Monograph

January 2004

Metconazole

Volume 1

Report and
Proposed Decision

Rapporteur Member State: Belgium

TABLE OF CONTENTS

Level 1	Statement of subject matter and purpose for which the monograph was prepared	Page
1.1	Purpose of the monograph (Document A)	7
1.2	Summary and assessment of information relating to the collective provision of dossiers (Document B)	7
1.3	Identity of the active substance (Annex IIA 1)	7
1.3.1	Name and address of applicant(s) for inclusion of the active substance in Annex I (Annex IIA 1.1)	7
1.3.2	ISO common name and synonyms (Annex IIA 1.3)	7
1.3.3	Chemical name (Annex IIA 1.4)	7
1.3.4	Manufacturer's development code number (Annex IIA 1.5)	7
1.3.5	CAS, ECC and CIPAC numbers (Annex IIA 1.6)	7
1.3.6	Molecular formula, molecular mass and structural formula (Annex IIA 1.7)	7
1.3.7	Manufacturer of the active substance (Annex IIA 1.2)	8
1.3.8	Method or methods of manufacture (Annex IIA 1.8)	9
1.3.9	Specification of the purity of the active substance (Annex IIA 1.9)	9
1.3.10	Identity of inactive isomers, impurities and additives (Annex IIA 1.10)	9
1.3.11	Analytical profile of batches (Annex IIA 1.11)	9
1.4	Identity of the plant protection product (Annex IIA 3.1; Annex IIIA 1)	9
1.4.1	Current, former and proposed trade names and development code numbers (Annex IIIA 1.3)	9
1.4.2	Manufacturer or manufacturers of the plant protection product (Annex IIIA 1.2)	9
1.4.3	Type of the preparation and code (Annex IIIA 1.5)	10
1.4.4	Function (Annex IIIA 1.6)	10
1.4.5	Composition of the preparation (Annex IIIA 1.4)	10
1.5	Uses of the plant protection product	10
1.5.1	Fields of use (Annex IIA 3.3; Annex IIIA 3.1)	10
1.5.2	Effects on harmful organisms (Annex IIA 3.2; Annex IIIA 3.2)	10
1.5.3	Summary of intended uses (Annex IIA 3.4; Annex IIIA 3.3 to 3.7, 3.9)	10
1.5.4	Information on authorizations in EU Member States (Annex IIIA 12.1)	13

Level 2	**Reasoned statement of the overall conclusions drawn by the Rapporteur Member State**	19
2.1.1	Identity	20
2.1.2	Physical and chemical properties	20
2.1.3	Details of uses and further information	20
2.1.4	Classification and Labelling	21
2.2	Methods of analysis	23
2.2.1	Analytical methods for analysis of the active substance as manufactured	23
2.2.2	Analytical methods for formulation analysis	23
2.2.3	Analytical methods for residue analysis	23
2.3	Impact on human and animal health	24
2.3.1	Effects having relevance to human and animal health arising from exposure to the active substance or to their transformation products	24
2.3.2	Acceptable daily intake (ADI)	34
2.3.3	Acute reference dose (ARfD)	34
2.3.4	Acceptable operator exposure level (AOEL)	34
2.3.5	Drinking water limit	34
2.3.6	Impact on human or animal health arising from exposure to the active substance or to impurities contained in it	35
2.4	Residues	35
2.4.1	Definition of the residues relevant to MRLs	35
2.4.2	Residues relevant to consumer safety	36
2.4.3	Residues relevant to worker safety	36
2.4.4	Proposed EU MRLs and compliance with existing MRLs	36
2.4.5	Proposed EU import tolerances and compliance with existing MRLs	36
2.4.6	Basis for differences, if any, in conclusions reached having regard to established or proposal CAC MRLs	36
2.5	Fate and behaviour in the environment	36
2.5.1	Definition of the residues relevant to the environment	36
2.5.2	Fate and behaviour in soil	36
2.5.3	Fate and behaviour in water	37
2.5.4	Fate and behaviour in air	38

2.6	Effects on non-target species	38
2.6.1	Effects on terrestrial vertebrates	38
2.6.2	Effects on aquatic species	38
2.6.3	Effects on bees and other arthropods	39
2.6.4	Effects on earthworms and other soil macro-organisms	39
2.6.5	Effects on soil micro-organisms	39
2.6.6	Effects on other non-target organisms (flora and fauna)	39
2.6.7	Effects on biological methods of sewage treatment	39
	Appendix 1 – List of end points (based on doc 1654/VI/94, Rev. 7, 22 Apr 1998)	40-67
Level 3	**Proposed decision with respect to the application for inclusion of the active substance in Annex I**	68
3.1	Background to the proposed decision	69
3.2	Proposed decision concerning inclusion in Annex I	69
3.3	Rational for the postponement of the decision to include the active substance in Annex I, or for the conditions and restrictions to be associated with a proposed inclusion in Annex I, as appropriate	69
Level 4	**Further information to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in the Annex I**	70
4.1	Identity of the active substance	71
4.2	Physical and chemical properties	71
4.2.1	Physical and chemical properties of the active substance	71
4.2.2	Physical and chemical properties of the plant protection product	71
4.3	Data on application and further information	71
4.4	Classification, packaging and labelling	71
4.5	Methods of analysis	71
4.6	Toxicology and metabolism	71
4.7	Residue data	71
4.8	Environmental fate and behaviour	71
4.9	Ecotoxicology	71

LEVEL 1

Metconazole

Statement of subject matter and purpose for which the monograph was prepared

1.1 Purpose of the monograph (Document A)

This monograph is submitted to support the application for the first inclusion of the existing active substance Metconazole in Annex I to Directive 91/414/EEC.

1.2 Summary and assessment of information relating to the collective provision of dossiers (Document B)

Not applicable as Metconazole is an existing active substance with only one applicant.

1.3 Identity of the active substance (Annex IIA 1)

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

BASF Agro B.V., Wädenswil Branch
Steinacherstrasse 101
CH-8820 Wädenswil

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BASF Aktiengesellschaft
Agrarzentrum
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D-67114 Limburgerhof, Germany

Phone : +49-621-60-27324
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1.3.2 ISO common name and synonyms (Annex IIA 1.3)

Metconazole

1.3.3 Chemical name (Annex IIA 1.4)

IUPAC nomenclature : (1*RS*,5*RS*:1*RS*,5*SR*)-5-(4-chlorobenzyl)-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl) cyclopentanol

CA nomenclature : 5-[(4-chlorophenyl)methyl]-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl) cyclopentanol

1.3.4 Manufacturer's development code number (Annex IIA 1.5)

Active substance : BAS 555 F; AC 900768; CL 900,768; WL 148271; KNF-S-474M
cis-isomer : CL 354801; trans-isomer : CL 354802

Formulation Metconazole 60 g/L SL : BAS 555 00 F ; SF 09381

1.3.5 CAS, ECC and CIPAC numbers (Annex IIA 1.6)

CAS number : 125116-23-6 (unstated stereochemistry)

EEC number : not assigned

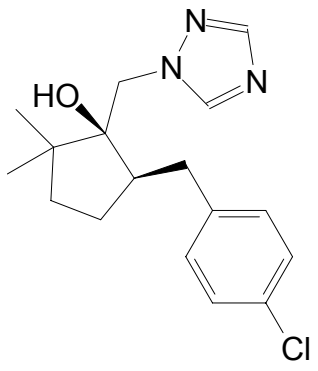
CIPAC number : 706

1.3.6 Molecular formula, molecular mass and structural formula (Annex IIA 1.7)

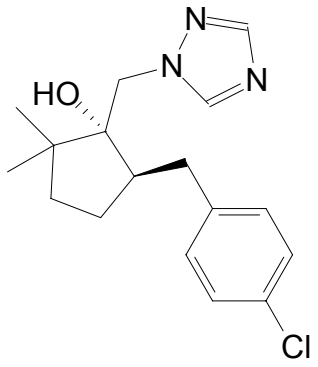
Molecular formula : $C_{17}H_{22}ClN_3O$

Molecular mass : 319.8 g/mol

Structural formula :



cis-isomer
CL 354801



trans-isomer
CL 354802

The active ingredient of Metconazole is a mixture of 4 diastereomers : CL 354801 ("cis-metconazole") is a mixture of S(OH), R and R(OH), S diastereomers, whereas CL 354802 ("trans-metconazole") is a mixture of S(OH), S and R(OH), R diastereomers.

1.3.7 Manufacturer of the active substance (Annex IIA 1.2)

Metconazole is manufactured for : BASF Agro B.V., Wädenswil Branch
Steinacherstrasse 101
CH-8820 Wädenswil

by : Kureha Chemical Industry Company Ltd.
1-9-11 Nihonbashi Horidome-cho
Chuo-ku
Tokyo 103, Japan

at currently two toll manufacturers :

1) Japan : Ibaraki Kasei Chemicals Co., Ltd.
Isohara 1309-2
Isohara-cho
Kitaibaraki-city
Ibaraki Pref., Japan

2) India : Rallis India, Ltd.
Agrochemical Division
Plot No. 3301
GIDC Estate
Ankleshwar 393 022, India

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1.3.8 Method or methods of manufacture (Annex IIA 1.8)

Confidential information, see Annex C

1.3.9 Specification of the purity of the active substance (Annex IIA 1.9)

min. 940 g/kg (sum of *cis*- and *trans*-isomers), with cis-metconazole (CL 354801) level not less than 800 g/kg and not more than 950 g/kg

1.3.10 Identity of inactive isomers, impurities and additives (Annex IIA 1.10)

Confidential information, see Annex C

1.3.11 Analytical profile of batches (Annex IIA 1.11)

Confidential information, see Annex C

1.4 Identity of the plant protection product (Annex IIA 3.1; Annex IIIA 1)

1.4.1 Current, former and proposed trade names and development code numbers (Annex IIIA 1.3)

Trade name : Caramba 60 SL ®

Code number : Metconazole 60 g/L SL; BAS 555 00 F ; SF 09381

1.4.2 Manufacturer or manufacturers of the plant protection product (Annex IIIA 1.2)

Manufacturer of the preparation : BASF Agro B.V., Wädenswil Branch
Steinacherstrasse 101
CH-8820 Wädenswil

Manufacturing site : BASF Agri-Production SAS
Z.I. Lyon Nord
Rue Jacquard – BP 73
F-69727 GENAY Cedex
France

Manufacturer of the active substance : Kureha Chemical Industry Company Ltd.
1-9-11 Nihonbashi Horidome-cho
Chuo-ku
Tokyo 103, Japan

Manufacturing sites : 1) Japan
Ibaraki Kasei Chemicals Co., Ltd.
Isohara 1309-2
Isohara-cho
Kitaibaraki-city
Ibaraki Pref., Japan

2) India
Rallis India, Ltd.
Agrochemical Division
Plot No. 3301
GIDC Estate
Ankleshwar 393 022, India

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1.4.3 Type of the preparation and code (Annex IIIA 1.5)

Soluble concentrate (SL)

1.4.4 Function (Annex IIIA 1.6)

Fungicide

1.4.5 Composition of the preparation (Annex IIIA 1.4)

Table 1.4.5-1 : Composition of Caramba 60 SL ®

Component	Content (g/L)	Function
Metconazole - pure a.s. - technical a.s. (min. purity : 94%)	 60 63.8	Active substance
Other components	Confidential information, see Annex C	

1.5 Uses of the plant protection product

1.5.1 Fields of use (Annex IIA 3.3; Annex IIIA 3.1)

Agriculture

1.5.2 Effects on harmful organisms (Annex IIA 3.2; Annex IIIA 3.2)

Metconazole shows both curative and protectant properties and has demonstrated long term activity as a foliar application.
When applied to foliage, metconazole is taken up into crop leaves, and exhibits penetrant, local, and acropetal systemicity.

1.5.3 Summary of intended uses (Annex IIA 3.4; Annex IIIA 3.3 to 3.7, 3.9)

Intended uses supported by available data are summarized in Table 1.5.3-1 herebelow.

Table 1.5.3-1 : Summary of intended uses supported by available data

Crop and/or situation (a)	Member State or Country	Formula-tion name	F, G or I (b)	Pests or Group of pest controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (k)	Remarks (l)
					Type (d-f)	Conc. Of a.s. (i)	Method kind (f-g)	Growth stage (j)	Number min max	Interval between applications; minimum	kg a.s./hl min max	water l/ha min max	kg a.s./ha		
Winter/ spring wheat	North and South Europe	Caramba 60 SL	F	Septoria spp. Septoria nodorum Septoria tritici Erysiphe graminis Puccinia striiformis Puccinia recondita Fusarium spp. Fusarium roseum Cladosporium spp.	SL	60 g/l	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	
Winter/ spring barley	North and South Europe	Caramba 60 SL	F	Erysiphe graminis Puccinia hordei Rhynchosporium secalis Pyrenophora teres	SL	60 g/l	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	
Winter/ spring oats	North and South Europe	Caramba 60 SL	F	Puccinia avenae	SL	60 g/l	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	
Rye	North and South Europe	Caramba 60 SL	F	Erysiphe graminis Rhynchosporium secalis Puccinia recondita	SL	60 g/l	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	
Triticale	North and South Europe	Caramba 60 SL	F	Septoria spp. Puccinia recondita	SL	60 g/l	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	
Oilseed rape	North and South Europe	Caramba 60 SL	F	Phoma lingam Alternaria spp. Alternaria brassicae Sclerotinia sclerotiorum Erysiphe graminis Cylindrosporium spp.	SL	60 g/l	spray	BBCH 14-73	1-2	14	0.0225-0.045	200-400	0.090	56	

1.5.4 Information on authorizations in EU Member States (Annex IIIA 12.1)

Table 1.5.4-1 : CARAMBA 60 SL - List of the authorized uses of metconazole in the EU, with an indication of actual uses. (prepared by the notifier)

Authorized uses							Actual uses
Member State or Country	Crop	Harmful organism(s)	Dose rate per application (kg a.s./ha)	No. of applica-tion(s)	Timing of application(s), growth stages, season	PHI (days)	1: actual = authorized uses 2: actual uses deviate from authorized uses
Austria	Wheat (1)	*Fusarium spp.* *Erysiphe graminis* *Puccinia striiformus* *Puccinia recondita* *Septoria tritici* *Septoria nodorum*	max. 0.090	1	spring; beginning of infestation or first symptoms visible up to BBCH 69	35	1
	Rye (1)	*Erysiphe graminis* *Puccinia recondita* *Rynchosporium secalis*	max. 0.090	1	in spring at beginning of infestation or first symptoms visible up to BBCH 69	35	1
	Triticale (1)	*Septoria tritici* *Septoria nodorum*	max. 0.090	1	spring; beginning of infestation or first symptoms visible up to BBCH 69	35	1
	Oilseed rape (BRSNW)	*Phoma lingam*	max. 0.090	2	1st applic: beginning of infesta-tion or first symptoms visible up to ca. mid of October. 2nd applic: shortly before BBCH 59	56	1
		Steadiness	max. 0.090	1	spring; BBCH 39-55	56	1
		Sclerotinia sclerotiorum	max. 0.090	1	beginning of infestation up to BBCH 65	56	1
	Barley (1)	*Erysiphe graminis* *Puccinia hordei* *Rynchosporium secalis* *Pyrenphora teres*	max. 0.090	1	spring; beginning of infestation or first symptoms visible up to BBCH 69	35	1

Authorized uses							Actual uses
Member State or Country	Crop	Harmful organism(s)	Dose rate per application (kg a.s./ha)	No. of applica-tion(s)	Timing of application(s), growth stages, season	PHI (days)	1: actual = authorized uses 2: actual uses deviate from authorized uses
Belgium	Winter wheat (TRZAW)	*Septoria spp.* *Puccinia recondita* *Puccinia striiformis*	max. 0.060 (5)	1-2	BBCH 39-59	n/a (3)	1
		Fusarium roseum	max. 0.060	1	only from BBCH 59	n/a (3)	1
	Winter barley (HORVW)	*Pyrenophora teres* *Rhynchosporium secalis* *Puccinia hordei*	max. 0.060 (5)	1-2	BBCH 31-39	n/a (3)	1
France	Winter / Spring barley (HORVW / HORVS)	*Rhynchosporium secalis* *Erysiphe graminis* *Puccinia hordei*	max. 0.090	1-2	BBCH 31-69	42	1
	Winter / Spring oats (AVESW / AVESA)	*Puccinia avenae*	max. 0.090	1-2	BBCH 31-69	42	1
	Winter rye (SECCW)	*Puccinia recondita* *Rhynchosporium secalis*	max. 0.090	1-2	BBCH 31-69	42	1
	Winter triticale (TRSEW)	*Puccinia recondita* *Septoria spp.*	max. 0.090	1-2	BBCH 31-69	42	1
	Canned peas (spring) (PIBST)	*Mycosphaerella pinodes* *Botrytis cinera* *Uromyces pisi-sativi*	max. 0.072	1-2	from BBCH 59	14	
	Field peas (winter and spring) (PIBSA)	*Mycosphaerella pinodes* *Botrytis cinera* *Uromyces pisi-sativi*	max. 0.072	1-3	from BBCH 59	14	1
France (continued)	Winter / Spring wheat (TRZAW / TRZAS)	*Puccinia striiformis* *Puccinia recondita* *Erysiphe graminis* *Septoria spp.* *Fusarium spp.*	max. 0.090	1-2	BBCH 31-69	42	1

Authorized uses							Actual uses
Member State or Country	Crop	Harmful organism(s)	Dose rate per application (kg a.s./ha)	No. of applica-tion(s)	Timing of application(s), growth stages, season	PHI (days)	1: actual = authorized uses 2: actual uses deviate from authorized uses
	Oilseed rape (BRSNW)	*Erysiphe graminis* *Cylindrosporium spp.* *Alternaria brassicea* *Sclerotinia sclerotiorum*	max. 0.072	1-2	BBCH 31-73	45	1
		Height reduction (i.e.use as plant growth regulator)	max. 0.072	1	BBCH 14-51	n/a	1
Germany	Wheat (1)	*Erysiphe graminis* *Puccinia striiformus* *Puccinia recondita* *Septoria tritici* *Septoria nodorum*	max. 0.090	2	spring; beginning of infestation or first symptoms visible up to BBCH 69	35	1
		Fusarium spp.	max. 0.090	1	spring; beginning of infestation or first symptoms visible up to BBCH 69	35	1
	Barley (1)	*Erysiphe graminis* *Puccinia hordei* *Rynchosporium secalis* *Pyrenphora teres*	max. 0.090	2	spring; beginning of infestation or first symptoms visible up to BBCH 69	35	1

Authorized uses							Actual uses
Member State or Country	Crop	Harmful organism(s)	Dose rate per application (kg a.s./ha)	No. of applica-tion(s)	Timing of application(s), growth stages, season	PHI (days)	1: actual = authorized uses 2: actual uses deviate from authorized uses
Germany (continued)	Rye (1)	*Erysiphe graminis* *Puccinia recondita* *Rynchosporium secalis*	max. 0.090	2	spring; beginning of infestation or first symptoms visible up to BBCH 69	35	1
	Triticale (1)	*Septoria species*	max. 0.090	2	spring; beginning of infestation or first symptoms visible up to BBCH 69	35	1
	Oilseed rape (BRSNW)	Steadiness	max. 0.090	1	spring; BBCH 39-59	56	1
		Phoma lingam	max. 0.090	2	1st applic: beginning of infesta-tion or first symptoms visible up to ca. mid of October. 2nd applic: shortly before BBCH 59	56	1
		Scerotinia scerotiorum	max. 0.090	1	beginning of infestation up to BBCH 65	56	1
Ireland	Winter wheat (TRZAW)	*Septoria tritici* *Septoria nodorum* *Erysiphe graminis* *Puccinia striiformis* *Puccinia recondita* *Fusarium spp.* *Cladosporium spp.*	max. 0.090	3.0 L/ha (2)	spring; BBCH 11-71	PHI not specified (4)	1
	Winter / Spring barley (HORVW / HORVS)	*Erysiphe graminis* *Puccinia hordei* *Rhynchosporium secalis* *Pyrenophora teres*	max. 0.090	3.0 L/ha (2)	spring; BBCH 11-71	PHI not specified (4)	1

Authorized uses							Actual uses
Member State or Country	Crop	Harmful organism(s)	Dose rate per application (kg a.s./ha)	No. of applica-tion(s)	Timing of application(s), growth stages, season	PHI (days)	1: actual = authorized uses 2: actual uses deviate from authorized uses
United Kingdom	Winter wheat (TRZAW)	*Septoria tritici* *Erysiphe graminis* *Puccinia striiformis* *Puccinia recondita* *Fusarium spp.*	max. 0.090	3.0 L/ha (2)	Up to and including BBCH 71 (caryopsis watery ripe)	BBCH 71	1
	Winter / Spring barley (HORVW / HORVS)	*Erysiphe graminis* *Puccinia hordei* *Rhynchosporium secalis* *Pyrenophora teres*	max. 0.090	3.0 L/ha (2)	Up to and including BBCH 71 (caryopsis watery ripe)	BBCH 71	1
	Oilseed rape (BRSNW)	*Alternaria spp.* *Sclerotinia sclerotiorum* *Phoma lingam*	max. 0.072	2.4 L/ha (2)	BBCH 71 (10% of pods at final size)	PHI not specified (4)	1

n/a denotes not applicable
(1) Form, i.e. winter or spring not specified the registration certificate
(2) Maximum total dose per crop based on the BAS 555 00 F formulation containing 60 g a.s./L; replaces number of applications
(3) See application stage
(4) Lastest stage of application BBCH 71
(5) To be mixed with 750 g/ha chlorothalonil

LEVEL 2

Metconazole

Reasoned statement of the overall conclusions drawn by the Rapporteur Member State

2.1.1 Identity

All points (Annex IIA and IIIA) have been addressed and the submitted information is acceptable, although for certain issues some confirmatory data are required.

The active ingredient of Metconazole is a mixture of 4 diastereomers : CL 354801 ("cis-metconazole") is a mixture of S(OH), R and R(OH), S diastereomers, whereas CL 354802 ("trans-metconazole") is a mixture of S(OH), S and R(OH), R diastereomers.
The dossier was submitted to support technical grade active substance produced at two different toll manufacturers, resp. Ibaraki Kasei and Rallis India. Both toll manufacturers use the same manufacturing process and the technical specification proposed for the Ibaraki Kasei source is identical to the one proposed for the Rallis India source (min. purity : 940 g/kg sum of cis- and trans isomers, with cis-metconazole level not less than 800 g/kg and not more than 950 g/kg).
As far as the Ibaraki Kasei source is concerned, the proposed min. purity and impurity profile are confirmed by an acceptable GLP 5-batch analysis study. For the Rallis India source, the submitted analytical profile of batches also indicates compliance with the proposed technical specification. However, as the report in question lacks a formal GLP-compliance statement and Quality Assurance Unit declaration, it is considered that a confirmatory batch analysis study containing the full set of GLP statements is still required for this source. For the sake of completeness, this study should also address the 'impurity 18' content of the Rallis India batches, to enable verification of compliance with the proposed certified limit for this compound.

Metconazole technical is stated not to contain any components of toxicological, ecotoxicological or environmental significance; N-nitrosamines, although theoretically possible, have not been detected.
For the Ibaraki Kasei batches, aforementioned N-nitrosamine statement is supported by experimental data. However, as the report in question lacks a formal GLP-compliance statement and Quality Assurance Unit declaration and does not address the Rallis India batches, it is considered that a confirmatory study containing the full set of GLP statements and providing N-nitrosamine data for batches originating from both manufacturing sources is still required.

2.1.2 Physical and chemical properties

Metconazole (BAS 555 F), a fungicide belonging to the chemical family of triazoles, is an odourless white powdered solid with a melting point range of 100.0 to 108.4°C and a relative density at 20°C of 1.14. Its very low vapour pressure (2.1 x 10^{-8} Pa at 20°C) and Henry's law constant (2.21 x 10^{-7} $Pa.m^3.mol^{-1}$ at 20°C) indicate that Metconazole is very slightly volatile. Its pKa values of 11.38 and 1.08 indicate that no dissociation occurs in the environmentally relevant pH-range. Metconazole is moderately soluble in water (30.4 mg/L at 20°C, no effect of pH) and readily soluble in organic solvents. Its octanol/water partition coefficient (log P_{ow} = 3.85 at 20°C, no effect of pH) indicates a potential for bioaccumulation in the environment. Metconazole is hydrolytically stable under environmentally relevant conditions (pH 4 to 9), but is moderately (pH 5) to slightly (pH 7 and 9) degradable by direct photolysis in aqueous solution (DT_{50} = 36.3 d at 25°C and pH 7). The a.s. is not highly flammable, not self heating and exhibits no explosive or oxidizing properties.

CARAMBA 60 SL®, a 60 g/L soluble concentrate (SL), is a clear, colourless to slightly yellowish liquid with a fusel-like odour. The pH of its aqueous dilution is essentially neutral. It is not explosive, not oxidizing and has an auto-ignition temperature of 289°C. It has a flash point of 43°C and therefore is classified as flammable. CARAMBA 60 SL® may be used as a solo product, but it was also shown to exhibit physical and chemical compatibility when combined with various mixture partners of different formulation types.
Its technical properties indicate that no particular problems are to be expected in the field when it is used as recommended. Accelerated and long term storage stability tests indicate that CARAMBA 60 SL® will exhibit good chemical and physical stability under commercial storage conditions. A minimum shelf life of 3 years can be recommended in suitable packs (e.g. HDPE). Its low temperature stability is acceptable.

2.1.3 Details of uses and further information

Details of uses

Metconazole is intended to be used as foliar spray application against fungal diseases on wheat, barley, oats, rye, triticale and oilseed rape. Metconazole exists as two isomers (cis and trans); the fungicidal activity of the compound appears to be largely associated with the cis-isomer.

Details of intended uses supported by available data are summarized in Table 1.5.3-1 in Level 1.

Further information

Acceptable information has been provided for the active substance as manufactured (recommendations concerning handling, storage, transport or fire, procedures for destruction or decontamination and emergency measures in case of an accident) and for the plant protection product (packaging, cleaning procedures, recommendations concerning handling, storage, transport or fire, emergency measures in case of an accident and procedures for destruction or decontamination).

2.1.4 Classification and Labelling

METCONAZOLE

Hazard symbols:	Xn N	
Indications of danger:	Harmful Dangerous to the environment	
Risk phrases:	R 22	Harmful if swallowed
	R 63	Possible harm to the unborn child
	R 51/53	Toxic to aquatic organisms May cause long-term adverse effects in the aquatic environment

Reasons for classification

For justification of R22 see B 6.2.1	Based upon the acute oral toxicity in both the rat (LD_{50}=595-727) and the mouse (LD_{50}=410-718)
For justification of R63 see B.6.6.2.2	Based upon the increased incidence of hydrocephaly in the rabbit developmental study at 10 mg/kg bw/d, in the absence of maternal toxicity
For justification of R51/53 see B.9.5	Given the toxicity for *Salmo gairdneri* (LC_{50} = 2.1 mg a.s./l) , *Daphnia magna* (EC_{50} = 4.2 mg a.s./l), *Selenastrum capricornutum* (EC_{50} = 1.7 mg a.s./l) and *Chironomus riparius* (NOEC = 2.12 mg a.s./l). The active substance is not readily biodegradable (2 - 5% Theoretical CO_2 being evolved in 28 days).

CARAMBA 60 SL®

Hazard symbols:	Xn N	
Indications of danger:	Flammable Harmful Dangerous to the environment	
Risk phrases:	R10	Flammable
	R36/37/38	Irritating to eyes, to respiratory system and skin
	R43	May cause sensitization by skin contact
	R63	Possible risk of harm to the unborn child (Dev. Cat 3)
	R65	Harmful: may cause lung damage if swallowed
	R51/53	Toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment

Safety Phrases: S2-24/25-36/37-60-61-62

Reasons for classification

For justification of R10 see B.2.2	Based upon the flash point determination (B.2.2.5) = 43°C.

For justification of R36/37/38 see B.6.11	Based upon the skin irritancy study (B.6.11.4), the eye irritancy study (B.6.11.5), the acute inhalation study (B.6.11.3) and carry-over of the labelling of a solvent, present at 26% w:w (>20%).
For justification of R63 see B.6.6.2.2	Based upon carry-over of the labelling of the a.s. (teratogenic effects in rabbit developmental study), present at 7% w:w (>5%).
For justification of R51/53 see B.9.2.11	Given the toxicity for *Onchorhynchus mykiss* (LC_{50} = 15 mg/l) , *Daphnia magna* (EC_{50} = 0.365 mg/l), *Selenastrum capricornutum* (EC_{50} = 8.38 mg./l). The active substance is not readily biodegradable.

2.2 Methods of analysis

2.2.1 Analytical methods for analysis of the active substance as manufactured

Acceptable analytical methodology (HRGC-FID) is available for the determination of active substance and significant impurities in the technical material, although impurity method M-2479 requires additional validation for some impurities (precision for impurities 7, 11-12 and 14; full validation for impurities 3 and 13).
New validation study is underway to provide the outstanding data (study protocol submitted; final report announced for end of February 2004).

No CIPAC methods exist for this a.s..

2.2.2 Analytical methods for formulation analysis

Acceptable analytical methodology (HPLC-UV) is available for the determination of the active substance Metconazole in the formulation (SL).

No CIPAC methods exist for this a.s..

2.2.3 Analytical methods for residue analysis

Acceptable analytical methodology is available for the determination of residues in food/feed of plant and animal origin, soil, water and air.

Food/feed

Fully validated multi-residue method DFG-S19 (GC-NPD) allows determination of all compounds included in the proposed residue definition (i.e. Metconazole, as sum of cis- and trans-isomer) in ***matrices of plant origin*** (dry crops, water containing crops, acidic crops and crops with high fat content) with a LOQ of 0.01 mg/kg for each isomer and thus enables enforcement of the relevant residue limits (proposed MRL's = 0.05 mg/kg (wheat, rye and triticale grain), 0.10 mg/kg (barley and oat grain), 0.10 mg/kg (rape seed)). Considering the interferences at the retention time of cis-metconazole detected in GC-NPD chromatograms of oilseed rape control samples, analysis by GC-MSD (as proposed for confirmation) is advised for crops with high fat content.
The other submitted GC-NPD methods (FAMS 050-01, FAMS 059-01, FAMS 059-02 and FAMS 057-01) also allow determination of Metconazole residues in plant matrices (resp. cereal grain and straw, oil seed rape and rape oil, and sugarbeet) with a LOQ of 0.01 mg/kg for each isomer (0.03 mg/kg for cereal straw), but as these methods were not or insufficiently validated by an independent laboratory, they can not be recommended for enforcement of MRL's.
A GC-MSD method is available for determination of metabolite Triazolylalanine (as derivative BEB 237) in wheat grain with a LOQ of 0.1 mg/kg. Although ILV was not addressed, which implies that the method is not acceptable for enforcement purposes, further data are not considered necessary since Triazolylalanine is not included in the proposed residue definition.

Multi-residue method DFG-S19 (GC-NPD) allows determination of Metconazole as its cis-and trans-isomer in ***matrices of animal origin*** with a LOQ of 0.01 mg/kg for each isomer. Considering the interferences at the retention time of cis-metconazole detected in GC-NPD chromatograms of bovine fat control samples, analysis by GC-MSD (as proposed for confirmation) is advised for fat.
Being fully validated, the method can be considered for enforcement in milk, meat, eggs and fat, although it is currently not deemed necessary to propose MRL's for food of animal origin.

Soil, water, air

Fully validated methods FAMS 055-02 and DFG S19 (GC-NPD) both allow determination of all compounds included in the proposed residue definition (i.e. Metconazole, as sum of cis- and trans-isomer) in ***soil*** with a LOQ of 0.01 mg/kg for each isomer and thus enable enforcement of the relevant residue limit (0.05 mg/kg = general upper limit).

Fully validated method FAMS 058-01 (GC-NPD) allows determination of all compounds included in the proposed residue definition (i.e. Metconazole, as sum of cis- and trans-isomer) in ***water*** with a LOQ of 0.05 µg/L for each isomer and thus enables enforcement of the relevant residue limits for drinking water (0.1 µg/L =

EU-drinking water limit) and for surface water (1.38 µg/L = NOEC for *Daphnia magna,* flow through).

Fully validated method FAMS 067-01 (GC-NPD) allows determination of Metconazole residues as its cis- and trans-isomer in ***air*** with a LOQ of 0.28 µg/m^3 for each isomer and thus enables enforcement of the relevant residue limit (C = 3 µg/m^3, based on proposed $AOEL_{syst}$ of 0.01 mg/kg b.w./d).

Body fluids

No methods are required for body fluids since the active substance is not classified as toxic or highly toxic.

2.3 Impact on human and animal health

2.3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to their transformation products

2.3.1.1 Toxicokinetics and metabolism

Rat studies:

Absorption and excretion.

Both the fate of Metconazole WL148271 (cis/trans, 85/15) and WL136184, radiolabelled with ^{14}C at either the cyclopentyl- or the triazole-moiety, were investigated in the Fisher F344 rat. In a bile-cannulation study of Metconazole cis, administered at a single low dose (2 mg/kg bw), it was observed that, after 48h, up to 83% of radioactivity was eliminated in the bile, while up to 12% had been eliminated renally, and ≤ 0.3% of dose was excreted via the feces. When total recovery of radioactivity was calculated based on radioactive levels in bile, urine, GIT, carcass, and cage washes, it appeared that 95-97% was absorbed after 48h. The absorption was rapid, since about 50-69% of dose was eliminated 6h after dosing.

When rats were treated at a single low dose of ^{14}C-Metconazole (cis/trans) without bile cannulation, about 59-72% was voided via the feces, and 14-24% was eliminated renally after 48h. By 72h, about 93-96% of dose was excreted, thus confirming the data of the former study. It was also observed that the contribution of renal elimination was slightly more important in the ♀ than in the ♂.

This elimination pattern at the low dose was not essentially different from that observed when the compound was administered during 14 days, or when rats were treated at a high dose (200 mg/kg), although elimination was delayed by approximately 24h and 48h respectively.

Distribution.

At low dosage, low levels of radioactivity were recovered into the blood, the plasma and the organs after 72h, due to the rapid elimination. The radioactivity was widely distributed, but adrenals, gastro-intestinal tract, and liver tended to concentrate the compound, as 2-3 ppm, 0.6-0.8 ppm, and 0.2-1.6 ppm were recovered respectively, in contrast to levels found in the blood (0.02-0.03 ppm). This distribution pattern was nearly replicated in the study with rats receiving a repeated dosage, and approximately the same radioactive residue levels were measured in the cited target organs (1.4-2.3 ppm, 0.5 ppm and 0.1-0.9 ppm in adrenals, GIT and liver respectively). For rats dosed at 164 mg/kg bw, the residue levels in most organs or tissues (at 120h) were 100 times those found at the low dose (2 mg/kg bw), except for the liver, the testes and the adrenal glands, where the high-dose: low-dose proportions were 2(♀)-31(♂), 6 and 1.5 respectively. This hypo-proportionality indicated that a saturable mechanism might be present in these tissues.

Metabolism

Rat metabolites were recovered in the excreta and liver from rats treated at a single or repeated low dose, and in the excreta, liver and adrenals from rats treated at a high dose. Moreover, the metabolites of the isomer mix and the cis-isomer were analysed at a high dose, thus permitting a comparison of the metabolic fate of both compounds.

First, as was expected, the major metabolites were recovered in the feces. It was observed that the chromatographic profiles of radioactive components in fecal extracts of rats treated with Metconazole, labelled at either side of the molecule, were very similar, irrespective of dosage or dose-rate.

Second, it was observed that, although the relative proportions of metabolites might vary with time, they were qualitatively comparable, and could thus be pooled for identification. Further, no significant difference was generally observed between sexes. A notable exception was the detection of metabolite M20 (1,2,4-triazole) in

the urine of ♀ rats, recovered after administration of [triazole-^{14}C]-Metconazole at the high dose. Further, metabolite M12 (a carboxylated derivative) was retrieved at a relative high proportion in the urine of mainly the ♀ in all metabolism studies.
Third, at the single low dose (2 mg/kg bw), a polar liver metabolite was characterised as a sulphate-conjugate of metabolite M1 (mono-hydroxylated derivative). In he high-dose study (164 mg/kg bw), the exact structure of the adrenals main metabolite remained unidentified.
Finally, it was observed that the parent compound was extensively metabolised as ≤ 2% of dose was recovered in the feces. The metabolic breakdown was not affected by isomer ratio, sex, dose or pre-treatment.

It was proposed that the main rat metabolites of Metconazole were :

- monohydroxy-metabolites, as a result of oxidation of benzylic methylene groups, or the methyl, methylene or methine groups of the cyclopentane ring (such as M1 and M21)
- hydroxyphenyl-metabolites (M15 and M19)
- carboxy-metabolites (M12 and M13)
- multi hydroxy metabolites (M18)
- mixed-function metabolites
- various sulphate conjugates of the abovementioned metabolites (M22)

Farm animal and plant studies:
Most metabolites recovered in both farm animal (goat) or plant (wheat, oilseed rape) metabolism were identical or similar to those found in the rat. The major metabolites of plants (triazolealanine and triazole acetic acid) were not of toxicological concern.

2.3.1.2 Dermal absorption

It was observed that, at 72h, the excretion of ^{14}C-Metconazole, formulated as a 60 g/l soluble liquid, was low, but has not come to an end. Some radioactivity was still present in the site of application, and could present a source of systemic exposition. An absorption rate of 3% was proposed for the concentrated product.
It was noted that the diluted product (representative tank-mix) was not tested. According to the current guidelines, the absorption of the in-use field concentration should be considered 100%.

2.3.1.3 Acute toxicity, local irritation and skin sensitisation

Metconazole is of moderate toxicity when administered orally to the rat. Based upon the LD_{50}-value, it appeared that the isomere-mix (cis/trans 85:15) was more toxic (by about a factor 2) than the cis (95:5) isomer. It was not known whether the difference was due to the presence of the trans-isomer in the isomer mixture. It was also noted that the ♀ were slightly more susceptible than the ♂.
The observed clinical signs were rather consistent in the studies with both compounds, occurred rapidly (within 4h) after dosing, and included non-specific signs such as unkempt appearance, hunched posture and diarrhea, but other signs such as abasia, ataxia, chromodacryorrhea, salivation and lacrimation were also observed. The clinical signs were resolved by the end of the observation period.
Metconazole did not provoke systemic toxicity to the rats when applied dermally or administered via inhalation. The compound was without local effects on the skin, and induced slight eye irritation in the rabbit, which was resolved within 8d after application.
Both patch-application and intradermal sensitisation tests demonstrated the absence of sensitisation potential.
Based upon the acute oral study with Metconazole, the compound is considered harmful by oral uptake, and should be classified accordingly (Xn;R22).
A summary of acute toxicity studies is given in tables 2.3.1.3-1a and b

Table 2.3.1.3-1a Summary of acute toxicity including irritancy and skin sensitisation of Metconazole cis/trans

Type of test	LD_{50} (mg/kg b.w.)	purity (%) batch n°	Classification	Reference
Rat, oral	♂: 727 ♀: 595	95.3% 89-01	**Xn; R22**	Gardner, 1990a
Mouse, oral	♂: 718 ♀: 410	95.3% 89-01	**Xn; R22**	Gardner, 1990a
Rat, dermal	>2000	95.3% 89-01	-	Gardner, 1990a
Rabbit, dermal	>2000	95.3% 89-01	-	Gardner, 1990a
Rat, 4h inhalation	>5.588 mg/l	95.3% 89-01	-	Collins, 1990
Rabbit, skin irritation	not irritant	95.3% 89-01	-	Gardner, 1990b
Rabbit, eye irritation	not irritant	95.3% 89-01	-	Gardner, 1990b
Guinea pig, skin sensitisation (M&K)	not sensitiser	97.9% AC 9339-114	-	Glaza, 1995

Table 2.3.1.3-1b Summary of acute toxicity including irritancy and skin sensitisation of Metconazole 95% cis

Type of test	LD_{50} (mg/kg b.w.)	purity (%) batch n°	Classification	Reference
Rat, oral	♂: 1627 ♀: 1312	95.2% 12, F900250	**Xn ; R22**	Gardner, 1991
Rat, dermal	>2000	95.2% 12, F900250	-	Gardner, 1991
Rabbit, skin irritation	not irritant	95.2% 12, F900250	-	Gardner, 1991
Rabbit, eye irritation	not irritant	95.2% 12, F900250	-	Gardner, 1991
Guinea pig, skin sensitisation (Buehler)	not sensitiser	95.2% 12, F900250	-	Gardner, 1991

2.3.1.4 Short-term toxicity studies

Both the isomer mix as the cis-isomer of Metconazole was tested in subacute (rat, mouse, dog) and subchronic assays (rat, dog).
In the 28 days-studies on Metconazole cis/trans and Metconazole cis in the rat, similar toxicological endpoints were detected at the top-dose, and included decrease in feed consumption and bodyweight, hematological disorders, and clinicochemical modifications such as increased transaminase activities (AST, ALT), gamma-glutamyl transpeptidase and alkaline phosphatase activity, the latter indicating a hepatotoxic effect. In a separate mechanistic study, it was also demonstrated that cytochrome P450-dependent enzymes were induced in the rat liver at doses corresponding to the lowest observed adverse-effect levels (1000 ppm, about 90 mg/kg bw/d). The effect was corroborated by organ gravimetric findings (liver weight increase) and by histopathology (centrilobular hypertrophy) at 1000 ppm and above. In addition, subtle signs of liver necrosis, and centrilobular vacuolation was observed, the latter indicating fatty degeneration.
At the top dose of both Metconazole cis/trans (3000 ppm) and Metconazole cis (10000 ppm), the decreased number of RBC, corpuscular volume and mean cellular haemoglobin concentrations (associated with increased reticulocyte counts with the cis-isomer) were indicative of slight microcytic hypochromic anemia. In addition, local irritative or inflammatory effects in the forestomach were present in most animals.

Administration of Metconazole during 90 days in the rat revealed the same toxicological endpoints as what was seen in the subacute studies. In short, mild anemia, increased transaminase, γ-GT and AP activities, increased liver and spleen weights, necropsy findings and histological lesions indicating hepatotoxicity (fatty vacuolation) and enzyme induction (centrilobular hypertrophy), signs of haemosiderosis in both liver and spleen (pigment deposit) and adrenal cortex vacuolation were the most relevant findings. As in the subacute studies, and as was anticipated from the LD_{50}-values, the isomeric mix was slightly more toxic than the cis-isomer. Indeed, based upon hepatocyte vacuolation, the NOAEL was 100 ppm (6.4 mg/kg bw/d) for Metconazole cis/trans, and 450 ppm (28.8 mg/kg bw/d) for Metconazole cis/trans. For both compounds, adrenals, liver and spleen were detected as target organs. In the mouse, both biochemical (additional study) and toxicological subacute effects were similar to those found in the rat.

In the dog, the subchronic toxicity profile was comparable with that observed in rodents, with liver and spleen effects at the top-dose in both sexes. However, based on the decreased feed consumption and bodyweight effects at 600 ppm (24.3 mg/kg bw/d), the NOAEL in the females was as low as 60 ppm, corresponding to 2.6 mg/kg bw/d. In the one-year feeding study, the NOAEL was set on basis of the increased alkaline phosphatase activity in both sexes at 300 ppm, or 10 mg/kg bw/d. Since in the 1 year-study, no effects were observed up to 300 ppm (also at the 90d sampling time), and this dose-level was higher than the NOAEL in the 90d-study, the 90d NOAEL was not taken into account. Of note was the emergence of lens degeneration in top-dose females in both 90d and 1 yr-feeding study (3000 ppm, 114 mg/kg bw/d). The cataractogenic potential of Metconazole was only apparent at the highest dose, after prolonged administration, and was related to the interference with steroid biosynthesis of the substance.

Table 2.3.1.4-1 Summary of short-term toxicity studies of Metconazole

study, species, doses (ppm)	NOAEL mg/kg bw/d *(ppm)*	LOAEL mg/kg bw/d *(ppm)*	critical effects	code, cis:trans (%), purity (%), batch nbr	references
28d, rat **30-100-1000-3000**	9.1 *(100)*	90.5 *(1000)*	↓bw, ↓MCHC, ↑γ-GT, ↑liver w, ↑liver pallor/enlargement, ↑hepatocellular vacuolation/hypertrophy	WL148172, 85:15 94.5 88-10	Esdaille, 1990
28d, rat **30-100-300-1000-10000**	27.3 *(300)*	89.3 *(1000)*	↓bw, ↓feed cons, ↑liver weight, ↑hepatocellular vacuolation	WL136184, cis, 99:1 98 ST87-181	Esdaille, 1991a
90d, mouse **30-300-2000**	4.6 *(30)*	50.5 *(300)*	↓cholesterol, ↑AST/ALT, ↑liver and spleen w, ↑hepatocellular vacuolation/hypertrophy	WL148172, 79.8:15.5 95.3 89-01	Clay, 1991
90d, rat **30-100-300-1000-3000**	6.4 *(100)*	19.2 *(300)*	↑hepatocellular vacuolation	WL148172, 81:19 94.5 89-01	Esdaille, 1991b
90d, rat **50-150-450-1350-4050**	28.8 *(450)*	88.6 *(1350)*	↓feed cons, ↓bw, ↓RBC parameters, ↑liver and spleen w, ↑AST/ALT, ↑γ-GT, ↑hepatocellular vacuolation	WL136184, cis, 99:1 98 88-05	Fokkema, 1992
90d,dog **60-600-6000**	2.6 *(60)*	24.5 *(600)*	↓feed cons, ↓bw gain	WL148172, 85:15 95.3 89-01	Pickersgill, 1991b
1 year, dog **30-300-1000-3000**	10 *(300)*	36.5 *(1000)*	↑alkaline phosphatase	WL148172, 85:15 95.3 89-01	Clay, 1992

2.3.1.5 Genotoxicity studies

The genotoxic potential of Metconazole cis/trans: 80/15 was investigated *in-vitro* in the Ames test and in a chromosomal aberration assay in CHO cells, and *in-vivo* in the mouse bone marrow micronucleus test and in an unscheduled DNA synthesis in rat liver cells. The genotoxic potential of Metconazole 95% cis was also investigated in a battery of tests both *in-vitro* and *in-vivo*. All the tests were negative with the exception of the chromosomal aberration assay performed with Metconazole cis/trans: 80/15, where structural chromosomal aberrations were induced in the presence of S9-mix, in both main and repeat experiments.
Overall, both Metconazole cis/trans: 80/15 and Metconazole 95% cis are considered not genotoxic.
A summary of genotoxicity studies is given in table 2.3.1.5-1a and b

Table 2.3.1.5-1a Summary of genotoxicity studies of Metconazole cis:trans

Type of test Cell/test species	Purity (%) batch n°	Conditions: doses, treatment duration	Results	References
In vitro genotoxicity tests				
Reverse mutation *S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) and *E.coli* (WP2 uvrA)	95.3% cis/trans: 79.8/15.5, 89-01	plate incorporation, ± S9 mix, solvent: acetone, up to 5000 µg/plate	negative	Brooks, 1990
Chromosome aberration assay in CHO-K1 cells	95.3% cis/trans:	solvent: acetone –S9: 24h, 1.56-12.5 µg/ml, 48h, 0.625-5 µg/ml	–S9 mix: negative + S9 mix:	Brooks, 1991b

Type of test Cell/test species	Purity (%) batch n°	Conditions: doses, treatment duration	Results	References
	79.8/15.5, 89-01	+S9: 3h/24h, 6.25-50 µg/ml, 3h/48h, 4.375-35 µg/ml	24h, **positive** at 50 µg/ml 48h: negative	
In vivo genotoxicity tests				
Bone marrow, micronucleus assay, CD-1 mice	97.9% AC 9339-114	Oral, in 0.5% CMC 400, 1000, 2000 mg/kg bw sacrifice: 24h, 48h, 72h	negative	Xu, 1995
UDS, rat (SD) hepatocytes	97.9% AC 9339-114	Oral, in 0.5% CMC 400, 1000, 2000 mg/kg bw treatment: 4h and 16h	negative	Pant, 1995

Table 2.3.1.5-1b Summary of genotoxicity studies of Metconazole 95% cis

Type of test Cell/test species	Purity (%) batch n°	Conditions: doses, treatment duration	Results	References
In vitro genotoxicity tests				
Reverse mutation *S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) and *E.coli* (WP2 uvrA)	95.2% B. n°12	plate incorporation assay, ±S9 mix, solvent: acetone doses up to 5000 µg/plate	negative	Brooks, 1991a
Gene mutation assay in mouse lymphoma cells L5478Y/TK$^{+/-}$	95.2% B. n°12	solvent: DMSO ?1st exp.: ± S9 mix: 12.5-75 µg/ml, ?2nd exp.: –S9 mix: 20-70 µg/ml, +S9 mix: 12.5-90 µg/ml	negative	Clements, 1991
Chromosome aberration assay in human lymphocytes	95.2% B. n°12	Solvent: acetone –S9 mix: ?3h/24h, 93.75, 375, 750 µg/ml, ?24h/24h, 5.86, 23.44, 46.88, 93.75 µg/ml ?48h/48h, 5.86, 11.72, 23.44, 46.88, µg/ml +S9 mix: 3h/24h, 93.75, 375, 750 µg/ml,	negative	Brooks, 1991c
In vivo genotoxicity tests				
Bone marrow, micronucleus assay, CD-1 mice	95.2% B. n°12	Oral, in 0.5% CMC 2 doses/day: 75, 150, 300 mg/kg bw sacrifice: 24h, 48h after 2nd dosing	negative	Marshall, 1991
UDS, rat (SD) hepatocytes	95.2% ST91/016	Oral, in 0.5% CMC 443, 1400 mg/kg bw treatment: 12-13h, 2-3h	negative	Dean, 1991

2.3.1.6 Long-term oral toxicity and carcinogenicity

The administration of Metconazole cis/trans (85:15) during 2 years to Fisher F344 rats at a dietary dose of 1000 ppm (45-55 mg/kg bw/d) resulted in a marginal (-5%) decrease in body weight at termination, and a slight increase in adrenal gland, liver and spleen weights. In the liver, severe midzonal or centrilobular vacuolation, indicating fatty degeneration (in line with observed clinicochemical findings such as total cholesterol and triglyceride depletions at intermediate sampling times), and occasionally inflammatory or necrotic changes were reported. The presence of eosinophilic and clear-cell foci at the top-dose was possibly a reflexion of proliferative changes, although no neoplasms were observed. The increased incidence of hepatocytes with pigment deposit might be indicative of slight haemosiderosis, as subtle haematological disturbances were noted, and this finding was also reported in earlier studies. The observed increase in centrilobular hypertrophy had also been reported in

the subchronic feeding study at the same dose-level, and was associated with the induction of CYP450-dependent metabolic enzymes.
In the spleen, the increased incidence of histiocytic foci (also observed in the subchronic studies) was also in line with the described haematological effects. Of note was the slightly increased incidence of adrenal cortical vacuolation. Finally, the administration of Metconazole was associated with local irritation effects in the forestomach. As the liver cell vacuolation and hypertrophy, adrenal vacuolation and the increased liver and spleen weights had been observed in either the chronic toxicity or the carcinogenicity study at 300 ppm and 1000 ppm, the NOAEL was determined on this base at 100 ppm, corresponding to 4.3 mg/kg bw/d. As there was no evidence of a treatment-related induction of tumours, the compound was not considered carcinogenic in the rat.

In the mouse, similar toxicological endpoints as in the rat were reported. At 300 ppm and above, slight body weight and body weight gain decreases, decreased cholesterol and triglyceride level, indicating interference with lipid metabolism, and increased liver weights were observed. Contrarily to rats, the transaminase activities were increased after 92 weeks of treatment. As in rats, liver cells showed vacuolation, hypertrophy, and lesions associated with necrotic degenerative changes, and at the top-dose, biliary/oval cell or multifocal hyperplasia were additionally described. Adrenals showed corticomedullary pigmentation. In contrast to rats, mice exhibited atrophic spleens.
As at 300 ppm (♀) and above (♂,♀), the combined incidence of adenoma and carcinoma was statistically significantly increased, it was considered that the compound was carcinogenic toward mice. Therefore, 30 ppm, corresponding to 4.4 mg/kg bw/d, was established as both a chronic toxicity and a carcinogenicity NOAEL.
Globally, as the tumours only appeared in the mice and not in the rat, and their emergence was explained by a Phenobarbital-like mechanism, and in the absence of genotoxic potential, it was considered that the compound was unlikely to be classified as a carcinogenic substance.

A summary of log-term toxicity and carcinogenicity studies is given in table 2.3.1.6-1

Table 2.3.1.6-1 Summary of long term toxicity and carcinogenicity studies of Metconazole

Study, species, doses (ppm)	**NOAEL mg/kg bw/d *(ppm)***	**LOAEL mg/kg bw/d *(ppm)***	**Critical effects**	**cis/trans (%) purity (%), batch n°**	**Refs**
2y, p.o., rat 10-100-300-1000 ***toxicity:***	4.3 *(100)*	13.1 *(300)*	↑liver / spleen weight, ↑hepatocellular vacuolation / hypertrophy	79.8:15.5 95.3 89-01	Taupin, 1992a
2y, p.o., rat 100-300-1000 ***toxicity:*** ***carcinogenicity:***	4.6 *(100)* 46.5 *(1000)*	13.8 *(300)*	↑adrenal cortex vacuolation, ↑hepatocellular vacuolation / hypertrophy	79.8:15.5 95.3 89-01	Taupin, 1992b
2y, p.o., mouse 30-300-1000 ***toxicity:*** ***carcinogenicity:***	4.4 *(30)* 4.4 *(30)*	43.6 *(300)* 43.6 *(300)*	***tox:*** ↓cholesterol/ triglycerides, ↑AST/ALT, ↑liver w, ↑adrenal pigment, ↑liver vacuolation/ hypertrophy/necrosis,↑spleen atrophy ***carc:*** ↑adenoma/carcinoma	79.8:15.5 95.3 89-01	Clay, 1992a

2.3.1.7 Reproductive and development toxicity

The 2-generation reproduction study was conducted in rats with the Metconazole cis-isomer at dietary concentrations of 0, 2, 8, 32 and 48 mg/kg bw/d. No effects on rats fertility were observed. The NOAEL for parental toxicity was 8 mg/kg bw/d based on the increase in ovarian weights observed at 32 mg/kg bw/d in F_1 females. The NOAEL for reproduction toxicity was 8 mg/kg bw/d, based on the increase of gestation length in F_1 dams, decrease in post-implantation survival and the reduced litter size in F_2 pups at 32 mg/kg bw/d. The NOAEL for offspring toxicity was 8 mg/kg bw/d based on the reduced pup weight gain in F_1 seen at 32 mg/kg bw/d.
Based on the absence of effect on fertility in the rat 2-generation study (only modification of fertility parameters at maternotoxic doses), no classification for fertility was proposed.

Developmental toxicity studies have been conducted in rats and rabbits with both the cis/trans mixture and the cis-isomer.

In the rat, Metconazole cis/trans and Metconazole cis (both compounds attaining purities of 94-95%) provoked fetal and developmental toxicity at maternotoxic doses. The toxicity of both compounds towards dams (decreased feed intake, bw gain), fetuses (postimplantation loss, decreased fetal weights and litter weights/size) at the top-dose was similar. The developmental NOAEL of the cis/trans isomer (12 mg/kg bw/d) was established upon the induction of ossification retardations and an increased incidence of lumbar/cervical ribs at 30 mg/kg bw/d. Notable was also the slight increase of hydrocephaly at the highest dose with Metconazole cis/trans. The developmental NOAEL of the cis-isomer (6 mg/kg bw/d) was determined on the increased incidence of bilateral hydroureter at 24 mg/kg bw/d.

In the rabbit, early studies on cis/trans and cis isomers at 94-95% purity, indicated the emergence of various malformations. However, except for hydrocephaly, and to a lesser extent for limb defects, it appeared that most findings occurred without dose-effect relationship, or were single incidences. Moreover, some effects were not replicated in additional studies. Whereas the malformations, occurring in singularity were sometimes within published historical controls, in-house data were not submitted, complicating a proper evaluation of observed events.
The occurrence of spurious malformations, even at low doses or in the controls, without expected findings at higher doses were interpreted by the notifier as an indication of the high spontaneous rate of malformation in the animals of this source (Intervet Ltd., UK), although this should then have been reflected in the historical control database. It was also suggested that these animals were of suboptimal health, as indicated by the high variability in pregnancy rate, maternal mortality, and abortion, but in the absence of proper reference data, and considering that abovementioned flaws were certainly not present in all studies, the argument was not convincing.

Taking into account malformations which appeared more consistently and/or exhibited a proper dose-effect relationship (as hydrocephaly), it was proposed by the rapporteur not to discard these studies, but to use them for the determination of developmental NOAEL, which was 4 mg/kg bw/d. These effects were observed at doses which were mostly maternotoxic but not always. Based on these developmental effects, and also on the fetal toxicity and maternal toxicity (both ranging from 4-10 mg/kg bw/d), it was concluded that rabbit was the most sensitive species (in the rat, maternal and fetal toxicity NOAELs were 24-30 mg/kg bw/d).
It was also considered that the effects in rabbits observed at the lower doses were probably irrelevant.

A new study, conducted in the NZW rabbit (from a different supplier) and with Metconazole cis/trans of a higher purity (98%), revealed no adverse effects towards developmental parameters, and developmental NOAEL was established at the top-dose (40 mg/kg bw/d).

According to the notifier, the purity, as well as the impurity profile of the batch used for the newest rabbit developmental study, was comparable with the specification of Metconazole cis/trans technical. The notifier made a statement, declaring that the batch ST 91/016 (Metconazole 95% cis, used in the rabbit study) was not representative of the current manufacturing process, as it contained analytes that do not met the current Metconazole specifications. Likewise, it was argued that Metconazole cis/trans with batch number B89-01 (old study) was of a lower purity that batch AC10575-61 (new study). However, it could not be determined with certainty whether the observed effects with the old batch were provoked by one or more impurities, or by the mother compound itself. Therefore, it was proposed by RMS to consider the effects seen with the older batch as relevant for the assessment of developmental toxicity.

In summary, both compounds were embryo- and fetotoxic at doses also producing maternal toxicity in rat developmental toxicity studies.
In the new rabbit study performed, using a high purity batch of Metconazole 85/15 cis/trans mixture and animals from a different source, increased resorptions, reduced litter size and fetal weight occurred at 40 mg/kg bw/d, a dose associated with reductions in maternal bodyweight gain. There was no evidence of teratogenicity.
In the old rabbit studies, malformations were observed at doses which were or were not maternotoxic. For additional information (see B.5.8.2), an investigative study on the effects of Metconazole isomers on rat embryos *in-vitro* was conducted (Bowden, 1991). It appeared that both the cis/trans mix and the cis isomer induced embryologic morphological abnormalities at doses at or lower than those inducing developmental retardation.

Metconazole is a fungicide belonging to the triazole family, which show to a certain extent a typical pattern for developmental toxicity in laboratory animals. They usually are embryotoxic, cause retarded development (decreased fetal weight and/or delayed ossification) and also induce variations and malformations.
Overall, the weight of evidence is that technical Metconazole is embryo/fetotoxic in rats and rabbits at doses

associated with maternal toxicity and has shown some evidence of teratogenic potential in rabbits at doses producing no to severe maternal toxicity. Therefore, classification as Repro. Cat. 3 (Xn; R63) was proposed.
A summary of reproduction and developmental toxicity studies is given in tables 2.3.1.7-1a and b

Table 2.3.1.7-1a Summary of reproductive and development studies of Metconazole WL148271 (cis/trans, 80/15) and Metconazole WL136184 (95% cis)

Type of test Doses (mg/kg/d)	Code Cis:trans Purity (%), batch n°	NOAEL mg/kg bw/d	LOAEL mg/kg bw/d	Critical effects	References
2 G, oral, rat 2, 8, 32, 48	**WL136184** **95% cis** 95.2% B 12	Parental: 8 Filial: 8 Repro: 8	Parental : 32 Filial: 32 Repro: 32	↑ovarian w (F_1) ↓bw gain (F_1 pups), ↓post-implantation survival (F_2) ↑gestation length, ↓post-implantation survival	Willoughby, 1992
Terato oral rat, d6-15 12, 30, 75 [PS: 37.5, 75, 150, 300]	**WL148271** **cis/trans: 80/15** 95.3% (79.8/15.5) B 89-01	Maternal: 12 Fetal: 30 Developmental: 12	Maternal: 30 Fetal: 75 Developmental: 30	↓ bw gain ↑embryonic mortality, ↑post-implantation loss, ↓litter/fetal weight ↑lumbar/cervical ribs (75: ↑hydrocephaly)	Masters, 1991a
Terato oral rat, d6-15 6, 24, 60 [PS, 1°: 6, 12, 24, 48; 2°: 6, 60,80]	**WL136184** **95% cis** 95.2% B 12	Maternal: 24 Fetal:24 Developmental: 6	Maternal: 60 Fetal: 60 Developmental: 24	↑clinical signs, ↑water-, ↓feed cons., ↓bw gain ↑resorptions, ↑post-implantation loss, ↓fetal weight ↑bilateral hydroureter at necropsy	Willoughby, 1992a
Terato, oral, rabbit, d6-28 5, 10, 20, 40 [PS: 1, 5, 10, 20, 40]	**WL148271** **cis/ trans: 80/15** 98.3% AC10575-61	Maternal: 10 Fetal: 10 Developmental: 40	Maternal: 20 Fetal: 20 -	↓bw gain ↑resorptions	Hoberman, 1997

PS: preliminary study

Table 2.3.1.7-1b Summary of reproductive and development studies of Metconazole WL148271 (cis/trans, 80/15) and Metconazole WL136184 (95% cis)

Type of test Doses (mg/kg/d)	Code Cis:trans Purity (%), batch n°	NOAEL mg/kg bw/d	LOAEL mg/kg bw/d	Critical effects	Refs
PS terato, oral, rabbit cis ; (-)cis: 10, 28, 80 trans: 10, 20, 40	**?WL136184 cis** 96.9% (B3454/078 ST89/324) **?WL161053 (-) cis** 91% (B 3454/081 ST89/323) **?WL153996 trans** 97.0% (B 88-08 ST89/312)	Maternal •cis, (-)cis: ≤ 10 •trans: 80 Fetal: •cis: 10 •(-)cis: 28 •trans: 80	Maternal: •cis, (-)cis: 10 Fetal : •cis ≥ 28, (-)cis: 80 •cis, (-)cis: 80 ↓cis: 80	↑clinical signs ↑post-implantation loss, ↓litter size, ↓litter weight ↑fetal deaths ↓fetal weight trans: no treatment-related effects	Masters, 1990
Terato, oral, rabbit, d7-19 *Main:* 4, 10, 25, 62.5 *Additional:* 2, 4, 10 [PS: 10, 30, 90]	**WL148271 cis/ trans: 80/15** 95.3% (83.7/16.3) B 89-01 ST 89/088	*Main:* Maternal: 10 Fetal: 4 Developmental: 10 *Additional:* Maternal / fetal: 10 Developmental: 4	Maternal: 25 Fetal: 10 Developmental: 25 --- Developmental: 10	↓feed cons., ↓bw gain ↑embryonic deaths, ↑post-implantation loss ↑hydrocephaly, ↑amelia No evidence of systemic maternal and fetal toxicity ↑ hydro/cebocephaly	Masters, 1991b
Terato, oral, rabbit, d7-19 2, 4, 10, 40 [PS: 2, 4, 10, 25, 40]	**WL136184 95% cis** 94.2% B 12 ST 91/016	Maternal: 4 Fetal: 10 Developmental: 4	Maternal: 10 Fetal: 40 Developmental: 10	↓feed cons., ↓bw gain ↑resorptions, ↓ litter size, fetal weight ↑hydrocephaly	Masters, 1992a
Terato, oral, rabbit, d7-19 0.5, 1, 2, 10, 40 (split doses)	**WL136184 95% cis** 95.5% B 12 ST 91/016	Maternal: 10 Fetal: 10 developmental: 10	Maternal: 40 Fetal: 40 Developmental: 40	↓feed cons., ↓bw gain ↑resorptions, ↓ litter size, ↓litter/fetal weight ↑forelimb flexures/ malrotated hindlimb	Masters, 1992b

PS: preliminary study

2.3.1.8 Neurotoxicity

No neurotoxicity studies were conducted.

2.3.1.9 Supplemental studies on metabolites or impurities

2.3.1.9.1 Acute oral toxicity of the metabolites

No toxicity studies on metabolites were conducted.

2.3.1.9.2 Genotoxicity of the metabolites

No toxicity studies on metabolites were conducted.

2.3.2 Establishment of an Acceptable Daily Intake (ADI)

Toxicity studies on either cis/trans or cis-Metconazole revealed following critical endpoints in subchronic, chronic or developmental studies:

(i) from the data of the reprotoxicity study on the rabbits, a developmental NOAEL of 4 mg/kg bw/d was established.

(ii) the mouse was identified as the most susceptible organism in the long-term toxicity studies. The lowest NOAEL, determined in the chronic study in the mouse was 4.4 mg/kg bw/d.

(iii) among the subchronic studies, the lowest relevant NOAEL was detected in the 90d mouse feeding study, where a NOAEL of 4.6 mg/kg bw/d was established

It was proposed to establish an overall NOAEL of 4 mg/kg bw/d, since the obtained values were grossly comparable.
However, in the light of the serious teratogenic effects, it seemed adviseable to add an additional assessment factor of 4, in order to obtain a sufficient margin of safety (1000 x) compared to the dose-level were the effect was observed. Therefore, with a NOAEL of 4 mg/kg bw/d, and an assessment factor of 400, the ADI is :

ADI = NOAEL / AF = 4/400 = **0.01 mg/kg bw/d**

2.3.3 Establishment of an Acute Reference Dose (ArfD)

As teratogenic effects were detected in the rabbit studies at 4 mg/kg bw/d, it is proposed to establish an acute reference dose on this basis. Taking into account an AF of 400, the following value is proposed:

ARfD = **0.01 mg/kg bw/d**

2.3.4 Establishment of an Acceptable Operator Exposure Level (AOEL)

As teratogenic effects were detected in the rabbit studies at 4 mg/kg bw/d, it is proposed to establish an acceptable operator exposure level on this basis. Taking into account an AF of 400, the following value is proposed:

AOEL = **0.01 mg/kg bw/d**

2.3.5 Establishment of the (theoretical) drinking water limit

On the basis that exposure through water drinking should not account for more than 10% (P) of the ADI, assuming an average consumption C of 2 l/person/day, and an average bodyweight of 60 kg, following drinking water limit may be derived:

Drinking water limit = (ADI * bw * P) / C = (0.01mg/kg bw/d* 60 kg* 0.1) / 2 l/d = **0.03 mg/l**

The maximum admitted concentration, as established in the guideline 80/77/EC, is 0.0001 mg/l.

2.3.6 Impact on human or animal health arising from exposure to the active substance or to impurities contained in it

Exposure of operators, bystanders and workers.

According to the UK POEM operator exposure model (field-crop: tractor mounted boom with hydrolic nozzles), no safe use would be expected with Metconazole, formulated as "BAS 555 00F" (60 g/l soluble liquid), both in the absence and in the presence of gloves during any task.

When operator exposure was estimated using the German model it was observed that no safe use was expected in the absence of PPE, but that the use was acceptable when gloves, coveralls and boots would be worn during the operations.

It was noted that the estimations were based upon a "worst case" adoption of a 100% absorption value of the tank spray mix.

Hence, it is recommended to include the safety phrases S36/37 (use of protective clothing and gloves) on the label.

2.4 Residues

2.4.1 Definition of the residues relevant to MRLs

Plant products
In the plant metabolism studies conducted in wheat and oilseed rape, the parent compound, triazolyl alanine and triazolyl acetic acid were identified as the major components of the total residues.
Triazolyl alanine and triazolyl acetic acid accounted for the major residue compounds in wheat grain while in oilseed rape, the parent compound was if not the major constituent of the residue, at least a valid indicator of the level of contamination of the commodity.

All the identified metabolites were covered toxicologically.

A completely validated method of analysis is available for the determination of residues of metconazole as cis- and trans-isomer in cereals and oilseed rape.

The residue definition for compliance with MRLs proposals is proposed as the parent compound (cis- and trans-isomers) only.
The same definition applies for risk assessment.

Livestock products
Metabolism studies have been submitted in lactating goats and laying hens.
The metabolism study in lactating goat indicated an extensive degradation of the parent compound. In all tissues, metconazole was, if not the major component of the total residue, at least a valid indicator of the level of contamination of the commodity.

All the metabolites identified in goat tissues were identical or structurally similar to those recovered in the rat and were therefore considered as out of any toxicological relevance.

In laying hens, no degradation pathway could be established since no tentative characterization of the metabolites was attempted. However, the theoretical intake calculation showed that the trigger value of 0.1 mg/kg diet was not exceeded. Therefore neither a metabolism study nor a feeding study were required for laying hens.

A multi-residue method of analysis for the determination of residues of metconazole as its cis-and trans-isomers in milk, egg, meat and fat is available.

The residue definition for compliance with MRLs proposals is proposed as the parent compound (cis- and trans-isomers) only.
The same definition applies for risk assessment.

2.4.2 Residues relevant to consumer safety

The total dietary intake of metconazole represents up to 8 % of the ADI and 15 % of the ARfD.

2.4.3 Residues relevant to worker safety

see point 2.3.6

2.4.4 Proposed EU MRLs and compliance with existing MRLs

Proposed MRLs for metconazole

Expression of the residue	Crops	MRLs (mg/kg)
Metconazole (*cis* and *trans* isomers)	Wheat	0.05
	Barley*	0.1
	Rye	0.05
	Triticale	0.05
	Oat	0.1
	Rape seed	0.1
* : MRL proposal based on the available residue data for Northern Europe only (no data for S.E.)		

2.4.5 Proposed EU import tolerances and compliance with existing MRLs

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2.4.6 Basis for differences, if any, in conclusions reached having regard to established or proposal CAC MRLs

-

2.5 Fate and behaviour in the environment

2.5.1 Definition of the residues relevant to the environment

Residue definition in soil, water and sediment is metconazole alone.

2.5.2 Fate and behaviour in soil

Aerobic metabolism
Besides the active substance, benzyl-ketone metabolite (CL 382389) unidentified components and several polar components were recovered at day 120 at level of 3.39% AR, 2.50% and 10.54% AR, respectively. Mineralization accounts for 10.3% AR at day 120.
The amount of bound residues increased steadily from 2% AR at day 0 to approximately 40% AR at day 120. Further analysis of the bound residues at 120 days showed 26, 10, and 1% of the applied radioactivity was associated with the humin (irreversibly bound), fulvic acid and humic acid fractions, respectively.
The HPLC chromatogram of the 120-day sample indicates multiple components in the polar fractions. These fractions were more polar than the benzyl-ketone metabolite or M-13.

DT_{50} of 84-598 days were determined in the aerobic degradation studies.

Anaerobic degradation
The rate of degradation of the a.s. under anaerobic conditions could not be determined : DT_{50} and DT_{90} > 120

days.
Levels of radioactivity associated with the non-extractable residue increased over the incubation period to approximately 10% AR after Day 56 and remained at this level in the subsequent samples.
Further analysis of the bound residues in the 120-day sample showed the radioactivity associated with the humin, fulvic acid, and humic acid fractions accounted for means of approximately 6, 1, and 0.1 % AR, respectively.
Low levels of CL 382389 (benzyl ketone) and a minor unidentified component were detected between day 28 and Day 56.

Soil photolysis
Metconazole was photolyzed on soil with an estimated half-life of approximately 73 days assuming average daylight of 12 hours (first order kinetics).

Mineralisation is negligible. Bound residues reached a maximum of 9.0% AR, under irradiation, at day 15. At least 4 photoproducts were formed (max 6.7% AR, under irradiation at day 4). No structure elucidation of these photoproducts was possible.

Field studies
Several field studies were performed in North European countries (United Kingdom, Germany, France)
The field DT_{50} were in the range 7-259 days; The field DT_{90} were in the range 28-854 days.

A soil accumulation study was performed. Metconazole residues were detected either close to or below the LOQ of 0.01 mg a.s./kg soil. A trend was observed where residue levels increased slightly following the second application and then decreased to essentially below the LOQ in the later October and March samplings.

The soil residues increase up to 0.03 mg a.s./kg soil after the incorporation of straw containing 0.11-0.10 mg a.s./kg in 1998, 1999 and 2000. Nonetheless, the level of metconazole residues in soil with and without incorporation of straw was below the LOQ (<0.01 mg a.s./kg) 300 days after the last application.

Soil Mobility
Metconazole is quickly and strongly adsorbed to soil. Mean Koc = 1000.6 l/kg, mean 1/n = 0.938
A thin layer chromatography on soil and an aged residue soil column studies confirm the low mobility of the a.s.

2.5.3 Fate and behaviour in water

Hydrolysis
Metconazole is hydrolytically stable under environmentally relevant conditions.

Photolysis
Metconazole is moderately (pH 5) to slightly (pH 7 and 9) degradable by direct photolysis.

Ready biodegradability
The a.s. is not readily biodegradable in the Sturm test (2 - 5% Theoretical CO_2 being evolved in 28 days).

Water/sediment study
The active substance was rapidly adsorbed to sediment (DT_{50} water of 1-15 days). The active substance is slowly degraded in the sediment (DT_{50} total system of 116-814 days)

No mineralization occurred. Bound residue reached maximum level of 19.7 and 28.5% AR , respectively in the river and in the pond systems. The metabolites were recovered at low level in both water/sediment systems (one occurrence of M13 at maximum level of 9.0 % in water, at day 152, in one water/sediment system; the notifier provided additional information on this metabolite)

PECgw
The endpoints which have been used were chosen in accordance with the FOCUS guidance (Koc, laboratory DT_{50}, correction of DT_{50} to 20°C and pF2, GAP, worst case interception parameters, monoculture scenario)
All the estimated concentrations were well below the 0.1 µg/l EU trigger value. PEC were not calculated for

Southern scenarios. However it can be expected that PEC under these pedo-climatic conditions will be below 0.1 µg/l

2.5.4 Fate and behaviour in air

Volatilisation on soil and plant
This study is made according to the BBA guideline; at this time, no specific study is required at EU level.
After 24 hours >85% of the applied metconazole remained on the substrates (plant, soil). Therefore, no significant losses of metconazole due to volatilization would be expected during the first 24 hours after application.

The DT_{50} of metconazole in air due to photochemical oxidative degradation is less than 6.5 hours. Therefore, no detailed assessment of atmospheric concentrations of metconazole is necessary.

2.6 Effects on non-target species

2.6.1 Effects on terrestrial vertebrates

The acute and short-term risk for large herbivorous and insectivorous birds is considered acceptable.
The rapporteur considers that the risk for large herbivorous and insectivorous birds is acceptable.
- The first tier assessment indicates acceptable acute and short-term risk
- The first tier assessment (worst case assumptions : 100% contaminated diet; NOEC based on continuous exposure of the birds during 22 weeks) indicates that the long term was 'almost acceptable'. The refinement that has been provided by the notifier indicates that acceptable uses could be identified.

The risk for large herbivorous and insectivorous mammals is considered acceptable.
- first tier assessment indicates that the acute risk to mammals is acceptable.
- First tier assessment indicates that the long term risk to insectivorous mammals is acceptable
- Refined risk assessment (considering actual residue level in cereal leaves) indicates that the long term TER is 2.9 (lower than 5). No refinement for PD and PT factors has been done. It can be considered that the risk is acceptable.

Metconazole has a potential for bioaccumulation. The TER_{lt} have therefore been calculated for birds and mammals consuming fish and earthworms. The long term risk for birds and mammals consuming contaminated fish or earthworms is considered acceptable.

We consider it necessary that lists of PD-values are established at a EU-level per crop and possible food source for the different mammal species. These lists should be available as an annex to the present guidance document on birds and mammals so that every risk evaluation will be established on the same basis.

2.6.2 Effects on aquatic species

The acute toxicity of metconazole on fish, daphnia and algae was tested. Additionally long term studies on fish, daphnia and chironomids were established. The risk for aquatic organisms resulting from the use of the active substance metconazole is considered acceptable if a buffer zone of 5 meters next to water bodies is taken into account.

Several studies (acute and long term) were conducted with the formulation. These studies demonstrated that the lead formulation is more toxic for aquatic organisms than the active substance. The risk for aquatic organisms resulting from the use of a formulation containing 60 g metconazole/L is considered acceptable if a buffer zone

of 15 meters next to water bodies is taken into account.

The BCF-values resulting from the 2 studies established are above 100 and as the active substance is not readily biodegradable, a higher tier risk assessment is considered necessary. An early life stage study was established resulting in a NOEC of 0.00291 mg a.s./L on basis of which the risk is considered acceptable if a buffer zone of 5 meters is taken into account. In addition the depuration half time is less than 1 day. Therefore it is considered that the risk for bioaccumulation of metconazole in fish is low.

2.6.3 Effects on bees and other arthropods

The acute oral and contact toxicity of metconazole and a 60 g metconazole/L SL formulation for bees was tested. The hazard quotients calculated for all use types indicate that the risk of metconazole to honey bees is negligible.

Studies of the effects of metconazole 60 g/L SL on *Aphidius rhopalosiphi*, *Typhlodromus pyri* and representatives of foliar and soil dwellings species are available. The risk from metconazole for non-target arthropods is considered acceptable. No further studies are considered necessary.

2.6.4 Effects on earthworms and other soil macro-organisms

The acute and long term risk for earthworms resulting from the application of metconazole or the tested 60 SL metconazole formulation, is considered acceptable. No further studies are required at the moment.

A study on the effects of a metconazole 60 g/L SL formulation on buried leaf material was tested. No significant difference was observed between the treatment plots and the control plots.

2.6.5 Effects on soil micro-organisms

The modifications of soil respiration and nitrification were lower than 25% after 28 days. The risk for soil micro-organisms is therefore considered acceptable.

2.6.6 Effects on other non-target organisms (flora and fauna)

The notifier established a study on the seedling emergence and a study on the vegetative vigour of non-target plants. The lowest NOEC from both studies was 27 g a.s./ha for soybean. This dose largely exceeds the drift dose at 1 m of the treated field (5 g a.s./ha). The risk for non-target flora is therefore considered acceptable.

2.6.7 Effects on biological methods of sewage treatment

The inhibitory effect of metconazole on the oxygen consumption of activated sludge was tested. The resulting EC_{50}-value after 3 hours was above 1000 mg a.s./L. The risk for biological methods of sewage treatment is therefore considered as acceptable.

List of end points (based on doc 1654/VI/94, Rev. 7, 22 Apr 1998)

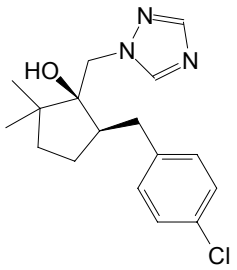
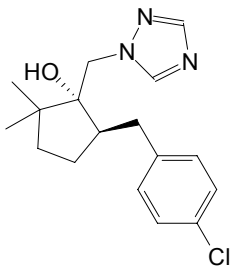
Identity, Physical and Chemical Properties, Details of Uses, Further Information, Methods of Analysis

Rapporteur Member State	Month and year	Active Substance (Name)
Belgium	January 2004	Metconazole

Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name)	Metconazole
Function (*e.g.* fungicide)	Fungicide
Rapporteur Member State	Belgium

Identity (Annex IIA, point 1)

Chemical name (IUPAC)	(1*RS*,5*RS*:1*RS*,5*SR*)-5-(4-chlorobenzyl)-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl) cyclopentanol
Chemical name (CA)	5-[(4-chlorophenyl)methyl]-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl) cyclopentanol
CIPAC No	706
CAS No	125116-23-6 (unstated stereochemistry)
EEC No (EINECS or ELINCS)	not assigned
FAO Specification (including year of publication)	not available
Minimum purity of the active substance as manufactured (g/kg)	min. 940 g/kg (sum of *cis*- and *trans*-isomers), with cis-metconazole (CL 354801) level not less than 800 g/kg and not more than 950 g/kg
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	No impurities are considered to be of toxicological, ecotoxicological or environmental concern
Molecular formula	$C_{17}H_{22}ClN_3O$
Molecular mass	319.8 g/mol
Structural formula	 cis-isomer CL 354801  trans-isomer CL 354802 The active ingredient of Metconazole is a mixture of 4 diastereomers : CL 354801 (“cis-metconazole”) is a mixture of S(OH), R and R(OH), S diastereomers, whereas CL 354802 (“trans-metconazole”) is a mixture of S(OH), S and R(OH), R diastereomers.

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity)	Melting point range : 100.0 – 108.4 °C (98.6%)
Boiling point (state purity)	Not applicable (not a low melting substance)
Temperature of decomposition	Not applicable
Appearance (state purity)	white powdered solid, odourless (98.6%)
Relative density (state purity)	D_4^{20} = 1.14 (98.6%)
Surface tension	64.8 mN/m at 20°C (90% saturated solution)
Vapour pressure (in Pa, state temperature)	2.1 x 10^{-8} Pa at 20°C
Henry's law constant (Pa m^3 mol^{-1})	2.21 x 10^{-7} Pa.m^3.mol^{-1} at 20°C
Solubility in water (g/l or mg/l, state temperature)	30.4 mg/L at 20°C in distilled Milli-Q water (pH ca. 7.5)
	no effect of pH
Solubility in organic solvents (in g/l or mg/l, state temperature)	solubility at 20°C in hexane : 1.40 g/L toluene : 103 g/L dichloromethane : 481 g/L methanol : 403 g/L 2-propanol : 132 g/L acetone : 363 g/L ethyl acetate : 260 g/L
Partition co-efficient (log P_{OW}) (state pH and temperature)	3.85 at 20°C (pH 7.2 - 8)
	Effect of pH was not investigated since there is no dissociation in water in the environmentally relevant pH-range
Hydrolytic stability (DT_{50}) (state pH and temperature)	pH 4 : stable at 50°C
	pH 7 : stable at 50°C
	pH 9 : stable at 50°C
Dissociation constant	pKa_1 = 11.38 pKa_2 = 1.08
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	acetonitrile solution : λ_{max} (nm) / ε (L.mol^{-1}.cm^{-1}) 196 / 17700 221 / 5900 226 (shoulder) / 4600 262 / 150 268 / 190 at λ > 290 nm : 2 maxima (determined in pH 7 buffer containing 0.1% acetonitrile) : at 310 nm : ε-value = 2686 L.mol^{-1}.cm^{-1} at 372.5 nm : ε-value = 1921 L.mol^{-1}.cm^{-1}
Photostability (DT_{50}) (aqueous, sunlight, state pH)	pH 5 : 27.5 d at 25°C pH 7 : 36.3 d at 25°C pH 9 : 35.8 d at 25°C
Quantum yield of direct phototransformation in water at Σ > 290 nm	2.19 x 10^{-7}
Flammability	not highly flammable

Explosive properties	not explosive

Summary of uses supported by available data (active substance)

Crop and/or situation (a)	Member State or Country	Formulation name	F, G or I (b)	Pests or Group of pest controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (k)	Remarks (l)
					Type (d-f)	Conc. Of a.s. (i)	Method kind (f-g)	Growth stage (j)	Number min max	Interval between applications; minimum	kg a.s./hl min max	water l/ha min max	kg a.s./ha		
Winter/ spring wheat	North and South Europe	Caramba 60 SL	F	*Septoria spp.* *Septoria nodorum* *Septoria tritici* *Erysiphe graminis* *Puccinia striiformis* *Puccinia recondita* *Fusarium spp.* *Fusarium roseum* *Cladosporium spp.*	SL	60 g/l	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	
Winter/ spring barley	North and South Europe	Caramba 60 SL	F	*Erysiphe graminis* *Puccinia hordei* *Rhynchosporium secalis* *Pyrenophora teres*	SL	60 g/l	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	
Winter/ spring oats	North and South Europe	Caramba 60 SL	F	*Puccinia avenae*	SL	60 g/l	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	
Rye	North and South Europe	Caramba 60 SL	F	*Erysiphe graminis* *Rhynchosporium secalis* *Puccinia recondita*	SL	60 g/l	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	
Triticale	North and South Europe	Caramba 60 SL	F	*Septoria spp.* *Puccinia recondita*	SL	60 g/l	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	
Oilseed rape	North and South Europe	Caramba 60 SL	F	*Phoma lingam* *Alternaria spp.* *Alternaria brassicae* *Sclerotinia sclerotiorum* *Erysiphe graminis* *Cylindrosporium spp.*	SL	60 g/l	spray	BBCH 14-73	1-2	14	0.0225-0.045	200-400	0.090	56	

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)

(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant - type of equipment used must be indicated

(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

Methods of Analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (principle of method)	HRGC-FID
Impurities in technical as (principle of method)	HRGC-FID *Additional validation required for impurities 3, 7, 11-14 (final report announced for end of February 2004)*
Plant protection product (principle of method)	HPLC-UV

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Enforcement method DFG-S19 : GC-NPD (Metconazole, as sum of cis- and trans-isomer); LOQ = 0.01 mg/kg for each isomer (wheat grain, grapes, pea, oilseed rape seed)
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Multiresidue method DFG-S19 : GC-NPD (Metconazole, as sum of cis- and trans-isomer); LOQ = 0.01 mg/kg for each isomer (milk, meat, eggs, fat) → can be considered for enforcement in these matrices, although currently no MRL's are proposed for products of animal origin
Soil (principle of method and LOQ)	Enforcement methods FAMS 055-02 and DFG S19 : GC-NPD (Metconazole, as sum of cis- and trans-isomer); LOQ = 0.01 mg/kg for each isomer
Water (principle of method and LOQ)	Enforcement method FAMS 058-01 : GC-NPD (Metconazole, as sum of cis- and trans-isomer); LOQ = 0.05 µg/L for each isomer (drinking water, surface water)
Air (principle of method and LOQ)	Enforcement method FAMS 067-01 : GC-NPD (Metconazole, as sum of cis- and trans-isomer); LOQ = 0.28 µg/m^3 for each isomer
Body fluids and tissues (principle of method and LOQ)	Not required (a.s. is not toxic or very toxic)

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	-

Mammalian toxicology

Absorption, distribution, excretion and metabolism in mammals (Annex IIA, point 5.1)

Rate and extent of absorption:	-oral: rapid (48h) and efficient (95-97%) -dermal: 3% (formulation concentrate)-100% (diluted spray mix, default absorption rate)
Distribution:	Widely distributed up to 72h, tendency for retention in adrenales, GIT, and liver

Potential for accumulation:	no evidence
Rate and extent of excretion:	Rapid, (67-80% within 48h) for the low dose; slower for the repeated dosing (65-82% within 96h) or for the high dose (67% within 96h) mainly in the faeces, following biliary excretion
Metabolism in animals	Extensive metabolisation, mainly by hydroxylation of cyclopentane- or benzyl ring
Toxicologically significant compounds (animals, plants and environment)	Metconazole

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral	LD_{50} ♂:727 mg/kg b.w.; ♀: 595 mg/kg b.w.
Mouse LD_{50}, oral	LD_{50} ♂:718 mg/kg b.w.; ♀: 410 mg/kg b.w.
Rabbit LD_{50} dermal	>2000 mg/kg bw
Rat LC_{50} inhalation	>5.6 mg/l air
Skin irritation	not irritant
Eye irritation	not irritant
Skin sensitisation (test method used and result)	not sensitizing

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect	liver toxicity (mouse, rat, dog)
Lowest relevant oral NOAEL / NOEL	4.6 mg/kg bw/d (90d mouse: hepatocellular vacuolation)
Lowest relevant dermal NOAEL / NOEL	not determined
Lowest relevant inhalation NOAEL / NOEL	not determined

Genotoxicity (Annex IIA, point 5.4)

In-vitro: positive in CHO (cis/trans): clastogenic with S9 at 24h but not at 48h sampling time, neither without S9 *In-vivo*: negative in mouse bone marrow and liver UDS

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effects	liver toxicity (hepatocellular vacuolation/ in mouse and rat; liver hypertrophy/necrosis, ALT/AST increase in mouse); spleen atrophy in mouse; reduced cholesterol/triglyceride levels (mouse); adrenal corticomedullary pigmentation (mouse)
Lowest relevant NOAEL / NOEL	4.3 mg/kg b.w./d (rat)
Carcinogenicity	mouse: liver cell adenoma/carcinoma; Phenobarbital-like mechanism (enzymatic induction, subsequent to hepatocellular necrosis and cell renewal) rat: not carcinogenic

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect	2G rat (cis): ↓bw gain (F_1 pups), ↑gestation length, ↓ post-implantation survival (F_2)
Lowest relevant reproductive NOAEL / NOEL	NOAEL pup toxicity: 8 mg/kg bw/d (↓bw gain NOAEL reproduction: 8 mg/kg bw/d (↑gestation length, ↓ post-implantation survival in F2)
Developmental target / critical effect	Rabbit: 4 mg/kg b.w./d: hydrocephaly
Lowest relevant developmental NOAEL / NOEL	NOAEL maternal: 4 mg/kg bw/d (↓feed consumption, ↓bw gain) NOAEL foetal: 4 mg/kg bw/d (↑embryonic deaths, ↑post-implantation loss) NOAEL development: 4 mg/kg bw/d

Neurotoxicity / Delayed neurotoxicity (Annex IIA, point 5.7)

no data, not necessary

Other toxicological studies (Annex IIA, point 5.8)

Investigation on enzyme induction	enzymatic induction in the liver (rat, mouse)

Investigation on in-vitro growth and developmental potential of rat embryos	inhibition of embryonal growth; induction of various abnormalities by cis/trans and cis Metconazole

Medical data (Annex IIA, point 5.9)

No data

Summary (Annex IIA, point 5.10)	Value	Study	Assessment factor
ADI	0.01 mg/kg bw/d	developmental rabbit	400
AOEL	0.01 mg/kg bw/d	developmental rabbit	400
ARfD (acute reference dose)	0.01 mg/kg bw/d	developmental rabbit	400
Drinking water limit	0.03 mg/l	(MAC=0.0001 mg/l)	

Dermal absorption (Annex IIIA, point 7.3)

in-vivo rat study (formulation concentrate)	3% (100 % by default for tank mix)

Acceptable exposure scenarios

(estimation by calculation in German Operator Exposure Model)

Operator	acceptable only with PPE (gloves, coverall, boots)
Workers	acceptable
Bystanders	acceptable

Classification (Annex IIA, point 10)

Xn ; R22- R63

Residues

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	Wheat, oilseed rape
Rotational crops	Wheat, lettuce, radish, carrot, lamb's lettuce
Plant residue definition for monitoring	Parent compound (cis- and trans- isomers)
Plant residue definition for risk assessment	Parent compound (cis- and trans- isomers)
Conversion factor (monitoring to risk assessment)	none

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	Goats, hens
Animal residue definition for monitoring	Parent compound (cis- and trans- isomers)
Animal residue definition for risk assessment	Parent compound (cis- and trans- isomers)
Conversion factor (monitoring to risk assessment)	none
Metabolism in rat and ruminant similar (yes/no)	yes
Fat soluble residue: (yes/no)	yes

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

.....	The studies performed in accordance with the good agricultural practices showed that the enrichment of edible plant parts of leafy vegetables, root vegetables and cereals, installed as succeeding crops, with metconazole is not sufficient to reach measurable levels for monitoring. The studies carried out at a much higher rate of application confirmed that the metabolic pathway of metconazole in succeeding crops is similar to that in the target crops.

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 introduction)

.....	Residues of metconazole expressed as cis- and trans-isomers in cereal green plant, straw and grain, rape seed and rape oil, carrots and lettuce can be considered as stable under frozen storage conditions for a period of 12 months.

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: Yes*	Poultry: No	Pig: No
Muscle	-	-	-
Liver	-	-	-
Kidney	-	-	-
Fat	-	-	-
Milk	-	-	-

Eggs	-	-	-

* : However, the study is not required considering that non significant residues (<0.01 mg/kg) may occur in the edible animal tissues taking into account the residue levels in potential feeding stuffs at the 1 x dose rate.

Summary of critical residues data (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Southern Europe	Trials results relevant to the critical GAP (a)	Recommendation/comments	MRL (mg/kg)	STMR (mg/kg) (b)
Winter wheat	N	Metconazole (sum of isomers) : -grain : <0.002, <0.02, <0.02, <0.01, <0.01, <0.01, <0.01, 0.04 mg/kg -straw : 0.25, 0.44, 0.53, 0.75, 0.64, 0.76, 0.57, 0.87 mg/kg	Rate of application : 85-90 g a.s./ha, 2 applications – BBCH : 32-39; 65-79 , PHI : 35 days.	0.05	0.02
	S	Metconazole (sum of isomers) : -grain : <0.02, <0.02, <0.02, <0.02, <0.02, <0.02, 0.05, 0.03 mg/kg -straw : 0.57, 0.23, 0.23, 0.23, 0.27, 0.30, 0.30, 0.16 mg/kg	Rate of application : 82-95 g a.s./ha, 2 applications – BBCH : 33-39; 65-77, PHI : 35 days		
Win-ter/spring barley	N	Metconazole (sum of isomers) : -grain : <0.01, 0.09, 0.03, 0.02, 0.01, 0.03, 0.01, <0.01, 0.05, 0.05, 0.03, 0.03, 0.01, 0.03, <0.01, <0.01 mg/kg -straw : 0.13, 1.06, 1.61, 0.23, 0.82, 0.99, 0.37, 0.15, 0.18, 0.73, 0.22, 1.33, 0.74, 1.37, 0.32, 0.03 mg/kg	Rate of application : 89-96 g a.s./ha, 2 applications BBCH 33; 71-75, PHI : 35-37 days.	0.1 **Possible extrapolation to oat (for Northern Europe only) accord-ing to EU Doc. 7525/VI/95-rev.7 (Table 3).**	0.025
	S	No data	-		
Winter rye	N	Metconazole (sum of isomers) : -grain : <0.01 mg/kg -straw : 0.37 mg/kg	Trial performed in accordance with the critical GAP.	**Possible extrapolation from wheat residue database to rye according to EU Doc. 7525/VI/95-rev.7 (Table 3)** **MRL proposal for rye : 0.05 mg/kg.**	0.02
	S	No data	-		

Triticale	N	Metconazole (sum of isomers) : -grain : <0.01 mg/kg -straw : 0.16 mg/kg	Trial performed in accordance with the critical GAP.	**Possible extrapolation from wheat residue database to triticale according to EU Doc. 7525/VI/95-rev.7 (Table 3)** **MRL proposal for Triticale : 0.05 mg/kg.**	0.02
	S	No data			
Oilseed rape	N	Metconazole (sum of isomers) : -seed : <0.01, <0.01, <0.01,<0.01, <0.01, 0.06, 0.04, 0.07 mg/kg.	Rate of application : 90 g a.s./ha, 2 applications – BBCH : 63-67; 69-71 , PHI : 56-70 days	0.1	0.025
	S	Metconazole (sum of isomers) : -seed : 0.04, 0.03, 0.11, 0.05, <0.01, 0.02, 0.05, 0.02, 0.02 mg/kg The residue value "0.11" can be considered as an outlier according to the DIXON Q- test.	Rate of application : 79-90 g a.s./ha, 2 applications – BBCH : 65; 69-75, PHI : 56-63 days		

(a) : Number of trials in which particular residue levels were reported.
(b) : Supervised Trials Median Residue : The median residue level estimated on the basis of supervised trials relating to the critical GAP

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

ADI	0.01 mg/kg bw/day
TMDI (European Diet) (% ADI)	-for the WHO European diet : 3.47 % of ADI -for the German diet for a 4-6 years old girl : 7.97 % of ADI -for the Pesticides Safety Directorate Consumer Exposure Model : 5.76 % and 7.21 % of ADI respectively for children and infants from UK.
NEDI (% ADI)	-
Factors included in NEDI	-
ARfD	0.01 mg/kg bw/day
Acute exposure (% ARfD)	15 % of ArfD for children from UK.

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/processed crop	Number of studies	Transfer factor	% Transference *
Not required			

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Expression of the residue	**Crops**	**MRLs (mg/kg)**
Metconazole (*cis* and *trans* isomers)	Wheat	0.05
	Barley*	0.1
	Rye	0.05
	Triticale	0.05
	Oat	0.1
	Rape seed	0.1
* : MRL proposal based on the available residue data for Northern Europe only (no data for S.E.)		

Fate and Behaviour in the Environment

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days ‡	10.30 % after 120 d, [^{14}C-3,5-triazole]-label (n= 1)
Non-extractable residues after 100 days ‡	39.24 % after 120 d, [^{14}C-3,5-triazole]-label (n= 1)
Relevant metabolites - name and/or code, % of applied (range and maximum) ‡	Benzyl-ketone metabolite (CL 382389) – 3.39 % at 120d (n= 1)

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation ‡	Mineralisation – 0.26 % after 120 d Non-extractable residues 8.58 % after 120 d No major metabolite [^{14}C-3,5-triazole]-label
Soil photolysis ‡	Mineralisation 1 % after 15 d (irradiated samples) Non-extractable residues 9 % after 15 d Unknown metabolite 1 : 5.0 % at 15 d Unknown metabolite 2 : 2.8 % at 15 d Unknown metabolite 3 : 1.0 % at 15 d Unknown metabolite 4 : 3.0 % at 15 d Mineralisation 0 % after 15 d (dark samples) Non-extractable residues 1.0 % after 15 d [^{14}C-3,5-triazole]-label

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Method of calculation	Laboratory: first order kinetics Field studies: mainly square root first order
Laboratory studies (range or median, with n value, with r^2 value) ‡	parent DT_{50lab} (22°C, aerobic): 185-598 d, mean = 297 d (n= 5, r^2 = 0.797-0.972) For FOCUS gw modelling parent DT_{50lab} (20°C, pF2, aerobic, 1st order kinetics): 122-598 d, mean = 247 d (n= 5, r^2 = 0.797-0.972)
	parent DT_{90lab} (22°C, aerobic):614-1987 d, mean = 986 (n= 5, r^2 = 0.797-0.972) according to DT_{50} quoted above)
	DT_{50lab} (study at 10°C, aerobic): 564 d (n= 1, r^2 = 0.7240)
	DT_{50lab} (20°C, anaerobic): >120 d (n= 1, no DT calculation)
	degradation in the saturated zone: no data submitted and no data required.
Field studies (state location, range or median with n value) ‡	DT_{50f}: UK and Germany, bare soil, 33-138 d, mean = 61 d (n= 4, r^2= 0.70-0.95) square root 1st order DT_{50f}: UK, Germany, France, bare soil, various formulations and application rates : 7-259 d, mean = 105 d (n= 24,) 1st order
	DT_{90f}: UK and Germany, bare soil, 363-457 d, mean = 408 d (n= 4, r^2= 0.70-0.95) square root 1st order DT_{90f}: UK, Germany, France, bare soil, various formulations and application rates : 28-854 d, mean = 347 d (n= 24, r^2 not mentioned) 1st order
Soil accumulation and plateau concentration ‡	UK, cereals, 2 appl. of 90 g a.s./ha/ year during 6 years - Residues detected at level either close to or below 0.01

	mg a.s./kg soil - Residues detected at max level of 0.03 mg a.s./kg soil, after incorporation of straw during 3 years

Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_f /K_{oc} ‡ K_d ‡ pH dependence (yes / no) (if yes type of dependence) ‡	K_{oc}: parent 726-1718 ml/g (mean 1000.6, $^1/_n$= 0.911-0.983, 5 soils) K_f: parent 6.74-39.35 ml/g (mean 16.7, 5 soils) No pH dependence

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching ‡	Soil thin layer chromatography confirming the low mobility of the a.s.
Aged residues column leaching ‡	BBA guideline Aged for : 90 d Precipitation: 200 mm Leachate: 0.54-0.87 % total residues in leachate (only metconazole) 88.17-92.42 % total residues/radioactivity retained in top 6 cm
Lysimeter/ field leaching studies ‡	Not required

PEC (soil) (Annex IIIA, point 9.1.3)

Method of calculation	DT_{50} (d): *259* days Kinetics: 1st order representative worst case from field studies.
Application rate	Crop: cereals 60 % plant interception: Number of applications: 2 Interval (d): 14 application : 90 g as/ha

$PEC_{(s)}$	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.048 mg a.s./kg		0.094 mg a.s./kg	
Short term 24h	0.048	0.048	0.094	0.094
2d	0.048	0.048	0.094	0.094
4d	0.047	0.048	0.093	0.094
Long term 7d	0.047	0.048	0.092	0.093
28d	0.045	0.046	0.087	0.091
50d	0.042	0.045	0.082	0.088
100d	0.037	0.042	0.072	0.083

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature) ‡	Hydrolytically stable at pH4, 5, 7, 9: 50°C
Photolytic degradation of active substance and relevant metabolites ‡	Xenon arc light source with UV filter, 25°C DT_{50} 27.5-36.3 days at pH 5, 7 and 9 hydroxymetconazole: 14.5 %AR (after 30 d at pH 7)
Readily biodegradable (yes/no) ‡	Not readily biodegradable, 2-5% Theoretical CO_2 evolved in 28 days
Degradation in water/sediment - DT_{50} water ‡ - DT_{90} water ‡ - DT_{50} whole system ‡ - DT_{90} whole system ‡	1-15 days (1st order, r^2= 0.915-0.932, n= 2) 3-49 days (1st order, r^2= 0.915-0.932, n= 2) 116-814 days (1st order, r^2= 0.922-0.923, n= 2) 384->1000 days (1st order, r^2= 0.922-0.923, n= 2)
Mineralization	0 %AR (at 100 d, n= 2)
Non-extractable residues	18.9-11.8 %AR (at 100 d, n= 2)
Distribution in water / sediment systems (active substance) ‡	Maximum of 51.0-78.4 y %AR in sediment after 30-100 days. DT_{50} in sediment similar to the DT_{50} whole system
Distribution in water / sediment systems (metabolites) ‡	occurrence of metabolite M13 (CL 359139) at max level of 9.0% at day 152, in water phase in one w/s system

PEC (surface water) (Annex IIIA, point 9.2.3)

PEC surface water

Method of calculation	First order kinetics, maximum DT_{50} of 15 days (water/sediment study)
Application rate	2 applications of 90 g a.s./ha, with an interval of 14 days, (cereals, oilseed rape)
Main routes of entry	Spray drift at 1 m (2.77% drift), 30 cm water body

$PEC_{(sw)}$	Single application Actual	Single application Time weighted average	Multiple application Actual (after second application)	Multiple application Time weighted average (after second application)
Initial	0.8 µg a.s./l	0.8 µg a.s./l	1.2 µg a.s./l	1.2 µg a.s./l
Short term 24h 2d 4d	0.8 µg a.s./l 0.8 µg a.s./l 0.7µg a.s./l	0.8 µg a.s./l 0.8 µg a.s./l 0.8 µg a.s./l	1.1 µg a.s./l 1.1 µg a.s./l 1.0 µg a.s./l	1.2 µg a.s./l 1.1 µg a.s./l 1.0 µg a.s./l
Long term 7d 14d 21d 28d 42d	0.6 µg a.s./l 0.4 µg a.s./l 0.3 µg a.s./l 0.2 µg a.s./l 0.1 µg a.s./l	0.7µg a.s./l 0.6 µg a.s./l 0.5 µg a.s./l 0.4 µg a.s./l 0.3 µg a.s./l	0.9 µg a.s./l 0.6 µg a.s./l 0.5 µg a.s./l 0.3 µg a.s./l 0.1 µg a.s./l	0.9 µg a.s./l 0.7 µg a.s./l 0.5 µg a.s./l 0.3 µg a.s./l 0.2 µg a.s./l

PEC sediment

Method of calculation	First order kinetics, maximum DT_{50} = 814 days (water/sediment study)
Application rate	2 applications of 90 g a.s./ha, with an interval of 14 days, (cereals, oilseed rape)
Main routes of entry	Spray drift at 1 m (2.77% drift), 1 cm sediment layer, 1.3 kg/dm^3

$PEC_{(sed)}$	Single application Actual	Single application Time weighted average	Multiple application actual	Multiple application Time weighted average
Initial	0.019 mg a.s/kg sediment (1 application)	-	0.038 mg a.s/kg sediment (after 2nd application)	-
Long term – accumulation through years	-	-		0.12 mg a.s/kg sediment (plateau average)

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	Model used: FOCUS_PELMO version 2.2 Scenarios : Châteaudun, Hamburg, Jokionen, Kremsmünster, Okehampton

	Crop: winter cereals, spring cereals, winter oilseed rape, summer oilseed rape Mean parent DT_{50lab} 247 d (normalisation to pF2, 20°C with Q10 of 2.2). Mean or median parent DT_{50f} x d (N scenarios), y d (S scenarios). K_{oc}: parent, mean 1000.6 l/lg, $^1/_n$= 0.938.
Application rate	Application rate: *90* g a.s./ha. 2 applications at interval of 14 days, at growth stage BBCH 10-19 (autumn and spring applications depending on the crop)

$PEC_{(gw)}$

Maximum concentration	-
Average annual concentration	Annual average concentrations in µg a.s./l (80th percentile) according to FOCUS guidance:

	Winter Cereals
Châteaudun	0.000
Hamburg	0.002
Jokionen	0.000
Kremsmünster	0.001
Okehampton	0.008
	Spring Cereals
Châteaudun	0.000
Hamburg	0.000
Jokionen	0.000
Kremsmünster	0.000
Okehampton	0.001
	Winter Oilseed Rape
Châteaudun	0.000
Hamburg	0.003
Kremsmünster	0.002
Okehampton	0.016
	Summer Oilseed Rape
Jokionen	0.000
Okehampton	0.001

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air ‡	Not studied - no data requested
Quantum yield of direct phototransformation	$\phi = 2.19 \times 10^{-7}$
Photochemical oxidative degradation in air ‡	DT_{50} of 6.5 hours derived by the Atkinson method of calculation
Volatilization ‡	from plant surfaces (BBA guideline): 5 % after 24 hours
	from soil (BBA guideline): 13-14 % after 24 hours

PEC (air)

Method of calculation	Expert judgement, based on vapour pressure (2.1 10^{-8} Pa at 20°C) and information on volatilisation from plants and soil.

PEC$_{(a)}$

Maximum concentration	negligible

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	Soil, water and sediment : metconazole alone, sum of cis- and trans-isomer

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	Not available
Surface water (indicate location and type of study)	Not available
Ground water (indicate location and type of study)	Not available
Air (indicate location and type of study)	Not available

Classification and proposed labelling (Annex IIA, point 10)

with regard to fate and behaviour data	R53

Effects on Non-target Species

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Acute toxicity to mammals ‡	LD_{50} (mouse) = 410 mg a.s./kg bw
Reproductive toxicity to mammals ‡	NOEC (rabbit, terato) = 4 mg a.s./kg bw/day
Acute toxicity to birds ‡	LD_{50} = 787 mg a.s./kg bw
Dietary toxicity to birds ‡	LC_{50} = 167.85 mg a.s./kg bw/day
Reproductive toxicity to birds ‡	NOEC (22 weeks) = 6.19 mg a.s./kg bw/day

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

First tier risk assessment (birds)

Application rate	Bird type	Time scale	FIR/bw	RUD (90%)	MAF	f_{twa}	ETE (mg a.s./kg bw/day)	TER	Annex VI trigger value
2 x 0.090 kg a.s./ha in cereals	Large herbivorous bird	acute	0.44	142	1.2	-	6.75	116.6	10
		short term	0.44	76	1.4	-	4.21	39.87	10
		long term	0.44	76	1.4	0.53	2.23	2.78	5
	Insectivorous bird	acute	1.04	52	-	-	4.87	161.6	10
		short term	1.04	29	-	-	2.71	61.94	10
		long term	1.04	29	-	-	2.71	2.28	5

Application rate (kg as/ha)	Crop	Category	Time-scale	TER	Annex VI Trigger
2 x 0.09	Cereals	Bird eating earthworms	Long term	6.19/0.37= 5.9	5
		Bird eating fish	Long term	6.19/0.033=189	5

Second tier risk assessment (birds)

Applica-tion rate	**Bird type**	**FIR/bw *)**	**Category**	**RUD (mean)**	**PT**	**PD**	**IF**	**f_{twa}**	**MAF**	**ETE (mg a.s./kg bw/day)**	**TER**	**Annex VI trigger value**
2 x 0.09 kg a.s./ha in cereals	Large herbivorous bird **(Goose)**	0.44	cereal green plant	20.75	1	1	1	0.53	1.0	0.44	**14**	5
	Insectivo-rous bird early **(Yellow-hammer)**	0.78	Arthropodes (soil surface)	29	0.02	0.65	0.5	-	-	0.013	-	-
		0.78	Arthropodes (in soil)	0	0.02	0.25	0.5	-	-	0.0	-	-
		0.78	weed seeds (soil surface)	40	0.02	0.10	0.5	-	-	0.003	-	-
										0.016	**387**	5
	Insectivo-rous bird late **(Marsh warbler)**	0.98	Foliar insects	29	0.027	1	1	-	-	0.07	**88.4**	5

First tier risk assessment (mammals)

Application rate	Mammal type	Time scale	FIR/bw	RUD (90%)	MAF	f_{twa}	ETE (mg a.s./kg bw/day)	TER	Annex VI trigger value
2 x 0.090 kg a.s./ha in cereals	Small herbivorous mammal	acute	1.39	142	1.2	-	21.32	19.23	10
		long term	1.39	76	1.4	0.53	7.05	0.57	5
	Insectivorous mammal	acute	0.63	14	-	-	0.79	519	10
		long term	0.63	5.1	-	-	0.29	13.8	5

Application rate (kg as/ha)	Crop	Category	Time-scale	TER	Annex VI Trigger
2 x 0.09	Cereals	Mammals eating earthworms	Long term	4 /0.47= 8.5	5
		Mammals eating fish	Long term	4/0.02 = 200	5

Second tier risk assessment (mammals)

Application rate	Mammal type	Time scale	FIR/bw	RUD (mean, based on analytical results)	MAF	f_{twa}	ETE (mg a.s./kg bw/day)	TER	Annex VI trigger value
2 x 0.090 kg a.s./ha in cereals	Small herbivorous mammal (vole)	acute	1.39	20.75	1	0.53	1.38	2.9	5

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2) ‡

Group	Test sub-stance	Time-scale	Endpoint	Toxicity (mg a.s./l)
Laboratory tests				
Salmo gairdneri	metconazole	72h	mortality	LC_{50} = 2.1
Onchorrhynchus mykiss	metconazole	28d	mortality	NOEC = 1.14
Onchorhynchus mykiss	metconazole	95d	survival	NOEC = 0.00291
Daphnia magna	metconazole	48h	immobilisation	LC_{50} = 4.2
Daphnia magna	metconazole	21d	reproduction	NOEC = 0.078
Selenastrum capricornu-tum	metconazole	72h	biomass	E_bC_{50} = 1.7
Chironomus riparius	metconazole	28d	emergence	NOEC = 2.12

Group	Test sub-stance	Time-scale	Endpoint	Toxicity (mg/l formulation)
Laboratory tests				
Onchorhynchus mykiss	metconazole 60 g/L SL	96h	mortality	LC_{50} = 14.83
Daphnia magna	metconazole 60 g/L SL	48h	immobilisation	EC_{50} = 0.365
Selenastrum capricornu-tum	metconazole 60 g/L SL	72h	biomass	E_bC_{50} = 5.13

Onchorhynchus mykiss	metconazole 60 g/L SL	28 d	mortality	NOEC = 0.242
Daphnia magna	metconazole 60 g/L SL	21 d	reproduction	NOEC = 0.020.8

Microcosm or mesocosm tests
Not required.

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

Application rate (kg as/ha)	Test substance	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
2 x 90 g a.s./ha in cereals and oilseed rape	metconazole	*Salmo gairdneri*	Acute	1 m	1750	100
	metconazole	*Onchorhynchus mykiss*	Long term	1 m	2.43	10
				5 m	**11.78**	**10**
	metconazole	*Daphnia magna*	Acute	1 m	3500	100
	metconazole	*Daphnia magna*	Long term	1 m	65	10
	metconazole	*S. capricornutum*	Acute	1 m	1417	10
	metconazole	*Chironomus riparius*	Long term	1 m	1767	10
	metconazole 60 g/L SL	*Onchorhynchus mykiss*	Acute	1 m	702.8	100
	metconazole 60 g/L SL	*Daphnia magna*	Acute	1 m	17.3	100
				5 m	84	100
				10 m	165	100
	metconazole 60 g/L SL	*S. capricornutum*	Acute	1 m	243.13	100
	metconazole 60 g/L SL	*Onchorhynchus mykiss*	Long term	1 m	11.47	10
	metconazole 60 g/L SL	*Daphnia magna*	Long term	1 m	0.986	10
				5 m	4.79	10
				10 m	9.4	10
				15 m	**13.65**	**10**

Bioconcentration

Bioconcentration factor (BCF) ‡	129.7
Annex VI Trigger:for the bioconcentration factor	100
Clearance time (CT_{50}) (CT_{90})	< 1 day
Level of residues (%) in organisms after the 14 day depuration phase	

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Acute oral toxicity	LD_{50} (72h) = 85 µg a.s./bee

Acute contact toxicity	LD_{50} (96h) > 100 µg a.s./bee

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
0.18	cereals and oilseed rape	oral	180/100 = 1.8	50
		contact	180/85 = 2.1	50

Field or semi-field tests Not required.

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5) ‡

Species	Stage	Test Substance	Dose	Endpoint	Effect	Annex VI Trigger
Laboratory tests						
Poecilus cupreus	Adult	Metconazole 60 g a.s./L SL	180 g a.s./ha	Mortality Feeding	E = -4.8%	30%
Pardosa	Adult	Metconazole 60 g a.s./L SL	2 x 90 g a.s./ha	Mortality Feeding	E = -0.5%	30%
Coccinella septempunctata	Larvae	Metconazole 60 g a.s./L SL	180 g a.s./ha	Mortality Fecundity	E = 66.45%	30%
Coccinella septempunctata	Larvae	Metconazole 60 g a.s./L SL	2 x 90 g a.s./ha	Mortality Fecundity	E = 22.3%	30%
Orius laevigatus	Adult	Metconazole 60 g a.s./L SL	2 x 90 g a.s./ha	Mortality Fecundity	E = 16.7%	30%
Aphidius rhopalosiphi	Adult	Metconazole 60 g a.s./L SL	2 x 90 g a.s./ha	Mortality Fecundity	E = -45.2%	30%
Typhlodromus pyri	Protonymphs	Metconazole 60 g a.s./L SL	180 g a.s./ha	Mortality Fecundity	E = 100%	30%
Typhlodromus pyri	Protonymphs	Metconazole 60 g a.s./L SL	1.1 g a.s./ha	Mortality Fecundity	E = 6.85%	30%
Typhlodromus pyri	Protonymphs	Metconazole 60 g a.s./L SL	2 x 90 g a.s./ha	Mortality Fecundity	E = 3.4%	30%

Field or semi-field tests
Not required

Effects on earthworms (Annex IIA, point 8.4, Annex IIIA, point 10.6)

Acute toxicity ‡	LC_{50} > 1000 mg a.s./kg soil
Reproductive toxicity ‡	NOEC = 1.8 mg a.s./kg soil

Toxicity/exposure ratios for earthworms (Annex IIIA, point 10.6)

Application rate	Crop	Time-scale	TER	Annex VI Trigger
2 x 90 g a.s./ha	cereals and oilseed rape	acute	>1000/(2 x 0.15) = 3333	10
		long term	=1.8/(2 x 0.15) = 6	5

Effects on soil micro-organisms (Annex IIA, point 8.5, Annex IIIA, point 10.7)

Nitrogen mineralization ‡	< 25% effect after 28 days at 1.2 mg a.s./kg dry soil (equivalent to 900 g a.s./ha)
Carbon mineralization ‡	< 25% effect after 28 days at 1.2 mg a.s./kg dry soil (equivalent to 900 g a.s./ha)

Effects on biological methods of sewage treatment (Annex IIA 8.7)

Respiration inhibition	EC_{50} (3h) > 1000 mg/L (nominal)

Classification and proposed labelling (Annex IIA, point 10)

with regard to ecotoxicological data	N, R51/53 (metconazole) N, R50/53 (Caramba)

LEVEL 3

Metconazole

Proposed decision with respect to the application for inclusion of the active substance in Annex I

3.1 Background to the proposed decision

The information provided by the notifier was sufficient to evaluate the a.s. according Directive 91/414/EEC. The evaluation of the data and the risk assessment which were performed showed that the use of the a.s. according to GAP do not cause unacceptable risk to human beings and to the environment.

3.2 Proposed decision concerning inclusion in Annex I

It is proposed to include metconazole in Annex I. It is considered that the confirmatory data requested in level 4 can be submitted before the end of the review process.

3.3 Rational for the postponement of the decision to include the active substance in Annex I, or for the conditions and restrictions to be associated with a proposed inclusion in Annex I, as appropriate

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LEVEL 4

Metconazole

Further information to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in the Annex I

4.1 Identity of the active substance

For the Rallis India source, the submitted analytical profile of batches indicates compliance with the proposed technical specification. However, as the report in question lacks a formal GLP-compliance statement and Quality Assurance Unit declaration, it is considered that a confirmatory batch analysis study containing the full set of GLP statements is still required for this source. For the sake of completeness, this study should also address the 'impurity 18' content of the Rallis India batches, to enable verification of compliance with the proposed certified limit for this compound (Annex IIA 1.11).

For the Ibaraki Kasei batches, the N-nitrosamine statement is supported by experimental data. However, as the report in question lacks a formal GLP-compliance statement and Quality Assurance Unit declaration and does not address the Rallis India batches, it is considered that a confirmatory study containing the full set of GLP statements and providing N-nitrosamine data for batches originating from both manufacturing sources is still required (Annex IIA 1.10, 1.11).

4.2 Physical and chemical properties of the active substance

-

4.3 Data on application and further information

-

4.4 Classification, packaging and labelling

-

4.5 Methods of analysis

Impurity method M-2479 requires additional validation for some impurities (precision for impurities 7, 11-12 and 14; full validation for impurities 3 and 13). New validation study is underway to provide the outstanding data (study protocol submitted; final report announced for end of February 2004) (Annex IIA 4.1.3).

4.6 Toxicology and metabolism

In some rabbit developmental studies, various malformations were detected in treated animals, compared to study controls. The notifier claimed that the incidence of these malformations were also higher in the historical controls of NZW rabbits of supplier Intervet Plc (UK). The full details of the historical incidences of studies conducted at Huntingdon Harrogate in the same period are warranted, in order to evaluate the relevance of the observed findings in the light of the spontaneous incidence. (Annex IIA 5.6)

4.7 Residue data

-

4.8 Environmental fate and behaviour

-

4.9 Ecotoxicology

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