-1 and DB-5 capillary columns gave good data for recoveries of fortifications from potatoes. Confirmatory analysis was done by injection of samples on a BPX-35 column. Control chromatograms for all crops confirmed the good specificity of the DFG S19 method.

Linearity: Calibration was performed using six to nine different calibration standards of Cymoxanil ranging from 0.010 to 5.0 µg/mL. The detector showed a linear response for all three applied capillary columns. The correlation coefficients were > 0.99, with exception of the DB-5 calibration, which revealed an r^2 of 0.98. The lower and upper fortification levels, including an exceeding of $\pm 20\%$ are covered by the calibration curve.

Accuracy: Recovery data from the DFG S19 validation study are summarised in table B.5.2.1-1. Average fortification recoveries ranged from 77% to 95% using the DB-1 column and met the acceptance criteria of 70% to 110% recovery. For the other tested crops the average recoveries were fulfilled.

Limit of quantification: The LOQ of the method for potatoes is 0.04 mg/kg.

Precision: Relative standard deviations for potatoes on the DB-1 column ranged from 6% to 13%. The other tested crops met the acceptance criteria for precision of less than 20% RSD.

Conclusion:

The method was sufficiently validated in accordance with the SANCO 825/00 guidance document in terms of specificity, linearity, accuracy, precision and the determined LOQ. A confirmatory analysis was performed, demonstrating the specificity of the method. The method is suitable as a multi-residue enforcement method for potatoes with a limit of quantification of 0.04 mg/kg using the non-polar column DB-1. For grapes and tomatoes the LOQ was determined 0.04 mg/kg with acceptable recovery rates using the DB-1 column. If columns with other polarity (e.g. DB-5 and BPX-35) are used, a full method validation using 5 replicates for each fortification level is required.

Independent Laboratory Validation:

Reference: Linkerhägner, M. (1999): Independent Laboratory Validation (ILV) of a multi-residue Enforcement Method (DFG S 19 modified) for the determination of Cymoxanil in dry, high water and oily crops. DuPont Report No. 2946.

Guideline: EU Directive 91/414, Annex II 4.2.5, EPA Pesticides Assessment Guidelines, Subdivision 0, 171-4 (d). German Federal Biological Research Center for Agriculture and Forestry. Residue Analytical methods for Post- Registration Control Purposes. R. Hänel and J. Siebers, July 21, 1998

GLP: Yes

Validity: The method is considered acceptable.

Principle of the method:

Minor modifications to the validated method (Kretschmer 1999, DuPont Report No. 2158) were made. A hot splitless injection at 200°C was used instead of a cold injection system to improve the variability of the NPD response. Two non-polar columns were used (DB-1 and DB-5, J&W, 15 m fused silica capillary columns, 0.32 mm i.d., 0.25 µm film thickness). The GC-NPD method was confirmed by GC-MSD using the same capillary columns and two ions traces (m/z: 167, 111) to verify the peak identity of Cymoxanil.

Findings: The validation data of the ILV is summarized in table B.5.2.1-1.

Specificity: Specificity was demonstrated by analysis of standards, blank controls and fortified samples for each crop. No background interferences were observed in gas chromatographic detection that affected the quantitative results for limit of quantification (LOQ) or 10x LOQ fortifications for all crops. No interference peak at or above the quantification limit was observed at the retention time of Cymoxanil in the control samples.

Confirmatory method:

Confirmation of the presence of Cymoxanil was tested by GC/MSD. For confirmation

analysis, one control and one fortified sample of each fortification level was analyzed for each sample matrix. Examples of GC/MSD chromatograms were presented with blank controls and LOD/LOQ estimation based on the signal to noise ratios.

Linearity: Calibration was performed using nine different calibration standards of Cymoxanil ranging from 0.027 to 4.01 µg/mL. The detector showed a linear response and the correlation coefficient was > 0.99. The calibration curve covers the demanded ±20% of the upper and lower limits of the fortification level.

Accuracy: Recovery data generated in the ILV are summarised in table B.5.2.1-1. Average fortification recoveries for potatoes in the ILV ranged from 85 to 89% and met the acceptance criteria of 70 to 110% recovery. Average recoveries for all other tested crops were fulfilled, with exception of hops in the confirmatory analysis.

Limit of quantification: The LOQ of the method for potatoes, grapes and tomatoes is 0.04 mg/kg. For tobacco a LOQ of 0.1 mg/kg was determined. In the confirmatory analysis by GC-MSD for hops a LOQ of 0.33 mg/kg was determined.

Precision: Relative standard deviations for potatoes ranged from 4.7% to 6.2% and 2.4% to 6.7% for all other tested crops.

Conclusion:

The ILV was sufficiently validated in accordance with the SANCO 825/00 guidance document, considering the specificity, linearity, accuracy, precision and the LOQ of the method. A confirmatory GC-MSD method was used to demonstrate the specificity of the applied method.

Residues of Cymoxanil in lettuce (plants):

Reference: Freschi G. (2001a): Validation of analytical method for the determination of residues of Cymoxanil in Lettuce (Plant). Oxon Report SIP1279.

Guideline: Cymoxanil, Method 513, DFG manual of Pesticide Residues Analysis, Volume II

GLP: Yes

Validity: The method considered acceptable.

Oxon reply to RMS data requirements (05.April 2006).

Principle of the method:

The method is based on the published multi-residue method DFG 513. Cymoxanil is extracted from lettuce by blending with ethyl acetate. The extract is washed with hexane, which is discarded and then partitioned into dichloromethane. The extract is further purified using a silica gel column. Determination is accomplished by capillary gas chromatography with a DB-5 column (30m x 0.53 mm i.d., 1.5 µm film thickness, J&W) and a nitrogen phosphorus detector.

Findings: The validation data are summarized in table B.5.2.1-1.

Specificity: Specificity was demonstrated by analysis of standards, blank controls and fortified samples of lettuce. No background interferences were observed during gas chromatographic analysis. No interference peak was observed at the retention time of Cymoxanil in the untreated control sample.

Linearity: Calibration was performed using three different calibration standards of Cymoxanil ranging from 0.5 to 2.5 µg/mL in triplicate analysis. The detector showed a linear response and the correlation coefficient was 0.996. The calibration curve covers the demanded $\pm 20\%$ of the upper and lower limits of the fortification levels, as shown by recalculation of the applicant.

Accuracy: Recovery data of accuracy for lettuce are summarised in table B.5.2.1-1. Average fortification are ranging from 96.7% to 101.4% for the fortification level 0.05 mg/kg and 0.5 mg/kg, respectively. The acceptance criteria of 70 to 110% recovery were met.

Limit of quantification: The LOQ of the method is reported with 0.05 mg/kg for lettuce.

Precision: Relative standard deviation for lettuce was ranging between 5.3% and 7.6% using five replicates for each fortification level. This shows acceptable precision since all values are less than 20%.

Conclusion:

The method is sufficiently validated in accordance to the SANCO 825/00 guidance document, considering the specificity, linearity, accuracy, precision and the determined LOQ of the method.

Residues of Cymoxanil in potatoes (tuber):

Reference: Freschi G. (2001b): Validation of analytical method for the determination of residues of Cymoxanil in Potatoes (Tuber). Oxon Report SIP 1277.

Guideline: Cymoxanil, Method 513, DFG manual of Pesticide Residues Analysis, Volume II

GLP: Yes

Validity: The method considered acceptable.

Principle of the method:

The method is based on the published multi-residue method DFG 513. Cymoxanil is extracted from potatoes by blending with ethyl acetate. The extract is washed with hexane, which is discarded and then partitioned into dichloromethane. The extract is purified using a silica gel column. Determination is accomplished by capillary gas chromatography with a DB-5 column (30m x 0.53 mm i.d., 1.5 µm film thickness, J&W) and a nitrogen phosphorus detector.

Findings: The validation data are summarized in table B.5.2.1-1.

Specificity: Specificity was demonstrated by analysis of standards, blank control samples and fortified samples of potatoes. No background interferences were observed in gas chromatographic analysis. No interference peak was observed at the retention time of

Cymoxanil in the untreated control sample.

Linearity: Calibration was performed using three different calibration standards of Cymoxanil ranging from 0.55-2.75 µg/mL in triplicates. The detector showed a linear response and the correlation coefficient was 0.996. The calibration curve covers the demanded $\pm 20\%$ of the upper and lower limits of the fortification levels, as shown by re-calculation of the applicant.

Accuracy: Recovery data of accuracy for potatoes are summarised in table 5.2.1-1. Average fortification recoveries are ranging from 99.8% to 101.1% for the fortification level 0.05 mg/kg and 0.5 mg/kg, respectively. The acceptance criteria of 70 to 110% recovery were met.

Limit of quantification: The LOQ of the method is reported with 0.05 mg/kg for potatoes.

Precision: Relative standard deviations for potatoes were ranging between 4.5% and 5.0% using five replicates for each fortification level. The data shows acceptable precision since all values are less than 20%.

Conclusion:

The method is sufficiently validated in accordance with the SANCO 825/00 guidance document, considering the specificity, linearity, accuracy, precision and the determined LOQ of the method.

Residues of Cymoxanil in tomatoes, grapes, potatoes and lettuce:

Reference: Wasser, C. (2002). Validation of analytical method for determination of residues of Cymoxanil in specimens of tomato, grapes, potatoes and lettuce. Oxon report No. A0087. Guidelines: Cymoxanil, Method 513, DFG manual of Pesticide Residues Analysis.

GLP: Yes

Validity: The method is considered acceptable.

Principle of the method:

Cymoxanil residues are extracted from crop samples with ethyl acetate. The aqueous extract is initially washed with hexane. The aqueous solution is then extracted with dichloromethane. The dichloromethane phase is evaporated by a rotavapor and the residues are dissolved in ethyl acetate. The solution is cleaned up on a silicagel column and subsequently residues of Cymoxanil are determined by gas chromatography using a NPD and a DB-5 capillary column (30 m x 0.53 mm i.d, 1.5 µm film thickness, J&W).

A HPLC method was used as a confirmatory technique within the study. This method uses acetonitrile/water as a mobile phase (20:80, pH 2.8) in an isocratic elution mode. The flow rate is 1.0 mL.min⁻¹ at 40°C on a RP-HPLC column (SB-phenyl column, 4.6 x 250 mm, 5 µm, Zorbax). The detection of Cymoxanil is achieved at 239 nm.

Findings: The validation data are summarized in table B.5.2.1-1.

Specificity: Specificity was checked by analysing controls and control samples spiked with Cymoxanil and comparison of these sample retention times to retention times of standard

solutions. Submitted chromatograms for all tested crops showed that no background interferences were observed within the retention time window of Cymoxanil.

Confirmatory method: Confirmation of the analytical method was performed by analysing the purified sample by RP-HPLC. In the RP-HPLC method retention times of controls and spiked samples were compared to standard solutions. No interferences of the tested samples matrices with retention times of Cymoxanil were detected, demonstrating the specificity of the method.

Linearity: Calibration of the GC method was performed using six different calibration standards of Cymoxanil ranging from 125 to 2500 ng/mL. The detector showed a linear response and the correlation coefficient was > 0.99 . The lower and upper fortification levels are covered by the calibration curve including an exceeding of $\pm 20\%$. The calibration curves of the confirmatory HPLC method was ranging between 100 ng/mL and 2500 ng/mL using 5 different concentrations. The detector showed a linear response and the correlation coefficient was > 0.99 . The lower and upper fortification levels are covered by the calibration curve including an exceeding of $\pm 20\%$.

Accuracy: For all tested crops the accuracy for both methods met the acceptance criteria of 70 to 110% recovery. Results are summarized in table B.5.2.1-1. Average fortification recoveries for the GC method ranged from 76% to 106% using the DB-5 column. The confirmatory HPLC method showed a recovery from 75% to 106% for all tested crops.

Limit of quantification: The LOQ's of both methods were 0.05 mg/kg for all tested crops.

Precision: Relative standard deviations for the GC-NPD method using the DB-5 column ranged from 3.6 to 10.9% for all tested crops. The RP-HPLC method revealed a RSD of 4.4% to 16.9 % for all tested crops.

Conclusion:

The method is sufficiently validated in accordance with the SANCO 825/00 guidance document, considering the specificity, linearity, accuracy, precision and the obtained LOQ. A confirmatory analysis was performed, demonstrating the specificity of the method.

Applicability of multi-residue methods:

Residues of Cymoxanil on lettuce specimens:

Reference: Freschi G. (2003a): Applicability and validation of a multiresidues analytical method on lettuce specimens (Plant). Oxon Report UAR/001/2003

Guideline: Workbook of multiresidue methods for pesticides residues analysis in vegetable products. ISTISAN Report 97/23, 1st edition.

GLP: No

Validity: The method is acceptable.

Principle of the method:

The analytical method involves initial extraction of Cymoxanil from homogenized (20 g) crop samples mixed with 20 g extrelut. The mixture was added onto a glass extraction column and extracted using ethyl-acetate at a flow rate of $5 \text{ mL} \cdot \text{min}^{-1}$. The eluate was evaporated to

dryness using a vacuum rotary evaporator, dissolved in methanol and analysed using GC-NPD with a non-polar stationary phase (HB-5 fused silica, 30 m, 0.32 mm i.d., 0.25 µm film thickness).

Findings: The validation data are summarized in table B.5.2.1-1.

Specificity: Specificity was demonstrated by analysis of standards, blank controls and fortified samples of lettuce. No background interferences were observed in gas chromatographic analysis. No interference peak was observed at the retention time of Cymoxanil in the untreated control sample.

Linearity: Calibration was performed using three different calibration standards of Cymoxanil ranging from 0.5, 1.0 and 5.0 mg/L in triplicate analysis. The detector showed a linear response and the correlation coefficient was 0.999. The calibration curve covers the demanded $\pm 20\%$ of the upper and lower limits of the fortification levels, as shown by re-calculation of the applicant.

Accuracy: Recovery data of accuracy for lettuce are summarised in table B.5.2.1-1. Average fortification recoveries are ranging from 84.8% to 86.2% for the fortification level 0.05 mg/kg and 1.0 mg/kg, respectively. The acceptance criteria of 70 to 110% recovery were met.

Limit of quantification: The LOQ of the method is reported with 0.05 mg/kg for lettuce.

Precision: Relative standard deviations for lettuce were ranging between 15.9 % and 19.4% for both fortification levels.

Conclusion:

No confirmatory analysis and ILV was performed. However, the applicant stated that this report is not proposed to support generation of residue data but to demonstrate the applicability of one among the many existing multiresidue methods as suggested by Directive 94/46/EC, Point IIA, 4.2. In the absence of a list of the officially recognised worldwide valid multiresidue techniques it was decided to check suitability of the methods suggested by Italian authority (ISS) for post-registration monitoring purposes. Considering this statement the validation is acceptable.

Residues of Cymoxanil on potato specimens:

Reference: Freschi G. (2003b): Applicability and validation of a multiresidues analytical method on potato specimens (tuber). Oxon Report UAR/002/2003

Guideline: Workbook of multiresidue methods for pesticides residues analysis in vegetable products. ISTISAN Report 97/23, 1st edition.

GLP: No

Validity: The method is acceptable

Principle of the method:

The analytical method involves initial extraction of Cymoxanil from homogenized (20 g) crop samples mixed with 20 g extrelut. The mixture was added onto a glass extraction column and

extracted using ethyl-acetate at a flow rate of 5mL.min⁻¹. The eluate was evaporated to dryness using a vacuum rotary evaporator, dissolved in methanol and analysed using GC-NPD with a non-polar stationary phase (HB-5 fused silica, 30 m, 0.32 mm i.d., 0.25 µm film thickness).

Findings: The validation data are summarized in table B.5.2.1-1.

Specificity: Specificity was demonstrated by analysis of standards, blank controls and fortified samples of lettuce. No background interferences were observed in gas chromatographic analysis. No interference peak was observed at the retention time of Cymoxanil in the untreated control sample.

Linearity: Calibration was performed using three different calibration standards of Cymoxanil ranging from 0.5, 1.0 and 5.0 mg/L in triplicate analysis. The detector showed a linear response and the correlation coefficient was 0.999.

Accuracy: Recovery data of accuracy for lettuce are summarised in table B.5.2.1-1. Average fortification recoveries are ranging from 87.8% to 96.4% for the fortification level 0.05 mg/kg and 1.0 mg/kg, respectively. The acceptance criteria of 70 to 110% recovery were met.

Limit of quantification: The LOQ of the method is reported with 0.05 mg/kg for potatoes.

Precision: Relative standard deviations for lettuce were ranging between 8.8 % and 19.8% for both fortification levels.

Conclusion:

The method was validated, but not performed under GLP conditions. No confirmatory analysis and ILV was performed. However, the applicant stated that this report is not proposed to support generation of residue data but to demonstrate the applicability of one among the many existing multiresidue methods as suggested by Directive 94/46/EC, Point IIA, 4.2. In the absence of a list of the officially recognised worldwide valid multiresidue techniques it was decided to check suitability of the methods suggested by Italian authority (ISS) for post-registration monitoring purposes. Considering this statement the validation is acceptable.

B.5.2.2 Analytical methods (residue) for food of animal origin

No residue definition is established for food of animal origin, therefore no analytical method is required.

Table B.5.2.1-1. Validation data for analytical methods for the determination of residues of Cymoxanil in food of plants

References	Matrix	Determined analyte	Method (column)	LOQ [mg/kg]	Fortification [mg/kg]	Range [%]	Average recovery [%]	RSD [%]	n
Kretschmer and Class, 1999	Potatoe	Cymoxanil	GC-NPD (DB-1)	0.04	0.04	61-86	77	13	5
			GC-NPD (DB-5)		0.40	88-102	95	6	5
			GC-NPD (BPX-35)		0.04	87-88	88	4*	2
			GC-NPD (BPX-35)		0.40	86-94	90		2
	Grape	Cymoxanil	GC-NPD (DB-1)	0.04	0.04	80-100	90	10*	2
			GC-NPD (DB-5)		0.40	84-92	88		2
			GC-NPD (BPX-35)		0.04	86-91	88	2	5
			GC-NPD (BPX-35)		0.40	77-97	88	10	5
			GC-NPD (DB-5)		0.04	89-91	90	7*	2
			GC-NPD (BPX-35)		0.40	101-103	102		2
	Tomatoe	Cymoxanil	GC-NPD (DB-1)	0.04	0.04	95-102	99	5*	2
			GC-NPD (DB-5)		0.40	105-106	105		2
			GC-NPD (BPX-35)		0.04	90-101	95	4	5
			GC-NPD (BPX-35)		0.40	100-102	101	1	5
	Hops	Cymoxanil	GC-NPD (DB-1)	0.1	0.04	75-89	82	11*	2
			GC-NPD (DB-5)		0.40	94-94	94		2
			GC-NPD (BPX-35)		0.04	75-93	84	10*	2
			GC-NPD (BPX-35)		0.40	92-94	93		2
			GC-NPD (DB-1)		0.10	67-86	79	11	5
			GC-NPD (DB-5)		1.0	68-93	82	11	5
	Tobacco (Kentucky)	Cymoxanil	GC-NPD (BPX-35)	0.1	0.10	101-102	102	5*	2
			GC-NPD (BPX-35)		1.0	91-95	97		2
			GC-NPD (BPX-35)		0.10	69-73	71	19*	2
			GC-NPD (BPX-35)		1.0	90-106	98		2

References	Matrix	Determined analyte	Method (column)	LOQ [mg/kg]	Fortification [mg/kg]	Range [%]	Average recovery [%]	RSD [%]	n
Linkerhäger, 1999	Tobacco (Virginia/ Adonis)	Cymoxanil	GC-NPD (DB-5)	0.10	0.10	81-117	102	13	5
			GC-NPD (BPX-35)		1.0	82-91	86	4	5
			GC-NPD (DB-1)	Not analysed	0.10	76-117	104	16	5
			GC-NPD (BPX-35)		1.0	75-87	79	6	5
			GC-NPD (DB-5)	0.1	0.10	100-107	103	6*	2
			GC-NPD (BPX-35)		1.0	106-116	111		2
	Tobacco (Virginia/ Golta)	Cymoxanil	GC-NPD (DB-1)	Not analysed	0.10	80-107	93	12*	2
			GC-NPD (BPX-35)		1.0	92-101	96		2
			GC-NPD (DB-5)	0.1	0.10	99-105	102	6*	2
			GC-NPD (BPX-35)		1.0	91-98	94		2
			GC-NPD (DB-1)	0.04	0.10	74-83	79	8*	2
			GC-NPD (BPX-35)		1.0	75-87	81		2
Linkerhäger, 1999	Potatoe	Cymoxanil	GC-NPD (DB-1)	0.04	0.04	79-90	85	4.7	5
			GC-NPD (BPX-35)		0.40	84-98	89	6.2	5
			GC-NPD (DB-5)	0.04	0.04	82-95	91	5.7	5
			GC-NPD (BPX-35)		0.40	77-85	81	4.1	5
			GC-NPD (DB-1)	0.1	0.10	82-97	88	6.7	5
			GC-NPD (BPX-35)		1.0	77-81	78	2.4	5
	Grape	Cymoxanil	GC-NPD (DB-5)	0.04	0.10	78-87	81	6.4	5
			GC-NPD (BPX-35)		1.0	83-91	86	3.7	5
			GC-NPD (DB-1)	0.04	0.04	---	83	---	1
			GC-NPD (BPX-35)		0.4	---	84	---	1
			GC-NPD (DB-5)	0.04	0.04	---	104	---	1
			GC-NPD (BPX-35)		1.0	---	86	---	1
Linkerhäger, 1999	Potatoe	Cymoxanil	GC-NPD (DB-1)	0.1 ^(§)	0.10	---	65	---	1
			GC-NPD (BPX-35)		1.0	---	82	---	1
			GC-NPD (DB-5)	0.33 ^(#)	0.10	---	n.d.	---	1
			GC-NPD (BPX-35)		1.0	---	73	---	1
			GC-NPD (DB-1)	0.1	0.10	---			
			GC-NPD (BPX-35)		1.0	---			

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References	Matrix	Determined analyte	Method (column)	LOQ [mg/kg]	Fortification [mg/kg]	Range [%]	Average recovery [%]	RSD [%]	n
Freschi, 2003a	Lettuce	Cymoxanil	GC-NPD (HB-5)	0.05	0.05	71.3-103	84.8	15.9	4
					1.0	64.9-105.6	86.2	19.4	4
Freschi, 2003b	Potatoes (tuber)		GC-NPD (HB-5)	0.05	0.05	72.1-111.0	87.0	19.8	4
					1.0	86.4-107.0	96.4	8.8	4
Freschi, 2001a	Lettuce	Cymoxanil	GC-NPD (DB-5)	0.05	0.05	89.4-107.3	101.4	7.6	5
					0.5	92-104.2	96.7	5.3	5
Freschi, 2001b	Potatoes	Cymoxanil	GC-NPD (DB-5)	0.05	0.05	95.0-107.3	100.1	5.0	5
					0.5	94.4-105.2	99.8	4.5	5
Wasser, 2002	Tomatoes	Cymoxanil	GC-NPD (DB-5)	0.05	0.05	70.6-92.9	82.5	10.9	5
	Grapes				0.5	70.5-81.6	75.9	7.2	5
					0.05	78.7-89.1	82.9	5.2	5
					0.5	76.6-90.8	82.2	6.7	5
	Potatoes				0.05	75.2-81.7	78.2	3.6	5
					0.5	97.5-111.6	105.3	5.6	5
	Lettuce				0.05	86.6-97.3	91.6	5.1	5
					0.5	102.9-109.4	106.1	2.4	5
	Tomatoes	Cymoxanil	HPLC-UV (confirmatory)	0.05	0.05	77.9-81.5	79.7	4.4*	2
					0.5	73.2-77.8	75.5		2
	Grapes				0.05	78.2-103.8	91.0	16.9*	2
					0.5	74.7-75	74.9		2
	Potatoes				0.05	78.5-79.1	78.8	6.6*	2
					0.5	84.2-90.3	87.3		2
	Lettuce				0.05	86.6-90.5	88.6	10.8*	2
					0.5	106.1-106.9	106.5		2

* RSD from both fortification levels

n.d not detected

(\$) semi-quantitative analysis

(#\$) LOQ based on signal to noise ratio of the upper fortification level

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B.5.3 Analytical methods (residue) for soil, water, air**B.5.3.1 Soil (Annex IIA 4.2.2, Annex IIIA 5.2.2)**

Reference: Melkebeke, T. (2000a); Validation of an analytical method for the determination of cymoxanil residues in soil. Oxon Report Notox: 281802.

Guidelines: SANCO 8064/VI/97- rev 4 (equivalent to SANCO/825/00)

GLP: Yes

Validity: The method is considered acceptable.

Principle of the method:

Residues of Cymoxanil are extracted from soil by shaking twice with a mixture of acetonitrile and aqueous acetate buffer (pH 4). Following centrifugation the supernatant is decanted, further acetate buffer is added and the sample is evaporated to leave the aqueous residue. The extract is partitioned twice with dichloromethane. The combined dichloromethane extracts are evaporated to dryness and reconstituted in acetonitrile/phosphoric acid prior to analysis by reversed-phase high performance liquid chromatography using a C₁₈ column (Hypersil ODS C₁₈, 250 x 4.6 mm i.d, 5 µm) with ultraviolet detection at 242 nm. Residues of Cymoxanil are confirmed by diode array detection (DAD).

A sandy loam standard soil was used for the validation. The specification of the soil is given in the following table.

Specification of soil	
Name	Speyer 2.1
Location	Rheinland-Pfalz/Rheinzabern. Landwirtschaftliche Untersuchungs- und Forschungsanstalt Speyer, 67346 Speyer, Germany
Classification	Not indicated
Texture (USDA)	Sand
Texture (DIN)	Sand
Horizon	20 cm
pH-CaCl ₂	6.0
% organic matter	0.97
% organic carbon	0.56
% clay, <2 µm	1.7
% silt, 2-53 µm	8.2
% sand, 53-2000 µm	90.2
% clay, <2 µm	1.8
% silt, 2-63 µm	9.9
% sand, 63-2000 µm	89.2
CEC (meq/100 g)	4
Water holding capacity (%)	29
Batch No.	F13399
Filed sampling date	August 16, 1999

Findings: The validation data are summarized in table B.5.3.1-1.

Specificity: Specificity of the analytical method for residues of Cymoxanil was demonstrated by the retention time of the analytes on the HPLC-column and by UV-adsorption (242 nm) at this specific retention time. No adsorption above the matrix response was observed at the detection wavelength of 242 nm.

Confirmatory method: Using the DAD in the HPLC method, the UV spectra of processed blank samples showed no UV adsorption above the matrix response as shown by relevant spectral figures. The interferences in processed blank samples did not exceed the 30% of the LOQ. Therefore, the method is specific for the quantitation of Cymoxanil in soil.

Linearity: Calibration was performed using seven different calibration standards of Cymoxanil ranging from 0.021mg/L to 8.13 mg/L. The detector showed a linear response and the correlation coefficient was > 0.99. This calibration range is equivalent to a sample concentration of 0.0021 mg/kg to 0.813 mg/kg. The lower and upper fortification levels are covered by the calibration curve including an exceeding of $\pm 20\%$.

Accuracy: The data of all three fortification levels of Cymoxanil residues in soil are summarised in table B.5.3.1-1. The mean recoveries ranged between 88% and 95%, which is within acceptable recovery range of 70 to 110%.

Precision: The relative standard deviations ranged from 5.8% to 12.1%, which is below the maximum acceptable value of 20%.

Limit of quantification:

The limit of quantification of the method for soil is 0.01 mg/kg.

Conclusion:

The method is sufficiently validated in accordance with the SANCO 825/00 guidance document considering the specificity, linearity, accuracy, precision and LOQ. Additionally, a confirmatory analysis using HPLC-DAD was performed, demonstrating the specificity of the method.

B.5.3.2 Water (including drinking water) (Annex IIA 4.2.3, Annex IIIA 5.2.3)

Reference: Cabusas, M.E.Y. (1999). Analytical method for the determination of cymoxanil in drinking, ground, and surface water using liquid chromatography with ultraviolet detection DuPont-2126

Guidelines: EEC 91/414/EEC; USEPA 166

GLP: No.

Validity: The method is considered acceptable.

Principle of the method:

Cymoxanil in a 400-mL acidified water sample (pH~3) was extracted and purified by passing the sample through a carbon solid phase extraction (SPE) cartridge where Cymoxanil was retained. Cymoxanil was eluted from the carbon cartridge using acetone, the eluate was evaporated to dryness, reconstituted with ethyl acetate and diluted with hexane. The resulting solution was further purified by passing it through a silica SPE cartridge where Cymoxanil was retained. After elution of Cymoxanil with 40/60/1% (v/v) hexane/ethyl acetate/methanol,

the eluate was evaporated to dryness, reconstituted with 20/80 (v/v) of methanol/0.01 % phosphoric acid and analyzed by reversed phase HPLC-UV using a phenyl-hexyl column (Phenomenex Luna, phenyl-hexyl, 100 mm x 4.6 mm i.d., 3 µm, single column method). Confirmatory analysis was achieved by a HPLC column switching method on a SB-CN column (Zorbax, SB-CN, 150 mm x 4.6 mm i.d., 5 µm) and C₁₈ column (Phenomenex Luna, C₁₈ 150 mm x 4.6 mm i.d., 5 µm). The mobile phase consists of water/ 0.01% H₃PO₄ (A) and acetonitrile/0.01% H₃PO₄ (B). A time scheduled gradient is used for elution of the analyte, ranging from 15% (B) to 95% (B) in both methods. Detection of the analyte is performed at 245 nm wavelength. Five different types of water were used for the validation. The specification of the different water types used in the study is given in the following table.

Specification of water					
	Brandy-wine river water	Delaware tap (municipal) water	Delmarva well (Maryland, ground water)	Chesapeake bay water	Lums pond (lake) water
pH	7.5	6.8-8.3	7.2	8.0	7.1
Calcium (mg/kg)	19	--	12	--	8.2
Magnesium (mg/kg)	7.1	--	4.6	--	4.5
Sodium (mg/kg)	11	3-76	10	--	10
Hardness (mg equiv CaCO ₃ /L)	76	89-212	49	--	39
Conductivity (mmhos/cm)	0.27	--	0.18	--	0.17
Total Dissolved Solids (mg/kg)	146	128-370	166	36	86
Total Suspended Solids (mg/kg)	12	--	2	--	6
Alkalinity (mg CaCO ₃ /L)	43	33-124	24	--	10
Total Organic Carbon (mg/kg)	3.7	0.7-4.0	1.2	2.3	4
Sulfate-Sulfur (mg/kg)	18	--	35	--	20
Total Nitrogen (mg/kg)	2.3	--	1.4	2.3	2.8
Nitrate - Nitrogen (mg/kg)	2.90	2.2-9.3	1.2	1.6	1.4
Total Phosphorous (mg/kg)	0.1	--	<0.1	0.07	0.1

Findings: The validation data are summarized in table B.5.3.1-1.

Specificity:

Analysis of control samples resulted in no significant background interference at the retention time of Cymoxanil. However, two out of four controls of Brandywine River water samples showed a small interference peak at the retention time of Cymoxanil (approx. 12% and 14% of the LOQ), probably due to a contamination during sample preparation. This is acceptable

since the interferences in the control samples were less than 30% of the LOQ and were not observed in all samples.

Confirmatory method: This method was found to be specific, no interferences were observed from the matrix components.

Linearity: Calibration was performed using eight different calibration standards of Cymoxanil ranging from 0.020 µg/mL to 1.0 µg/mL. A typical calibration example (Chesapeake Bay water) showed a linear response of the detector and revealed a correlation coefficient of > 0.99. The lower and upper fortification levels are covered by the calibration curve including an exceeding of ± 20%.

Accuracy: The mean recoveries of the primary method for all 5 tested water samples using 5 replicates are ranging from 91% to 104 % for the fortification level of 0.10 ppb and from 87% to 93% for the 1.0 ppb fortification level, respectively. The confirmatory method using a reduced replicate set showed a mean recovery of 99% to 107% for the 0.1 ppb fortification level and 87% to 95% for the 1.0 ppb fortification level, respectively. All recoveries are within the acceptable limits of 70 to 110%.

Precision: The relative standard deviations ranged from 2 to 11% for the primary method and 0 to 12% for the confirmatory method. These numbers are well below the maximum acceptable value of 20% RSD.

Limit of quantification: The limit of quantification of both methods is 0.10 µg/L.

Conclusion:

The method is sufficiently validated in accordance with the SANCO 825/00 guidance document considering the specificity, linearity, accuracy, precision and LOQ. A confirmatory analysis was performed, demonstrating the specificity of the method.

B.5.3.3 Air (Annex IIA 4.2.4, Annex IIIA 5.2.4)

Reference: Melkebeke, T. (2000b). Validation of an analytical method for the determination of Cymoxanil residues in air. Oxon Report, Notox No: 257805.

Guidelines: SANCO 8064/VI/97- rev 4 (equivalent to SANCO/825/00)

GLP: Yes

Validity: The method is considered acceptable.

Principle of the method:

Tenax (Supelco ORBO™ - 402 Tenax 100/50 mg) was selected as an adsorber material for the analysis of air samples. In the desorption test, Cymoxanil was spiked straight on the adsorber and dried. Air was tested at two concentration levels of 0.5 µg and 50 µg per adsorber. In the long term efficiency test, spiked test air (0.5 µg and 50 µg per adsorber) was conditioned at 35°C and 80% relative humidity at a flow rate of 3 L.min⁻¹ using a sampling time of 6 hours. These amounts are corresponding to a concentration range in air of 0.46 µg/m³ - 46 µg/m³, equivalent to 0.1 x C and 10 x C.

After treatment in the test system, the active ingredient was eluted with 5 mL acetonitrile and quantified. A HPLC method was used for the quantitative analysis of Cymoxanil in organic

solvent. A reversed phase (Hypersil ODS, C₁₈, 250 x 4 mm i.d. 5µm) column was applied with 60/40 water/acetonitrile as mobile phase and detection of the analyte at 242 nm. Confirmation of the methodology was achieved by a photodiode array detector using the same analytical conditions as for the primary method.

Findings: The validation data are summarized in table B.5.3.1-1.

Specificity: The retention time of Cymoxanil in the calibration solutions and processed spiked samples remained unchanged. No interferences were observed in the blank sample eluate. The criterion that interferences in the processed blank samples should not exceed 30% of the LOQ was met.

Confirmatory method: There was a good agreement at the Cymoxanil retention time between the UV-spectrum (210-300 nm) of the calibration solution and the spiked sample eluate (long term efficiency test- 6 hours trapping). These findings confirmed the specificity of the analytical system for detecting Cymoxanil in air using the applied adsorber extracts.

Linearity: Calibration was performed using a six point calibration curve ranging from 0.08 to 1.25 mg/L. A typical calibration example showed a linear response of the detector and revealed a correlation coefficient of > 0.99 in the desorption and long term efficiency test. The lower and upper fortification levels are covered by the calibration curve including an exceeding of ± 20%.

Accuracy: The accuracy of the desorption step, determined as the overall recovery of individual samples from the desorption test was 92% (RSD of 11%) for the 0.5 µg/tube and 94% (RSD of 2 %) for the 50 µg/tube. The accuracy of the long term efficiency test, determined as the overall recovery of the individual samples was 86% (RSD of 13%) for the 0.5 µg/tube and 97% (RSD of 4 %) for the 50 µg/tube.

Extraction efficiency: Overall mean extraction efficiency of Cymoxanil from the desorption test was 93% (n=10) showing sufficient extraction efficiency.

Breakthrough behaviour: No breakthrough was observed for none of the 5 samples collected during the long term efficiency test. All responses were below the limit of detection.

Precision: For the desorption test the RSD was 11 % at a mean recovery of 92%. For the long term efficiency test the RSD was 13%. In both cases the acceptance criterion of RSD < 20% was met.

Limit of quantification: The limit of quantification of the analytical method for air was set at 0.5 µg/adsorber, equivalent to a Cymoxanil concentration in air of 0.46 µg/m³.

Conclusion:

The method is sufficiently validated in accordance to the SANCO 825/00 guidance document considering the specificity, linearity, accuracy, precision and LOQ. A confirmatory analysis was performed, demonstrating the specificity of the method.

B.5.4 Analytical methods (residue) for body fluids and tissues (Annex IIA 4.2.5, Annex IIIA 5.2.5)

The submission of an analytical method for the determination of residues in body fluids and tissues is not necessary, because the active substance is not classified as toxic or highly toxic.

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Table B.5.3.1.-1 Validation data for analytical methods for the determination of residues in soil, water, air:

References	Matrix	Determined analyte	Method	LOQ	Fortification level	Range [%]	Average [%]	RSD [%]	n
Melkebeke, 2000a	Soil	Cymoxanil	HPLC-UV	0.01 mg/kg	0.01 mg/kg	80-112	92	12.1	6
					0.05 mg/kg	85-100	95	5.8	6
					0.5 mg/kg	81-95	88	6.2	6
Cabusas, 1999	Delaware tap (municipal) water	Cymoxanil	HPLC-UV (primary method)	0.10 µg/L	0.10 µg/L	76-101	91	11	5
	Delmarva well (Maryland, ground water)				1.0 µg/L	75-91	85	8	5
	Chesapeake bay water				0.10 µg/L	99-111	104	4	5
	Brandy-wine river water				1.0 µg/L	87-98	93	5	5
	Lums pond (lake) water				0.10 µg/L	91-110	100	7	5
	Delaware tap (municipal) water				1.0 µg/L	81-94	89	6	5
	Delmarva well (Maryland, ground water)				0.10 µg/L	101-106	104	2	5
	Chesapeake bay water				1.0 µg/L	83-99	90	7	5
	Brandy-wine river water				0.10 µg/L	80-102	92	10	5
	Lums pond (lake) water				1.0 µg/L	81-92	87	5	5
	Delaware tap (municipal) water		HPLC-UV (confirmatory method)	0.10 µg/L	0.10 µg/L	88-111	99	12*	3
	Delmarva well (Maryland, ground water)				1.0 µg/L	74-93	87	10*	4
	Chesapeake bay water				0.10 µg/L	105	105	0*	2
	Delmarva well (Maryland, ground water)				1.0 µg/L	92-97	95	3*	3
	Chesapeake bay water				0.10 µg/L	95-113	104	9*	3
	Brandy-wine river water				1.0 µg/L	87-93	90	3*	5
	Lums pond (lake) water				0.10 µg/L	105-108	107	1*	3
	Chesapeake bay water				1.0 µg/L	88	88	0*	2
	Delmarva well (Maryland, ground water)				0.10 µg/L	102-104	103	1*	3
	Chesapeake bay water				1.0 µg/L	90-92	91	2*	2

References	Matrix	Determined analyte	Method	LOQ	Fortification level	Range [%]	Average [%]	RSD [%]	n
Melkebeke, 2000b	Air	Cymoxanil	HPLC-UV (desorption test)	0.46 µg/m ³	0.46 µg/m ³ (0.5 µg/tube)	82-108	92	11	5
					46 µg/m ³ (50 µg/tube)	92-97	94	2	5
		Cymoxanil	HPLC-UV (long-term effic. test)	0.46 µg/m ³	0.5 µg/tube 50 µg/tube	72-102 83-91	86 87	13* 4*	5 5#

* calculated by RMS since only RSD's over all fortification levels are provided or only CV's are reported

one outlier not included in the calculation

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B.5.5 Evaluation and assessment

B.5.5.1 Active substance and formulation analysis

Cymoxanil was determined in technical active substance and the plant protection product by HPLC with UV detection. Acceptable validation data have been submitted from both applicants (see table B.5.5.1-1). The methods of analysis for impurities in support of batch analyses are presented in the confidential section (Annex C/Vol 4).

Table B.5.5.1-1: Summary of analytical methods for technical active substance and formulation analysis

Matrix	Analyte	Applicant	Type of method	Validation	References
Technical active substance	Cymoxanil	DuPont	HPLC-UV	Full	E.I DuPont, 1995, method T3217.220.01.ES
	Impurities	DuPont	HPLC-UV	Full	E.I DuPont, 1995, method T3217.220.02.ES
Technical active substance	Cymoxanil	Oxon	HPLC-UV	Full	Fraschini, 1997; Freschi, 2003
	Impurities	Oxon	HPLC-UV	Full	Fraschini, 1997; Freschi, 2003
DPX-KP 481 50 WG (250 g/L)	Cymoxanil	DuPont	HPLC-UV	Full	Flament, 1999a and 1999b; Vindevoghel, 1999
Cymoxanil 50 WP (500 g/L)	Cymoxanil	Oxon	HPLC-UV	Full	Freschi, 2001

A CIPAC method (419/TC/M/3) exists for the determination of Cymoxanil in the technical material and (419/WG/M/3) for the determination of the active substance in the formulation DPX-KP 481 50 WG.

The applicability of the existing CIPAC method (CIPAC 419/WP/M/3) for the formulation Cymoxanil 50 WP is required since notifier B (OXON) stated that the applicability was not proved but it is assumed that it works since the method for testing the pure active substance in the technical one does not substantially differ from CIPAC method for WP formulations.

B.5.5.2 Residue analysis

For the residues analyses of crops, animal products and environmental samples, where information has been submitted, it fulfils the following criteria:

- Adequate limit of determination (plant material and products: adequate for MRLs, soil, water and air);
- Mean recovery 70%-110%;
- Relative standard deviation of recovery rates <20%;
- Interfering blanks lower than 30% of the limit of determination;

e) Readily available equipment and reagents used.

For **potatoes** the GC-NPD method from Kretschmer, Class (1999) was acceptably validated. Some individual recoveries of potatoes were low, although all mean recoveries were acceptable at 0.04 mg/kg and 0.40 mg/kg levels. Therefore the method of analysis is regarded as suitable for concentrations at 0.04 to 0.40 mg/kg within an acceptable precision. The ILV performed by Linkerhägner (1999) confirmed the method validation results, all average recoveries were within the acceptable range. The LOQ was confirmed with 0.04 mg/kg for potatoes.

For matrices with high water, high acid content, or commodities which are difficult to analyse, the method validation results showed some deficiencies, therefore a full method validation according to Sanco 825/00 guideline is expected, if an intended use is proposed.

A GC-NPD method (Freschi, 2001b, report SIP 1277) was acceptably validated using fortification levels of 0.05 mg/kg and 0.5 mg/kg for potatoes. All individual recoveries were within the acceptable range, within an acceptable precision of the applied method. An ILV (Wasser, 2002) confirmed the method validation results with a LOQ of 0.05 mg/kg for potatoes. Since the residues and feeding studies were performed with a LOQ of 0.05 mg/kg, this value is considered to be more representative.

For **lettuce** a GC-NPD method (Freschi, 2001a, report SIP 1277) was acceptably validated using fortification levels of 0.05 mg/kg and 0.5 mg/kg. All individual recoveries were within the acceptable range, within an acceptable precision of the applied method. An ILV (Wasser, 2002) confirmed the method validation results with a LOQ of 0.05 mg/kg for lettuce.

The GC-NPD methods for lettuce and potatoes performed by Freschi (2003a and 2003b) were submitted to show the applicability of existing multiresidue methods for Cymoxanil determination. However, since for these methods an ILV, confirmatory analyses and GLP conditions are missing, these methods can be considered for information only.

For **soil** a HPLC-UV method (Melkebeke, 2000a) was acceptably validated using fortification levels of 0.01 mg/kg to 0.5 mg/kg. All individual recoveries were within the acceptable range, obtaining acceptable relative standard deviations and a LOQ of 0.01 mg/kg. Therefore the method of analysis is considered valid. A confirmatory analysis was performed within the method using a diode array detection (DAD) of the analyte.

For **water** a HPLC-UV method (Cabusas, 1999) was validated. All tested water types showed acceptable average recoveries and relative standard deviations. The LOQ of the method was determined with 0.10 µg/L. A confirmatory analysis using columns of different polarity supported the validity of the applied method.

For **air** acceptable validation data (Melkebeke, 2000b) were submitted using a HPLC-UV method after trapping the analyte. Full method validation was shown with acceptable average recoveries and relative standard deviations. Therefore the method of analysis is considered valid. A confirmatory analysis was performed within the method using a diode array detection (DAD) of the analyte.

The submitted methods enable the enforcement of the following relevant residue definitions and limits (see table B.5.5.2-1). An overview of the accepted methods for residue analysis is given in table B.5.5.2-2. Main parameters of the analytical methods for different matrices are summarised in table B.5.5.2-3, respectively.

Table B.5.5.2-1: Summary of relevant residue definitions and limits

Matrix	Residue definition	LOQ	Residue limit/ Toxic concentration for non- target organisms
Food of plant origin: Potatoes Lettuce	Cymoxanil	0.05 mg/kg 0.05 mg/kg	0.05 ^{#)} mg/kg proposed MRL 0.05 mg/kg proposed MRL
Food of animal origin	Not required, no residue definition/no MRL is proposed		
Soil	Cymoxanil	0.01 mg/kg	EC ₅₀ > 1 g/kg soil dw earth worm
Drinking water	Cymoxanil	0.10 µg/L	0.10 µg/L EU drinking water limit
Surface water	Cymoxanil	0.10 µg/L	NOEC 58.1 µg/L <i>Cyprinodon variegatus</i>
Air	Cymoxanil	0.46 µg/m ³	6 µg/m ³ based on a proposed AOEL _{systemic} of 0.02 mg/kg bw/day
Body fluids	Not necessary, the active substance is not classified as toxic or very toxic		

^{#)} Proposed setting based on LOQ study of Freschi G. (2001b) and in correspondence with residue trials

Table B.5.5.2-2: Overview of accepted residue analytical methods

Matrix type/ crop group	Author, Year (Primary Method)	Author, Year (Confirmatory Method)	Author, Year (Indep. Lab Validation)
Potatoes	Kretschmer and Class, 1999; (GC-NPD, DB-1 column)	Kretschmer and Class, 1999; (GC-NPD, BPX-35 column)	Linkerhägner, M., 1999; (GC-NPD, GC-MSD*)
	Freschi G. 2001b; (GC-NPD, DB-5 column)	Wasser, C., 2002; (HPLC-UV, SB- phenyl column)	Wasser, C., 2002; (GC-NPD, DB-5 column)
Lettuce	Freschi G. 2001a; (GC-NPD, DB-5 column)	Wasser, C., 2002; (HPLC-UV, SB- phenyl column)	Wasser, C., 2002; (GC-NPD, DB-5 column)
Food of animal origin	No method necessary	—	—
Soil	Melkebeke, T., 2000a; (HPLC-UV, C ₁₈ column)	Melkebeke, T., 2000a; (HPLC-DAD, C ₁₈ column)	—
Drinking water/ Surface water	Cabusas, M.E.Y., 1999; (HPLC-UV, Phenyl-hexyl column)	Cabusas, M.E.Y., 1999; (HPLC-UV, column switching, SB-CN and C ₁₈ columns)	—
Air	Melkebeke, T., 2000b; (HPLC-UV, C ₁₈ column)	Melkebeke, T., 2000b; (HPLC-DAD, C ₁₈ column)	—
Body fluids	Not required	—	—

* Additional confirmatory analysis within ILV

B.5.6 References relied on

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Annex II					
IIA, 4.1.2	E.I. du Pont	1995	Method No. T3217.220.01.ES, Revision No.1. Determination of Cymoxanil in technical Cymoxanil. Reversed-phase liquid chromatographic (RPLC) assay method. GLP: No. Published: No	Y	DuPont
IIA, 4.1.2	Fraschini C.	1997	Cymoxanil techn. Analytical Profile of Oxon Production. Final study, Sipcam report No. 004/97 GLP: Yes Published: No	Y	Oxon
IIA, 4.1.2	Freschi G.	2003	Cymoxanil techn. Analytical Profile of Oxon Production. Final study, Sipcam report No. 001/2003 GLP: Yes Published: No	Y	Oxon
IIA, 4.1.2	Freschi G.	2001	Cymoxanil 50 WP, Shelf life at ambient temperature. Sipcam Report 005/99 GLP: Yes Published: No	Y	Oxon
IIA, 4.2.1/01	Kretschmer, S., Class, T.	1999	Method assessment and validation of an analytical multi-residue enforcement method (DFG S19 modified) for the determination of residues of cymoxanil in plant material (grape, potato, tomato, hops cones, post-cured tobacco). PTRL Europe DuPont-2158 GLP: Yes Published: No	Y	DuPont
IIA, 4.2.1/02	Linkerhagner, M.	1999	Independent laboratory validation (ILV) of a multi-residue enforcement method (DFG S19 modified) for the determination of cymoxanil in dry, high water, and oily crops Dr. Specht & Partner, Germany DuPont-2946 GLP: Yes Published: No	Y	DuPont

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
IIA, 4.2.1/03	Freschi, G.	2003a	Applicability and validation of a multiresidues analytical method on lettuce specimens (plant) SIPCAM S.p.A, Salerano sul Lambro, Italy UAR/001/2003 GLP: No Published: No	Y	Oxon
IIA, 4.2.1/04	Freschi, G.	2003b	Applicability and validation of a multiresidues analytical method on potato specimens (tuber) SIPCAM S.p.A, Salerano sul Lambro, Italy UAR/002/2003 GLP: No Published: No	Y	Oxon
IIA, 4.2.1/05	Freschi, G.	2001a	Validation of the analytical method for determination of residues of cymoxanil in lettuces (plant) SIPCAM S.p.A, Salerano sul Lambro, Italy SIP1279 GLP: Yes Published: No	Y	Oxon
IIA, 4.2.1/06	Freschi, G.	2001b	Validation of the analytical method for determination of residues of cymoxanil in potato (tuber) SIPCAM S.p.A, Salerano sul Lambro, Italy SIP1277 GLP: Yes Published: No	Y	Oxon
IIA, 4.2.1/07	Wasser, C.	2002	Validation of analytical method for determination of residues of cymoxanil in specimens of tomato, grapes, potatoes and lettuce Anadiag S.A., Haguenau, France A0087 GLP: Yes Published: No	Y	Oxon
IIA, 4.2.2/01	Melkebeke, T.	2000a	Validation of an analytical method for the determination of cymoxanil residues in soil Notox B.V., 's-Hertogenbosch, The Netherlands 281802 GLP: Yes Published: No	Y	Oxon

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
IIA, 4.2.3/01	Cabusas, M.E.Y.	1999	Analytical method for the determination of cymoxanil in drinking, ground, and surface water using liquid chromatography with ultraviolet detection DuPont Experimental Station DuPont-2126 GLP: No Published: No	Y	DuPont
IIA, 4.2.4/01	Melkebeke, T.	2000b	Validation of an analytical method for the determination of cymoxanil in air Notox B.V., 's-Hertogenbosch, The Netherlands 257805 GLP: No Published: No	Y	Oxon
Annex III					
IIIA, 5.1.1./01	Flament, C.	1999a	Validation of the analytical method to verify the certified limits of cymoxanil (DPX- T3217) and famoxadone (DPX-JE874) in: DuPont water-dispersible granular formulation DPX-KX007, containing 300 g/kg cymoxanil and 225 g/kg famoxadone; DuPont suspension concentration formulation DPX-KX007, containing 240 g/L cymoxanil and 180 g/L famoxadone; DuPont water-dispersible granular formulation DPX-KP481, containing 250 g/kg cymoxanil and 250 g/kg famoxadone, Method 2 DuPont European Research and Development Centre (ERDC) DuPont-1916 GLP: Yes Published: No	N	DuPont

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Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
IIIA, 5.1.1/02	Flament, C.	1999b	Validation of the analytical method to verify the certified limits of cymoxanil (DPX-T3217) and famoxadone (DPX-JE874) in: DuPont water-dispersible granular formulation DPX-KX007, containing 300 g/kg cymoxanil and 225 g/kg famoxadone; DuPont suspension concentration formulation DPX-KX007, containing 240 g/L cymoxanil and 180 g/L famoxadone; DuPont water-dispersible granular formulation DPX-KP481, containing 250 g/kg cymoxanil and 250 g/kg famoxadone DuPont European Research and Development Centre (ERDC) DuPont-1659 GLP: Yes Published: No	N	DuPont
IIIA, 5.1.1/04	Vindevoghel, C.	1999	Validation of the analytical method to verify the certified limits of cymoxanil (DPX-T3217) and famoxadone (DPX-JE874) in: DuPont water-dispersible granular formulation DPX-KX007, containing 300 g/kg cymoxanil and 225 g/kg famoxadone; DuPont suspension concentration formulation DPX-KX007, containing 240 g/L cymoxanil and 180 g/L famoxadone; DuPont water-dispersible granular formulation DPX-KP481, containing 250 g/kg cymoxanil and 250 g/kg famoxadone, Method 3 DuPont European Research and Development Centre (ERDC) DuPont-2731 GLP: Yes Published: No	N	DuPont
IIIA 5.1	Freschi G.	2000	Cymoxanil 50 WP: shelf life at ambient temperature SIPCAM S.p.A., Italy, Report 005/99 GLP: Yes Published: No	Y	Oxon

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