Draft Assessment Report

DIFENOCONAZOLE

Volume 1

Rapporteur Member State: Sweden

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KEMI
KEMIKALIEINSPEKTIONEN
SWEDISH CHEMICALS INSPECTORATE

Volume 1

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Level 1

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

1.1 Purpose for which the monograph was prepared

This document has been prepared as a result of the evaluation of the dossier submitted by Syngenta Ltd. under Article 8(2) of Council Directive 91/414/EEC for the first inclusion of difenoconazole in Annex I. Syngenta Ltd. has made the submission in the capacity of manufacturer and registration data holder of the existing avtive substance difenoconazole.

The introduction to this document is a brief overview of the identity, major physical and chemical properties of difenoconazole and intended uses of the plant protection products SCORE 250EC (Syngenta code numbers A-7402 T) and DIVIDEND 030 FS (Syngenta code number A-9142 G) which are the representative formulations selected to support the application.

1.2 Summary and assessment of information relating to the collective assessment of dossiers

Not applicable since Syngenta Ltd. is the sole applicant for the existing active ingredient difenoconazole (CGA 169374).

1.3 Identity of the active substance (Annex IIA 1)

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

Applicant: Syngenta Ltd.
Address: Priestley Road
Surrey Research Park
Guildford Surrey GU2 7 YH
Great Britain
Contact Person: [redacted]
Position: [redacted]
Telephone No: [redacted]
Telefax No: [redacted]
E-mail: [redacted]

1.3.2 Common name and synonyms (Annex IIA 1.3)

Difenoconazole (ISO published)

1.3.3 Chemical name

IUPAC: 1-[2-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-4-methyl[1,3]dioxolan-2-ylmethyl]-1H-[1,2,4] triazole

CA: 1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole

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

Code no.	The period for which it was used	Remarks (e.g. which countries has the code been used in)
CGA 169374	From 1989-present (source the e-Pesticide Manual v. 3.1)	Used in all countries. The Ciba-Geigy code has been retained following the merger to Syngenta

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

CAS No.: 119446-68-3

EEC No.: Not allocated

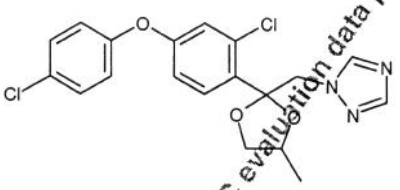
CIPAC No.: Not allocated

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

Molecular formula: $C_{19}H_{17}Cl_2N_3O_3$

Molecular mass: 406.3

Structural formula:



1.3.7 Manufacturers of the active substance (Annex IIA 1.2)

Manufacturer: [redacted]

Contact Point: [redacted]

[redacted]

Location of plant: [redacted]

1.3.8 Method of Manufacture (Annex IIA 1.8)

Confidential information (see Volume 4, Annex C).

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

Technical active substance contains difenoconazole at a minimum of 940 g/kg (see Annex C for further details).

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

Confidential information (see Volume 4, Annex C).

1.3.11 Analytical profile of batches (Annex IIA 1.11)

Confidential information (see Volume 4, Annex C).

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

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

SCORE 250 EC

Current trade names: BARDOS 250 EC (Austria), GEYSER (Belgium and France), GEYSER 250 EC (Luxembourg), PLOVER (UK), SCORE (France, Germany and Spain), SCORE 25 EC (Italy and Spain), SCORE 250 EC (Greece, Ireland, the Netherlands and Portugal) and SICO 250 EC (France)

Development code numbers: A-7402 T

DIVIDEND 030 FS

Current trade names: DIVIDEND (Hungary, Poland, Slovak Republic, Slovenia and Spain) and DIVIDEND 030 FS (Danmark and Sweden)

Development code numbers: A-9142 G

1.4.2 Manufactures of the plant protection product (Annex IIIA 1.2)

SCORE 250 EC

Manufacturer: [redacted]

Location of plant: [redacted]

Contact Point: [redacted]

DIVIDEND 030 FS

Manufacturer: [redacted]

Location of plant: [redacted]

Contact Point: [redacted]

1.4.3 Type of preparation and code (Annex IIIA 1.5)

SCORE 250 EC

Physical state: liquid

Nature: emulsifiable concentrate

GIFAP code: EC

DIVIDEND 030 FS

Physical state: liquid

Nature: flowable concentrate for seed treatment

GIFAP code: FS

1.4.4 Function (Annex IIA 3.1; Annex IIIA 1.6)

SCORE 250 EC

Fungicide

DIVIDEND 030 FS

Fungicide for seed treatment

1.4.5 Composition of the preparation (Annex IIIA 1.4)

SCORE 250 EC

content of pure active substance :	**250 g / l**	**(23.2 % w / w)**
limits :	235 – 265 g / l	(21.8 – 24.6 % w / w)
content of technical active substance :	260.4 g / l	(24.2 % w / w)
limits :	244.8 – 276 g / l	(22.7 – 25.7 % w / w)

at a typical purity of the technical active substance of 96 %

Information on the formulants is confidential, see Annex C.

DIVIDEND 030 FS

content of pure active substance :	30 g / l	(2.86 % w / w)
limits :	27 – 33 g / l	(2.6 – 3.1 % w / w)
content of technical active substance :	31.3 g / l	(2.98 % w / w)
limits :	28.1 – 34.4 g / l	(2.7 – 3.3 % w / w)

at a typical purity of the technical active substance of 96 %

Information on the formulants is confidential, see Annex C.

1.5 Use of the plant protection product (Annex IIA 3.2 to 3.4; Annex IIIA 3.1 to 3.7, 3.9 and 12.1)

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

Difenoconazole is a systemic triazole fungicide that controls a broad-spectrum of foliar, seed and soil-borne diseases, caused by Ascomycetes, Basidiomycetes and Deuteromycetes, in cereals, soya, rice, grapes, pome fruit, stone fruit, potatoes, sugar beet and several vegetable and ornamental crops. It is applied by foliar spray or seed treatment.

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

Difenoconazole is a systemic triazole fungicide used for long-lasting preventative and curative broad-spectrum control of cereal, fruit and vegetable diseases including powdery mildew, rust, scab and leaf spots. It acts by interference with the ergosterol biosynthesis in target fungi by inhibition of the C-14-demethylation of sterols, which leads to morphological and functional changes of the fungal cell membrane.

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

Table 1 .5.3.a. Good Agricultural Practice (GAP) for Products Containing Difenoconazole.

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		
Pome fruit	EU (N/S)	Score A7402T	F	*Podosphaera leucotricha* *Venturia inaequalis*	EC	250 g/l	High vol spray or mist blower	Spray programme beginning at flowering (BBCH 61)	1-4	10-14	0.00375	500 1500	0.01875 0.05625	28	EU(N)
											0.0075	500 1000	0.0375 0.0750	14	EU (S)
Carrot	EU (N/S)	Score A7402T	F	*Alternaria dauci* *Erysiphe heraclei*	EC	250 g/l	High vol spray	BBCH 42/43	1-3	14	-	100 500	0.125	14	
Wheat	EU (N/S)	Dividend A9142G	F	*Fusarium spp. Tilletia spp.*	FS	30 g/l	Seed treatment	BBCH 00	1	-	0.03-0.06 kg as/tonne	-	0.005 0.012	-	kgas/ha rate depends on seeding rate
Barley	EU (N/S)	Dividend A9142G	F	*Pyrenophorma granimea*	FS	30 g/l	Seed treatment	BBCH 00	1	-	0.03-0.06 kg as/tonne	-	0.005 0.012	-	kgas/ha rate depends on seeding rate
Triticale	EU (N/S)	Dividend A9142G	F	*Fusarium spp. Tilletia spp.*	FS	30 g/l	Seed treatment	BBCH 00	1	-	0.03-0.06 kg as/tonne	-	0.005 0.012	-	kgas/ha rate depends on seeding rate

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		
Rye	EU (N/S)	Dividend A9142G	F	*Fusarium spp. Urocystis occulata*	FS	30 g/l	Seed treatment	BBCH 00	1	-	0.03-0.06 kg as/tonne	-	0.005 0.012	-	kgas/ha rate depends on seeding rate
Oats	EU (N/S)	Dividend A9142G	F	*Ustilago avenae Pyrenphora avenae Cochliobolus sativum Fusarium culmorum Gibberella avenacea Pythium ultimum*	FS	30 g/l	Seed treatment	BBCH 00	1	-	0.03-0.06 kg as/tonne	-	0.005 0.012	-	kgas/ha rate depends on seeding rate

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

1.5.4 Information on authorization in EU Member states (Annex IIIA 12.1)

Country	Crops	Harmful organisms	a) Rate of application b) Number of applications c) Timing of application (growth stages/season) d) PHI
Austria	Asparagus	*Pleospora herbarum* *Puccinia asparagi*	a) 0.100 kg a.i./ha b) 3 c) d)
	Barley group/seed	*Fusarium spp.* *Helminthosporium spp.*	a) 0.050 kg a.i./tonne b) 1 c) Seed treatment d)
	Cabbage	*Alternaria spp.* *Phoma spp.* *Pseudocercosporella spp.*	a) 0.125 kg a.i./ha b) 3-4 c) d) 21
	Cabbage, Chinese	*Alternaria spp.* *Phoma spp.* *Pseudocercosporella spp*	a) 0.075-0.125 kg a.i./ha b) 3-4 c) d) 21
	Carrot	*Alternaria dauci* *Erysiphe heraclei*	a) 0.075-0.125 kg a.i./ha b) 2-3 c) d) 14
	Celery	*Septoria apiicola*	a) 0.075-0.125 kg a.i./ha b) 4 c) d) 14
	Oat group/seed	*Fusarium spp.* *Pyrenophora avenae* *Septoria spp.*	a) 0.50 kg a.i./tonne b) 1 c) Seed treatment d)
	Rye/seed	*Fusarium spp.*	a) 0.50 kg a.i./tonne b) 1 c) Seed treatment d)
	Sugar beet	*Cercospora beticola* *Erysiphe betae*	a) 0.075-0.100 kg a.i./ha b) <2 c) d) 28
	Triticale group/seed	*Fusarium spp.* *Septoria spp.* *Tilletia caries*	a) 0.050 kg a.i./tonne b) 1 c) Seed treatment d)
	Wheat group/seed	*Fusarium spp.* *Septoria spp.* *Tilletia caries* *Tilletia controversa*	a) 0.050 kg a.i./tonne b) 1 c) Seed treatment d)
	Wheat, winter	*Fusarium spp.* *Septoria spp.* *Tilletia caries* *Tilletia controversa*	a) 0.125 kg a.i./ha b) 1 c) Foliar application d)
Belgium	Apple	*Podosphaera leucotricha* *Venturia inaequalis*	a) 0.025 kg a.i./ha b) c) d)14
	Asparagus	*Botrytis cinerea* *Pleospora allii* *Puccinia asparagi*	a) 0.125 kg a.i./ha b) c) d)

Country	Crops	Harmful organisms	a) Rate of application b) Number of applications c) Timing of application (growth stages/season) d) PHI
	Beet group	*Erysiphe betae* *Eryphise polygoni* *Ramularia beticola* *Uromyces betae*	a) 0.105 kg a.i./ha b) c) d) 21
	Beet group	*Erysiphe betae* *Eryphise polygoni* *Ramularia beticola* *Uromyces betae*	a) 0.125 kg a.i./ha b) c) d) 21
	Beet group	*Cercospora beticola* *Erysiphe betae* *Eryphise polygoni* *Ramularia beticola* *Uromyces betae*	a) 0.100 kg a.i./ha b) c) d) 28
	Broccoli	*Alternaria brassicae* *Alternaria brassicicola* *Mycosphaerella brassicicola*	a) 0.125 kg a.i./ha b) 1-2 c) d) 14
	Brussels sprouts	*Alternaria brassicae* *Alternaria brassicicola* *Mycosphaerella brassicicola*	a) 0.125 kg a.i./ha b) 1-2 c) d) 21
	Cabbage group	*Alternaria brassicae* *Alternaria brassicicola* *Mycosphaerella brassicicola*	a) 0.125 kg a.i./ha b) 1-2 c) d) 21
	Carrot	*Alternaria dauci* *Erysiphe heraclei*	a) 0.125 kg a.i./ha b) 1-3 c) d) 14
	Cauliflower	*Alternaria brassicae* *Alternaria brassicicola* *Mycosphaerella brassicicola*	a) 0.125 kg a.i./ha b) 1-2 c) d) 14
	Celeriac	*Septoria apiicola*	a) 0.125 kg a.i./ha b) 1-4 c) d) 15
	Chicory, coffee	*Alternaria cichorii* *Erysiphe cichoracearum* *Puccinia hieracii*	a) 0.125 kg a.i./ha b) 1 c) d) 30
	Chicory, witloof	*Alternaria cichorii* *Erysiphe cichoracearum* *Puccinia hieracii*	a) 0.125 kg a.i./ha b) 1 c) d) 30
	Kale	*Alternaria brassicae* *Alternaria brassicicola* *Mycosphaerella brassicicola*	a) 0.125 kg a.i./ha b) 1-2 c) d) 21
	Ormanental group	*Venturia spp.*	a) b) c) d)
	Pear	*Podosphaera leucotricha* *Venturia pirina pyrina*	a) 0.025 kg a.i./ha b) c) d) 14

Country	Crops	Harmful organisms	a) Rate of application b) Number of applications c) Timing of application (growth stages/season) d) PHI
	Salsify	*Erysiphe cichoracearum*	a) 0.125 kg a.i./ha b) 1-4 c) d) 63
	Wheat group	*Erysiphe graminis* *Leptosphaeria nodorum* *Puccinia spp.*	a) 0.120 kg a.i./ha b) c) d)
Denmark	Barley, spring		a) 0.075 kg a.i./tonne b) c) Seed treatment d)
	Rye, winter	*Fusarium spp.* *Urocystis occulta*	a) 0.075 kg a.i./tonne b) c) Seed treatment d)
	Rye/seed		a) 0.056 kg a.i./tonne b) 1 c) Seed treatment d)
	Triticale group/seed		a) 0.056 kg a.i./tonne b) 1 c) Seed treatment d)
	Wheat group/seed	*Fusarium spp.* *Septoria spp.* *Tilletia spp.* *Ustilago spp.*	a) 0.056 kg a.i./tonne b) 1 c) Seed treatment d)
	Wheat, winter	*Fusarium spp.* *Septoria spp.* *Tilletia caries* *Tilletia controversa*	a) 0.075 kg a.i./tonne b) c) Seed treatment d)
Finland	Barley, spring/seed	*Cochliobolus sativus*	a) 0.113 kg a.i./tonne b) 1 c) Seed treatment d)
France	Apple	*Venturia inaequalis*	a) b) 10-15 c) d) 30
	Apricot	*Minilinia fructigena* *Podosphaera tridactyla*	a) b) c) d) 14
	Asparagus	*Pleospora allii* *Puccinia asparagi*	a) 0.125 kg a.i./ha b) ≤3 c) end June – beg. August d)
	Banana		a) 0.100 kg a.i./ha b) c) d)
	Brussels sprouts	*Alternaria spp.* *Mycosphaerella brassicicola*	a) 0.125 kg a.i./ha b) c) d) 21

Country	Crops	Harmful organisms	a) Rate of application b) Number of applications c) Timing of application (growth stages/season) d) PHI
	Cabbage	*Alternaria spp.* *Mycosphaerella brassicicola*	a) 0.125 kg a.i./ha b) c) d) 21
	Carrot	*Alternaria spp.* *Erysiphe heraclei*	a) 0.125 kg a.i./ha b) c) d) 14
	Cauliflower	*Alternaria spp.* *Mycosphaerella brassicicola*	a) 0.125 kg a.i./ha b) c) d) 14
	Celery	*Septoria apiicola*	a) 0.125 kg a.i./ha b) c) d)
	Cereal group	*Gibberella fujikuroi* *Leptosphaeria herpotrichoides* *Tilletia foetida*	a) 0.050 kg a.i./tonne b) c) Seed treatment d)
	Chicory, witloof	*Gibberella fujikuroi* *Leptosphaeria herpotrichoides* *Tilletia foetida*	a) 0.125 kg a.i./ha b) c) d) 21
	Grape	*Guignardia bidwelii* *Pseudopeziza tracheiphila* *Uncinula necator*	a) 0.030 kg a.i./ha b) ≤ 4 c) one month before to one month after flowering d) 21
	Grape	*Guignardia bidwelii* *Pseudopeziza tracheiphila* *Uncinula necator*	a) 0.030 kg a.i./ha b) ≤ 10 c) various d)
	Linseed	*Oidium lini* *Phoma spp.*	a) 0.125 kg a.i./ha b) c) d)
	Pea group		a) 0.100 kg a.i./ha b) 2 c) until BBCH 40-45 d) 28
	Pea, field	*Ascochyta spp.* *Botrytis cinerea*	a) 0.125 kg a.i./ha b) 2 c) beginning flowering then 14 days later d) 30
	Pea, garden	*Ascochyta pisi* *Botrytis cinerea*	a) 0.125 kg a.i./ha b) c) d) 15
	Peach	*Monilinia laxa* *Sphaerotheca pannosa*	a) b) c) d) 14
	Pear	*Venturia pirina pyrina*	a) 0.125 kg a.i./ha b) 10-15 c) last application end July d) 30

Country	Crops	Harmful organisms	a) Rate of application b) Number of applications c) Timing of application (growth stages/season) d) PHI
	Plum	*Monilinia fructigena*	a) b) c) d) 14
	Rape	*Alternaria brassicae* *Pseudocercosporella capsellae* *Pyrenopeziza brassicae* *Sclerotinia sclerotiorum*	a) 0.125 kg a.i./ha b) 1-2 c) various d) 30
	Rose, French	*Diplocarpon rosae* *Phragmidium mucronatum* *Sphaerotheca pannosa*	a) b) c) d)
	Salsify	*Oidium spp.*	a) 0.125 kg a.i./ha b) c) d)
	Sugarbeet	*Cercospora beticola* *Erysiphe betae* *Ramularia beticola* *Uromyces betae*	a) 0.090 kg a.i./ha b) 1-2 c) first symptoms then 3-4 weeks later d)
	Sugarbeet	*Cercospora beticola* *Erysiphe betae* *Ramularia beticola* *Uromyces betae*	a) 0.125 kg a.i./ha b) 2 c) first symptoms then 3-4 weeks later d)
	Sugarbeet	*Cercospora beticola* *Erysiphe betae* *Ramularia beticola* *Uromyces betae*	a) 0.100 kg a.i./ha b) 2 c) first symptoms then 3-4 weeks later d) 30
	Sunflower	*Phoma spp.*	a) 0.125 kg a.i./ha b) c) d)
	Tomato	*Alternaria solani* *Phytodecta sp.*	a) 0.125 kg a.i./ha b) ≤ 2 c) when plants growing d) 20
	Tomato	*Alternaria solani* *Phoma destructive*	a) 0.125 kg a.i./ha b) ≤ 3 c) fruit maturation d) 20
	Wheat group	*Fusarium spp.* *Puccinia spp.* *Septoria spp.*	a) 0.075 kg a.i./ha b) c) d)
	Wheat group	*Erysyphe graminis* *Puccinia recondite* *Septoria spp.*	a) 0.125 kg a.i./ha b) 1 c) beginning of earing d) 30
	Wheat group	*Gibberella fujikuroi* *Leptosphaeria herpotrichoides* *Tilletia foetida*	a) 0.050 kg a.i./tonne b) c) Seed treatment d)
	Wheat group	*Gibberella fujikuroi* *Leptosphaeria herpotrichoides* *Tilletia foetida*	a) 0.050 kg a.i./tonne b) c) Seed treatment d)

Country	Crops	Harmful organisms	a) Rate of application b) Number of applications c) Timing of application (growth stages/season) d) PHI
	Wheat group/seed	*Septoria spp.* *Tilletia caries*	a) 0.030 kg a.i./tonne b) c) Seed treatment d)
Germany	Asparagus	*Puccinia asparagi* *Stemphylium spp.*	a) 0.100 kg a.i./ha b) 3 c) d)
	Beet, fodder	*Cercospora beticola* *Erysiphe betae* *Ramularia beticola*	a) 0.100 kg a.i./ha b) 2 c) at first sign of symptoms d) 28
	Beet, fodder	*Cercospora beticola* *Erysiphe betae* *Ramularia beticola*	a) 0.100 kg a.i./ha b) 2 c) d) 28
	Beet, red	*Cercospora beticola* *Ramularia beticola*	a) 0.100 kg a.i./ha b) 3 c) d) 28
	Blackberry	*Phragmidium violaceum* *Rhabdospora ruborum*	a) 0.100 kg a.i./ha b) 3 c) > harvest d)
	Broccoli	*Alternaria spp.* *Mycosphaerella brassicicola*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Brussels sprouts	*Alternaria brassicae*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Brussels sprouts	*Erysiphe cruciferarum*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Cabbage group	*Alternaria spp.* *Mycosphaerella brassicicola*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Cabbage group	*Alternaria brassicae* *Alternaria brassicicola* *Leptosphaeria maculans* *Mycosphaerella brassicicola*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Cabbage, Chinese	*Alternaria spp.*	a) 0.100 kg a.i./ha b) 3 c) d) 14
	Cabbage, Chinese	*Alternaria brassicae* *Alternaria brassicicola* *Leptosphaeria maculans* *Erysiphe cruciferarum*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Carrot	*Alternaria dauci* *Alternaria radicina* *Cercospora carotae* *Erysiphe heraclei*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Cauliflower	*Alternaria spp.* *Mycosphaerella brassicicola*	a) 0.100 kg a.i./ha b) 3 c) d) 21

Country	Crops	Harmful organisms	a) Rate of application b) Number of applications c) Timing of application (growth stages/season) d) PHI
	Celeriac	*Septoria spp.* *Puccinia apii* *Septoria apiicola*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Celery, bleached	*Puccinia apii* *Septoria apiicola*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Chicory, coffee	*Erysiphe cichoracearum* *Puccinia hieracii*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Cucumber	*Alternaria alternator.* *Erysiphe cichoracearum* *Sphaerotheca fuliginea*	a) 0.100 -0.200 kg a.i./ha b) 3 c) d) 3
	Herb group	*Leveillula spp.* *Puccinia spp.* *Septoria spp.* *Erysiphe f.spp.*	a) 0.100 kg a.i./ha b) 2 c) d) 14
	Horseradish	*Erysiphe cruciferarum* *Septoria spp.*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Jerulasem artichoke	*Puccinia helianthi*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Leek	*Alternaria spp.* *Alternaria porri* *Cladosporium alliiporri* *Puccinia allii*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Ormanental group	*Erysiphe polyphaga* *Puccinia chrysanthemi* *Ramularia deusta*	a) 0.100 kg a.i./ha b) 3 c) d)
	Parsley, turnip-rooted	*Erysiphe heraclei* *Puccinia rubiginosa* *Serptoria spp.*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Parsnip	*Erysiphe f.spp.* *Septoria spp.*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Rape, winter	*Leptosphaeria maculans*	a) 0.250 kg a.i./ha b) 1 c) d)
	Raspberry	*Didymella applanata* *Phragmidium rubiidaei*	a) 0.100 kg a.i./ha b) 3 c) > harvest d)
	Rye	*Urocystis occulta* *Gerlachia nivale*	a) 0.250 kg a.i./tonne b) 1 c) Seed treatment d)
	Rye	*Urocystis occulta* *Gerlachia nivale*	a) 0.075 kg a.i./tonne b) 1 c) Seed treatment d)

Country	Crops	Harmful organisms	a) Rate of application b) Number of applications c) Timing of application (growth stages/season) d) PHI
	Salsify	*Erysiphe cichoracearum* *Septoria spp.*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Strawberry	*Diplocarpon earlianum earliana* *Mycosphaerella fragariae*	a) 0.100 kg a.i./ha b) 2 c) d)
	sugarbeet	*Cercospora beticola* *Erysiphe betae* *Ramularia beticola*	a) 0.100 kg a.i./ha b) 2 c) at first sign of symptoms d) 28
	Swede	*Erysiphe cruciferarum* *Pseodocercosporella capsellae*	a) 0.100 kg a.i./ha b) 3 c) d) 21
	Wheat, winter	*Erysiphe graminis* *Leptosphaeria nodorum* *Puccinia recondita* *Puccinia striiformis* *Drechslera triticirepentis*	a) 0.125 kg a.i./ha b) 1 c) from beg. of ear emergence until start of flowering BBCH 59-69 d) 35
	Wheat, winter	*Erysiphe f.spp.* *Puccinia spp.* *Septoria spp.*	a) 0.125 kg a.i./ha b) 3 c) d) 35
	Triticale group	*Gerlachia nivale*	a) 0.075 kg a.i./tonne b) 1 c) Seed treatment d)
	Wheat, winter	*Fusarium culmorum* *Septoria nodorum* *Tilletia caries* *Tilletia controversa* *Ustilago tritici* *Gerlachi nivale*	a) 0.250 kg a.i./tonne b) 1 c) Seed treatment d)
	Wheat, winter	*Fusarium culmorum* *Septoria nodorum* *Tilletia caries* *Tilletia controversa* *Ustilago tritici* *Gerlachi nivale*	a) 0.100 kg a.i./tonne b) 1 c) Seed treatment d)
Great Britain (UK)	Broccoli	*Alternaria spp.* *Mycosphaerella brassicicola*	a) 0.075 kg a.i./ha b) 1-3 c) d) 21
	Brussels sprouts	*Alternaria spp.* *Mycosphaerella brassicicola*	a) 0.075 kg a.i./ha b) 1-3 c) d) 21
	Cabbage	*Alternaria spp.* *Mycosphaerella brassicicola*	a) 0.075 kg a.i./ha b) 1-3 c) d) 21
	Cauliflower	*Alternaria spp.* *Mycosphaerella brassicicola*	a) 0.075 kg a.i./ha b) 1-3 c) d) 21

Country	Crops	Harmful organisms	a) Rate of application b) Number of applications c) Timing of application (growth stages/season) d) PHI
	Rape	*Alternaria spp.* *Leptosphaeria maculans* *Pyrenopeziza brassicae*	a) 0.125 kg a.i./ha b) 1-2 c) d)
	Wheat, winter	*Puccinia recondita sp. Tritici* *Septoria tritici*	a) 0.075 kg a.i./ha b) 1 c) before grain early milk-ripe stage (GS 59-71) d)
Greece	Apple	*Venturia inaequalis*	a) 0.063-0.094 kg a.i./ha b) 1-4 c) d) 30
	Asparagus	*Puccinia asparagi*	a) 0.075-0.125 kg a.i./ha b) 3 c) d)
	Sugarbeet	*Cercospora beticola*	a) 0.030-0.045 kg a.i./ha b) c) d) 30
	Sugarbeet	*Cercospora beticola*	a) 0.063-0.125 kg a.i./ha b) 1-2 c) 1-2 months before harvest d) 20
	sugarbeet	*Cercospora beticola* *Erysiphe betae* *Ramularia beticola*	a) 0.100 kg a.i./ha b) 1-2 c) d) 28
Ireland	Beet, fodder	*Cercospora spp.* *Erysiphe betae* *Ramularia spp.* *Uromyces betae*	a) 0.075-0.125 kg a.i./ha b) 1 c) d) 28
	Brussels sprouts	*Alternaria brassicae* *Mycosphaerella brassicicola*	a) 0.125 kg a.i./ha b) 4 c) when crop has minimum 80% ground cover d) 21
	Cabbage group	*Alternaria brassicae* *Mycosphaerella brassicicola*	a) 0.125 kg a.i./ha b) 3 c) when crop has minimum 80% ground cover d) 21
	Sugarbeet	*Cercospora betae* *Erysiphe betae* *Ramularia beticola* *Uromyces betae*	a) 0.075-0.125 kg a.i./ha b) 1 c) d) 28
	Wheat group	*Alternaria spp.* *Cladosporium spp.* *Puccinia recondita* *Puccinia striiformis* *Septoria spp.*	a) 0.075-0.125 kg a.i./ha b) 1 c) GS 59-71 d)
Italy	Apple	*Venturia inaequalis* *Podosphaera leucotricha*	a) b) 1-4 c) d) 14
	Pear	*Venturia inaequalis* *Podosphaera leucotricha*	a) b) 1-4 c) d) 14

Country	Crops	Harmful organisms	a) Rate of application b) Number of applications c) Timing of application (growth stages/season) d) PHI
	Sugarbeet	*Cercospora beticola*	a) 0.050-0.075 kg a.i./ha b) 1-3 c) d) 21
	Sugarbeet	*Cercospora beticola* *Erysiphe betae*	a) 0.050-0.070 kg a.i./ha b) 2-3 c) d) 21
Luxembourg	Apple	*Venturia inaequalis*	a) b) c) from 1st warnings d)
	Apple	*Podosphaera leucotricha*	a) b) c) from 1st appearance of the symptoms d)
	Grape	*Guignardia bidvellii* *Pseudopeziza tracheiphila* *Uncinula necator*	a) 0.030 kg a.i./ha b) c) d)
	Pear	*Venturia inaequalis*	a) b) c) d)
	Sugarbeet	*Erysiphe betae* *Erysiphe polygoni* *Ramularia beticola* *Uromyces betae*	a) 0.125 kg a.i./ha b) c) d)
The Netherlands	Apple	*Venturia inaequalis*	a) 0.026-0.056 kg a.i./ha b) 1-4 c) d) 21
	Apple	*Venturia inaequalis*	a) 0.026-0.056 kg a.i./ha b) 3-4 c) d) 21
	Pear	*Venturia inaequalis*	a) 0.026-0.056 kg a.i./ha b) 1-4 c) d) 21
	Sugarbeet, planted	*Cercospora beticola* *Erysiphe betae* *Ramularia beticola* *Uromyces betae*	a) 0.100 kg a.i./ha b) 1-2 c) d) 28
	Wheat, spring	*Puccinia recondita sp. tritici* *Septoria tritici*	a) 0.125 kg a.i./ha b) 1 c) d) 42
	Wheat, winter	*Puccinia recondita sp. tritici* *Septoria tritici*	a) 0.125 kg a.i./ha b) 1 c) d) 42
Portugal	Apple	*Podosphaera leucotricha* *Venturia inaequalis*	a) 0.038-0.050 kg a.i./ha b) 3 c) d) 14

Country	Crops	Harmful organisms	a) Rate of application b) Number of applications c) Timing of application (growth stages/season) d) PHI
	Bean group	*Colletotrichum lindemuthianum* *Uromyces appendiculatus*	a) 0.125 kg a.i./ha b) 2 c) d) 7
	Carrot	*Alternaria dauci* *Erysiphe f.spp.*	a) 0.125 kg a.i./ha b) 3 c) d) 14
	Field bean	*Alternaria solani*	a) 0.125 kg a.i./ha b) 2 c) d) 14
	Ornamental group		a) 0.125 kg a.i./ha b) 2 c) d)
	Pea	*Erysiphe polygoni*	a) 0.100-0.125 kg a.i./ha b) 2 c) d) 7
	Pear tree group	*Venturia pirina pyrina*	a) 0.038-0.050 kg a.i./ha b) 3 c) d) 14
	Sugarbeet, planted	*Cercospora beticola* *Erysiphe betae* *Ramularia beticola*	a) 0.125 kg a.i./ha b) 2 c) d) 28
	sugarbeet	*Cercospora beticola* *Erysiphe betae* *Ramularia beticola*	a) 0.100 kg a.i./ha b) 1-2 c) d) 28
Spain	Asparagus	*Puccinia asparagi*	a) 0.125 kg a.i./ha b) 3 c) BBCH 49 d) 30
	Barley group/seed	*Pyrenophora graminea*	a) 0.030-0.060 kg a.i./tonne b) c) Seed treatment d)
	Celery	*Septoria spp.*	a) 0.075-0.125 kg a.i./ha b) 4 c) BBCH 19 d) 14
	Garlic	*Puccinia spp.*	a) 0.125 kg a.i./ha b) 3-4 c) BBCH 49 d) 30
	Lettuce	*Alternaria spp.*	a) 0.125 kg a.i./ha b) 3 c) BBCH 45-49 d) 14
	Medlar tree, common		a) 0.075 kg a.i./ha b) 3-5 c) d) 14
	Olive	*Cycloconium oleaginum*	a) b) c) exclusively in spring d)

Country	Crops	Harmful organisms	a) Rate of application b) Number of applications c) Timing of application (growth stages/season) d) PHI
	Ornamental group	*Puccinia spp.*	a) 0.075-0.125 kg a.i./ha b) 5 c) at flowering d)
	Pome fruit	*Venturia spp.*	a) 0.075 kg a.i./ha b) 3-5 c) BBCH 56-71 d) 14
	Pome fruit	*Venturia spp.*	a) 0.075 kg a.i./ha b) 3-5 c) BBCH 71-74 d) 14
	Pome fruit group	*Gymnosporangium fuscum* *Septoria spp.*	a) 0.075 kg a.i./ha b) 3-5 c) BBCH 74 d) 14
	Pome fruit group	*Venturia spp.*	a) 0.075 kg a.i./ha b) 3-5 c) BBCH 56-71 d) 14
	Pome fruit group	*Venturia spp.*	a) 0.075 kg a.i./ha b) 3-5 c) BBCH 71-74 d) 14
	Potato	*Alternaria solani*	a) 0.200 kg a.i./ha b) 3-4 c) BBCH 49 d) 30
	Sugar beet	*Cercospora beticola* *Erysiphe betae*	a) 0.075-0.125 kg a.i./ha b) 1-3 c) BBCH 49 d) 30
	Sugar beet	*Cercospora spp.* *Oidiopsis spp.* *Roystonea spec.*	a) 0.075-0.100 kg a.i./ha b) 1-3 c) d) 30
	Tomato		a) 0.125-0.200 kg a.i./ha b) 2-4 c) d) 7
	Wheat group/seed	*Cochliobolus sativus* *Fusarium spp.* *Septoria spp.* *Tilletia caries* *Ustilago spp.*	a) 0.030-0.060 kg a.i./tonne b) c) Seed treatment d)
Sweden	Cereal group		a) 0.060-0.080 kg a.i./tonne b) c) Seed treatment d)

Level 2

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

2.1.1 Identity

All points (Annex II, section 1 and Annex III, section 1) have been addressed and the information provided is sufficient and acceptable.

2.1.2 Physical and chemical properties

2.1.2.1 Physical and chemical properties of the active substance

Study reports with regard to physical and chemical properties of the active substance have been submitted for all reported parameters.

All tests have been performed according to the methods recommended in Annex II of the directive 91/414/EEC except the hydrolysis rate, which was determined by an in-house method. Furthermore, all of the tests have been performed in accordance with GLP, except the vapour pressure for difenoconazole. All the tests and the methods used are considered acceptable.

Difenoconazole as manufactured is an off-white powder with a slightly sweet odour. The relative density is 1.39 and the pure material has a melting point of 82-83 °C. The solubility is not pH dependant under environmentally relevant pH and was measured to be approximately 15 mg/l and the log P_{ow} was determined to be 4.36 at pH 8. It is stable towards both hydrolysis and photolysis. The half-life of difenoconazole in the reaction with OH-radicals in the atmosphere is 4.9 days.
Difenoconazole technical has no explosive or oxidizing properties and should not be regarded as highly flammable or auto-flammable.

2.1.2.2 Physical and chemical properties of the plant protection product

Data for two representative formulations, Score 250 EC and Dividend 030 FS was submitted:

Score 250 EC

All tests on the physical and chemical properties of Score 250 EC have been performed with the obsolete formulation A-7402 G. However this procedure is acceptable since A-7402 G and the representative formulation A-7402 T (Score 250 EC) are considered equivalent regarding the physical and chemical properties (see Annex C for further details).

Study reports with regard to physical and chemical properties of the preparation have been submitted for all relevant parameters.
The tests have been performed according to the methods recommended in Annex III of the directive 91/414/EEC, except the oxidizing properties, which was assessed in accordance with the Recommendation on the Transport of Dangerous Goods, Manual of Test and Criteria. Part III, section 34. United Nations, 1995. Furthermore, all of the tests have been performed in accordance with GLP, except some studies performed in connection with the storage stability studies. All the tests and the methods used are considered acceptable.

Score 250 EC (A-7402 T) is a clear yellow to brown liquid emulsion concentrate formulation with a penetrating odour. The formulation is not oxidizing or explosive and has an auto-ignition temperature of 445 °C. pH of a 1% suspension of the formulation is 6.3. The formulation was proven to be stable in accelerated storage tests for at least 2 weeks at 54 °C and for at least 18 weeks at 30 °C, when kept in the sales packaging. Moreover, the shelf life of the product at ambient temperature, when kept in the sales packaging, was proved to be at least two years. All other physical and chemical properties indicate that no particular problems are to be expected when used and stored as recommended on the label.

Dividend 030 FS

Study reports with regard to physical and chemical properties of the preparation have been submitted for all relevant parameters.
The tests have been performed according to the methods recommended in Annex III of the directive 91/414/EEC, except the oxidizing properties, which was assessed in accordance with the Recommendation on the Transport of Dangerous Goods, Manual of Test and Criteria. Part III, section 34. United Nations, 1995. Furthermore, most of the tests have been performed in accordance with GLP except the appearance, some assessments performed in connection with the storage stability studies, the persistent foaming, the suspensibility, the wet sieve test and the pourability. All the tests and the methods used are considered acceptable.

Dividend 030 FS (A-9142 G) is a red flowable concentrate for seed treatment with a sweetish, chalky odour. The formulation is not oxidizing or explosive and has an auto-ignition temperature of 485 °C. pH of a 1% suspension of the formulation is 7.2. When the viscosity was tested Dividend 030 FS was shown to be pseudoplastic in its flow behaviour (i.e it is a non-Newtonian liquid). The formulation was proven to be stable in accelerated storage tests for at least 2 weeks at 54 °C and for at least 18 weeks at 30 °C when kept in the sales packaging. Moreover, the shelf life of the product at ambient temperature, when kept in the sales packaging, was proved to be at least two years. All other physical and chemical properties indicate that no particular problems are to be expected when used and stored as recommended on the label.

2.1.3 Details of uses and further information

DIVIDEND 030FS

The systemic, broad-spectrum fungicide 'Dividend' (A-9142 G) is a flowable concentrate containing 30 g/L difenoconazole. It is intended for use as a seed treatment to control a broad-spectrum of diseases in cereals. The

main use of A-9142 G is on winter wheat in Northern Europe with an equivalent maximum field rate of 12.3 g ai/ha based on a seed planting rate of 205 kg seed/ha and a seed coating of 6 g ai/100 kg seeds.

SCORE 250EC

The systemic, broad-spectrum fungicide A-7402 T (Score® 250 EC) is an emulsifiable concentrate containing 250 g/L difenoconazole. It is intended for use as a foliar spray to control a broad-spectrum of diseases in pome fruit and vegetables. The proposed use patterns for critical uses in pome fruit and carrots in northern and southern Europe (NE, SE) with maximum use rates of 4 applications of 75 g ai/ha at 7-day intervals in pome fruit and 3 applications of 125 g ai/ha at 14-day intervals in carrots.

2.1.4 Classification and labelling

2.1.4.1 Classification and labelling of the active substance

Proposal for classification and labelling

Symbol letters	Xn
	N
Indications of danger	Harmful
	Dangerous for the environment

Proposal of danger and safety instructions and proposed labelling

Risk phrases	R22:	Harmful if swallowed
	R50/53:	Very toxic to aquatic organisms may cause long-term adverse effects in the aquatic environment.
Safety phrases	S46:	If swallowed, seek medical advice immediately and show this container or label.
	S60:	This material and its container must be disposed of as hazardous waste.
	S61:	Avoid release to the environment. Refer to safety data sheet.

2.1.4.2 Classification and labelling of the preparation

DIVIDEND 030FS

Proposal for classification and labelling

Symbol letters	None
Indications of danger	Dangerous for the environment

Proposal of danger and safety instructions and proposed labelling

Risk phrases	R52/53:	Harmful to aquatic organisms may cause long-term adverse effects in the aquatic environment.
Safety phrases	S2:	Keep out of the reach of children.
	S13:	Keep away from food, drink and animal feeding stuff.
	S20/21:	When using do not eat, drink or smoke.
	S35:	This material and its container must be disposed of in a safe way.
	S57:	Use appropriate containment to avoid environmental contamination.

SCORE 250EC

Hazard symbol(s) :	N	
Indication of danger :	Dangerous for the environment	
Risk phrases :	R 51/53 :	Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Safety phrases :	S 2 :	Keep out of the reach of children
	S 13 :	Keep away from food, drink and animal feeding stuffs
	S 20/21:	When using do not eat, drink or smoke
	S 35 :	This material and its container must be disposed of in a safe way
	S 57 :	Use appropriate containment to avoid environmental contamination

2.2 Methods of analysis

2.2.1 Analytical methods for analysis of the active substance as manufactured

An analytical method was developed for determination of difenoconazole in difenoconazole technical grade. The method was based on dissolving the technical material in acetone and analysing the solution by GC using flame ionisation detection and a DB-5 column.

The method is considered acceptable for its purpose and the validation complied with almost all requirements in SANCO/3030/99 rev. 4, 11/07/00.

Details on the analytical method for the determination of impurities in the technical active substance is regarded as confidential information and can be found in Annex C.

2.2.2 Analytical methods for formulation analysis

Analytical methods were developed for determination of difenoconazole in formulation products Dividend and Score. Dividend was dissolved in water and treated by ultrasonic bath and filtration/centrifugation before determination of the analyte by liquid chromatography using a Nucleosil C18 column, acetonitrile:water mobile phase (60 + 40) buffered at pH7 and UV detection at 240 nm. Score was dissolved in 1,2-dichlorbenzene and the analyte determined by gas chromatography using flame ionisation detection and a wide bore SE-54 column.

The validation of the methods complied with requirements in SANCO/3030/99 rev. 4, 11/07/00.

2.2.3 Analytical methods for residue analysis

Food and feed

In the determination of difenoconazole in food of plant origin an extended version of the multimethod DFG 19 was presented for monitoring and a method aimed at monitoring difenoconazole and a metabolite (CGA 205375) in "animal food products" was also presented. In the analysis of difenoconazole in food of plant origin different extraction procedures were used. The extractions of the pesticide from the crop matrices were performed using acetone and ethylacetate/cyclohexane (1 +1) for apple and lettuce (extraction modules E 1), same solvents but different procedural details for wheat grain (module E2) and acetone/acetonitrile (1 + 9) for oil seed rape (module E7) followed by clean-up procedures according to module GPC and module C1 (silica gel mini column). Finally, RP-HPLC-MS/MS was used for quantitation of difenoconazole (C18 column; acetonitrile/1% acetic acid). The LOQ was 0.01 mg/kg. Animal food samples were extracted by acetonitrile:water (80 + 20 v/v), cleaned-up by solid-phase extraction (Oasis) and quantified by RP-HPLC-MS/MS (C18 column; acetonitrile/0.2% formic acid). The LOQ was 0.01 mg/kg (for each of difenoconazole and the metabolite).

Several (three) pre-registration methods intended for analysis of difenoconazole in food of plant origin (wheat, tomato, carrot, potato, apple/pear) were based on the same extraction step, using methanol:ammonium hydroxide (8+2) under reflux conditions, followed by alternative clean-up techniques, such as the use of silica-gel SepPak, charcoal:magnesium oxide:celite columns and phenyl BondElut, and also using the same end determination technique, GC-NPD (packed column, OV-17). Another alternative method for the analysis of difenoconazole in carrot used methanol extraction, clean-up on basic aluminium oxide and end determination using GC-ECD (DB1 capillary column). The LOQ:s were in range 0.01 – 0.05 mg/kg.

One pre-registration method for determination of difenoconazole and the metabolite CGA 205375 in animal food products used extraction with acetonitrile:ammonium hydroxide (95+5), followed by SepPak clean-up (silica gel) and final determination using RP-HPLC-MS/MS (column switch system: 1. RP 16 amide; water:acetonitrile (45+55), followed by 2. C18; water:acetonitrile (30+70), 0.1% formic acid). Depending on matrix the LOQ was 0.01 mg/kg or 5-10 µg/l.

Soil

In one monitoring method difenoconazole was extracted from soil using methanol/ammonia (80 +20, v/v; reflux conditions) and quantitated after centrifugation by RP-HPLC-MS/MS (ODS column; acetonitrile/0.2% formic

acid). Other monitoring methods used the same extraction condition but other final determination techniques, such as GC-ECD (packed column, OV-17) and GC-AFID (packed column, OV-17) or GC-NPD (packed column, OV-17) after additional clean-up using silica SepPak when needed. These methods used HPLC-MS/MS as confirmation (conditions as in the first method mentioned above, applied to soil). LOQ:s for the monitoring methods were in the range 0.01 – 0.05 mg/kg.

One pre-registration method aimed at analysis of CGA 205375 (metabolite) also used the aforementioned extraction condition followed by clean-up on a phenyl-coated silica column and final determination by HPLC-UV at 270 nm (column switch-system: 1. C18; acetonitrile:water (40+60), followed by 2. ODS-2; acetonitrile:water (55+45)). LOQ was 0.02 mg/kg. An alternative pre-registration method used acetonitril extraction, silica cartridge clean-up and final determination by capillary GC-ECD (DB-17). In this case, the LOQ was 0.05 mg/kg.

Free 1,2,4-triazole in soil was determined in a pre-registration method using water extraction, derivatization (2,4-dinitro-fluorobenzene), C18 column clean-up and final determination (as derivate) by HPLC-UV at 270 nm (column switch-system: 1. nucleosil NH2; tert. -butylmethylether:ethanol (1000+30) followed by 2. Lichrospher Si 100; tert. -butylmethylether:ethanol (1000+80)). The LOQ was 0.01 mg/kg. Total concentration of 1,2,4-triazole (common moiety) was anaysed using methanol/ammonia extraction mentioned above (80 +20, v/v; reflux conditions) of triazole-containing analytes, followed by oxidation ($KMnO_4$) and derivatization of the liberated 1,2,4-triazole moiety (2,4-dinitro-fluorobenzene), which was finally determined (as derivate) by HPLC-UV at 270 nm (column switch-system: see previous). The LOQ was 0.05 mg/kg (expressed as difenoconazole).

Water

Using a monitoring method difenoconazole was extracted from water (drinking and surface) by SPE (phenyl phase) and quantitated by GC-ECD (DB-17 column). A pre-registration method used a very similar procedure (but a DB1 column in the GC determination). Two alternative confirmation procedures were assigned to both methods, a. RP-HPLC-UV (236 nm; two different column switch systems was used in the two methods) and b. RP-HPLC-MS/MS (e.g. the conditions used in the monitoring HPLC-MS/MS method applied to soil analysis). The LOQ in each method was 0.1 µg/l.

Air

Using a monitoring method difenoconazole was adsorbed from air using an XAD-2 adsorbent and desorbed into acetonitrile under sonification before quantitation by RP-HPLC-MS/MS (C18 column; acetonitrile/0.2% formic acid). In an alternative very similar monitoring method difenoconazole was desorbed into methanol before final determination by capillary GC-ECD (DB1). In this case confirmation was performed using the previous HPLC-MS/MS method. The LOQ:s were 0.99 – 1 µg/m^3.

The validation of all of the residue monitoring methods complied with requirements in SANCO/825/00 rev.6, 20/06/00, except some deviations of minor importance.

Two pre-registration methods, REM 7/86 (analysis of difenoconazole in soil) and AG-544A (analysis of difenoconazole in animal food products) were not fully validated according to requirements in SANCO/3029/99,

rev.4, 11/07/00. According to the notifier the AG-544A method and validation were presented in the dossier only to support a modified version of the method, aimed at the analysis of difenoconazole and a metabolite (CGA 205375) in animal food products.
All other pre-registration methods complied with the requirements in SANCO/3029/99.

2.3 Impact on human and animal health

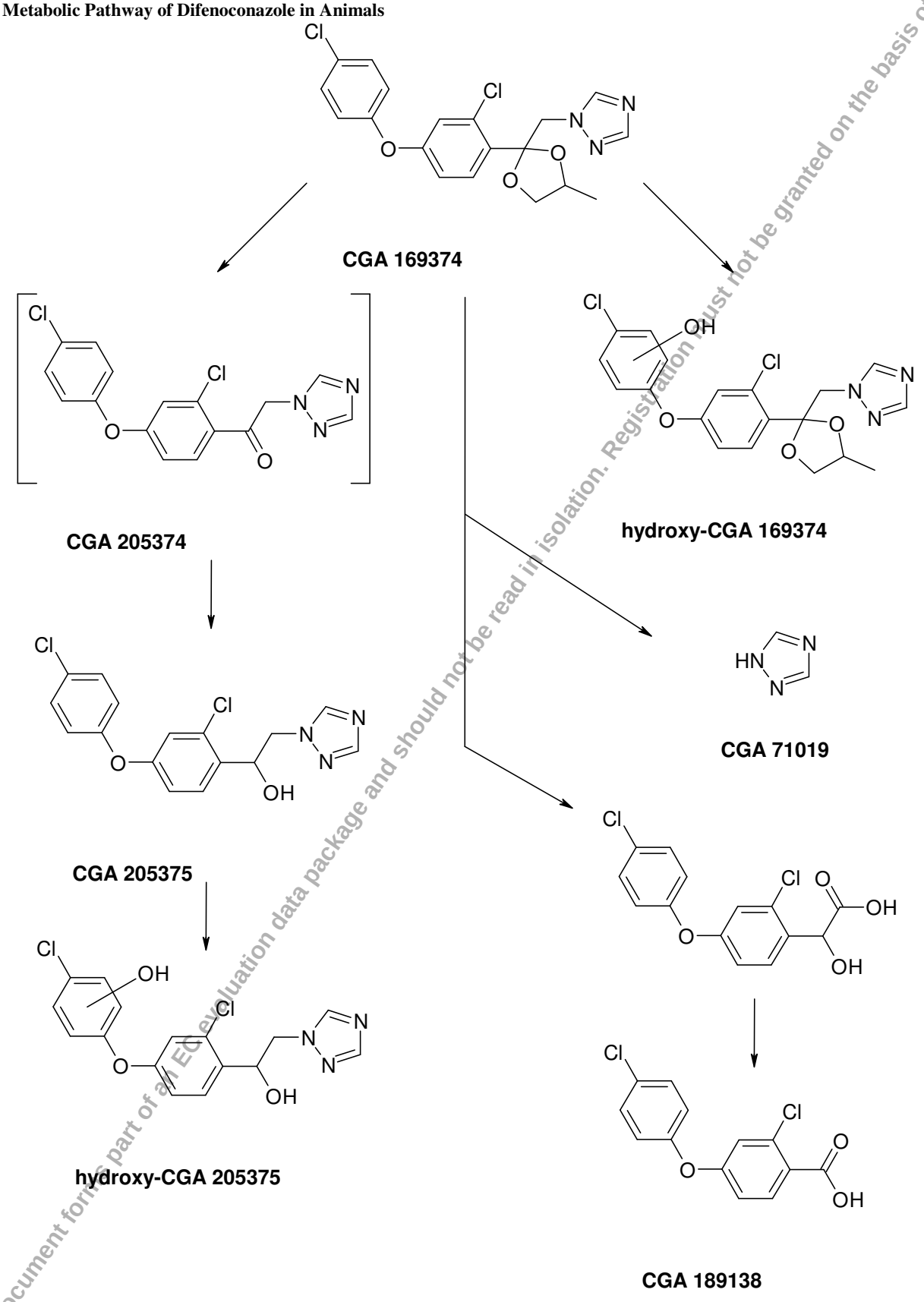
2.3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities contained in the active substance or to their transformation products

2.3.1.1 Toxicity of active ingredient

2.3.1.1.1 Toxicokinetics (absorption, distribution, excretion and metabolism)

A single oral dose of difenoconazole (0.5 mg/kg bw) was almost completely absorbed (>80%) based on a biliary and urinary excretion in bile duct cannulated rats of approximately 73-76% and 14-9% within 48 hours. The rapid elimination of difenoconazole was extensive and involved an entero-hepatic recirculation with a major excretion of biliary metabolites in faeces (>77%). After repeated administration of difenoconazole (0.5 mg/kg bw), more than 98% of the total activity applied was excreted within seven days after administration of the last dose. There were no differences in excretion profiles between the sexes. Administration of higher doses resulted in lower absorption and slower elimination kinetics of difenoconazole.
According to whole body autoradiography performed at 2 and 24 hours post administration of radiolabelled difenoconazole (0.5 mg/kg bw), most of the radioactivity was found in the bile and in the gastrointestinal tract. Initially, the tissue concentrations in liver, kidney and adrenal glands were higher than in plasma but after seven days only the concentration in fat was comparable to the plasma concentration. Tissue residues in females tended to be lower than in males. A pre-treatment with unlabelled test substance had no effect on the tissue distribution.
The difenoconazole molecule was extensively metabolised to three main metabolites, hydroxy-CGA 205375 (two isomeric forms), hydroxy-CGA 169374 (two isomeric forms) and CGA 205375 (1-[2-[2-chloro-4-(4-chloro -phenoxy)-phenyl]-2-1H-[1,2,4]triazol-yl]-ethanol), that together accounted for an average of 68% of the dose in faeces. The extensive biliary elimination was consistent with the relatively high molecular weights of the major metabolites. The urinary profile of metabolites was more complex and showed more variability between the two radiolabelled forms (^{14}C-phenyl labelled difenoconazole and ^{14}C-triazole labelled difenoconazole) administered. The metabolite 1, 2, 4-triazole was determined to account for <10% of the radioactivity in male rats. An additional metabolite, CGA 189138 (chlorophenoxy-chlorobenzoic acid), was isolated from the liver.

Metabolic Pathway of Difenoconazole in Animals



2.3.1.1.2 Acute toxicity

Table 2.3.1.a. Summary of acute toxicity, irritation and sensitisation studies with difenoconazole

Study	Dose levels	Results	Classification
Acute oral LD_{50} Argus et al., 1987	1000, 2000 and 3000 mg/kg	male and female 1453 mg/kg	**Xn, R22**
Acute oral LD_{50} Hartmann, 1990	1000 and 2000 mg/kg	>2000 mg/kg	N/R
Acute dermal LD_{50} Mastrocco et al., 1987	Limit test, 2010 mg/kg	>2010 mg/kg bw	N/R
Acute inhalation LC_{50} Hartmann H.R., 1991	Limit test, 3458 mg/m^3	>3300 mg/m^3	N/R
Skin irritation Glaza, S.M., 1991	0.5g	non-irritating	N/R
Eye irritation Glaza, S.M., 1991	0.05g	non-irritating	N/R
Skin sensitisation (modified Buehler) Mastrocco et al., 1987	0.5g	non-sensitising	N/R

According to the Council Directive 67/548/EEC, difenoconazole should be classified as R 22, "Harmful if swallowed" based on the acute oral LD_{50} of 1453 mg/kg. There were no signs of dermal irritation in the acute toxicity study. Signs of ocular irritation were observed in rabbits but the mean values of the readings were below the thresholds defined in the Council Directive 67/548/EEC hence classification is not required. There were no sensitisation effects observed in the modified Buehler test.

2.3.1.1.3 Short term toxicity

Table 2.3.1.b. Summary of short-term toxicity studies with difenoconazole.

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
ORAL: 28-day in rat					
Suter, P., 1986a	27/27, 156/166 and 914/841 mg kg^{-1} day^{-1} (M/F) 0, 250, 1 500, 10 000 ppm	Orally via the diet	**NOAEL: M/F:156/166 mg kg^{-1} day^{-1}** **1500 ppm** NOEL: M/F: <27/27 mg kg^{-1} day^{-1} <250 ppm	**LOAEL: M/F: 914/841 mg kg^{-1} day^{-1}** **10 000 ppm** LOEL: M/F: 27/27 mg kg^{-1} day^{-1} 250 ppm	**↓ Body weight** **↓ Carcass weight** **↓ Organ weight** 10 000 ppm: Altered clinical chemical parameters Altered blood parameters ↓ PT time Dysproteinemia
90-day in rat					
Suter, P., 1986b ***(Wistar rats)***	0, 3.3/3.5, 19.9/21.4 and 120.9/ 128.5 mg kg^{-1} day^{-1} (M/F) 0, 40, 250 and 1500 ppm	Orally via the diet	**NOAEL: M/F: 20/21 mg kg^{-1} day^{-1}** **250 ppm** NOEL: M/F: 3.3/3.5 mg kg^{-1} day^{-1} 40 ppm	**LOAEL: M/F: 120.9/ 128.5 mg kg^{-1} day^{-1}** **1500 ppm** LOEL: M/F: 20/21 mg kg^{-1} day^{-1} 250 ppm	**↓ Body weight** **↓ Carcass weight** **↓ Heart weight (11%)** **↓ Food consumption** 1500 ppm: Altered blood parameters Altered clinical chemistry parameters Dysproteinemia ↑ Liver weight ↑ Serum albumin
Cox, R.H., 1987a ***(Sprague Dawley rats)***	0, 1.3/1.7, 13/17, 51/66, 105/131 and 214/275 mg kg^{-1} day^{-1} (M/F) 0, 20, 200,750, 1500 and 3000 ppm	Orally via the diet	**NOAEL: M/F: 51/66 mg kg^{-1} day^{-1}** **750 ppm** NOEL: M/F: 1.3/1.7 mg kg^{-1} day^{-1} 20 ppm	**LOAEL: M/F: 105/131 mg kg^{-1} day^{-1}** **1500 ppm** LOEL: M/F: 13/17 mg kg^{-1} day^{-1} 200 ppm	**↓ Body weight** **↓ Body weight gain** 1500 ppm: ↓ Carcass weight Altered clinical chemistry parameters Hepatocellular enlargement 750 ppm: ↓ RBC parameters dysproteinemia ↑ Liver weight ↓ Body weight gain (F)
90-day in mouse					
Cox, R.H., 1987b	0, 3.3/4.6, 34.2/45.2 and 440/639 mg kg^{-1} day^{-1} (M/F) 0, 20, 200, 2500, (7500 and 15000)	Orally via the diet	**NOAEL: M/F: 34.2/45.2 mg kg^{-1} day^{-1}** **200 ppm** NOEL: M/F: 3.3/4.6 mg kg^{-1} day^{-1}	**LOAEL: M/F: 440/639 mg kg^{-1} day^{-1}** **2 500 ppm** LOEL: M/F: 34.2/45.2 mg kg^{-1} day^{-1}	**↓ Ovary weight** **↓ Body weight gain** 2500 ppm: ↑ Liver weight Macroscopic liver enlargement Hepatocellular vaculoization

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
	ppm				Hepatocellular coagulative necrosis Hepatocellular enlargement
			20 ppm	200 ppm	
6 months in dog					
O'Connor et al., 1987	0, 3.6/3.4, 31.3/34.8, 96.6/110.6 and 157.8/203.7 mg $kg^{-1}day^{-1}$ (M/F)	Orally via the diet	**NOAEL: M/F: 31.3/ 34.8 mg kg^{-1} day^{-1}**	**LOAEL: M/F: 96.6/110.6 mg kg^{-1} day^{-1}**	**6000 ppm:** **↓Body weight** **↓Food consumption** **↓Carcass weight** **↓ Prostate weight**
	0, 100, 1000, 3000 and 6000 ppm		**1000 ppm**	**3000 ppm**	**Cataract**
			NOEL: M/F: 3.6/ 3.4mg kg^{-1} day^{-1}	LOEL: M/F: 96.6/110.6 mg kg^{-1} day^{-1}	6000 ppm: ↓ Ovary weight (n.s.) ↓ Uterus weight (n.s.) ↑ Platelet count ↓ Calcium Dysproteinemia 3000 ppm: ↑ Liver weight (F) ↑ ALP (F)
			100 ppm	1000 ppm	↓ Food consumption (M)
1-year in dog					
Rudzki et al., 1988	0, 0.71/0.63, 3.4/3.7, 16.4/19.4 and 51.2/44.3 mg $kg^{-1}day^{-1}$ (M/F)	Orally via the diet	**NOAEL: M/F: ≥ 51.2/44.3 mg kg^{-1} day^{-1}** **≥ 1500 ppm**	**LOAEL: Could not be established**	
	0, 20, 100, 500 and 1500 ppm		NOEL: 51.2/44.3 mg $kg^{-1}day^{-1}$	LOEL: 51.2/44.3 mg $kg^{-1}day^{-1}$	1500 ppm: ↓ Food consumption ↓ Body weight gain
			100 ppm	500 ppm	↑ ALP (M)
DERMAL: 28-day in rat					
Gerspach, R., 2000	0, 10, 100 or 1000 $kg^{-1}bw\ day^{-1}$	Dermal	**NOAEL 1 000 $kg^{-1}bw\ day^{-1}$**	**LOAEL >1 000 $kg^{-1}bw\ day^{-1}$**	
			NOEL: 100 $kg^{-1}bw\ day^{-1}$		1000 ppm: ↑ Liver weight ↓ Bilirubin levels Hepatocellular hypertrophy ↓ Food consumption Hypertrophy of thyroid gland Hyperkeratosis of application site
M = male; F = female					

The short term toxicity was investigated in rats, dogs and mice. All of the studies were performed according to GLP principles with the exception of the 28 day study of oral toxicity in rats. The quality of this study was still considered acceptable.

Short term toxicity in the rat

The short term toxicity in rat was represented by one oral 28 day study, two oral 90 day studies and a 28 day study on dermal toxicity. A 90-day dermal study was not performed because of the limited effects seen in the 28-day study. Short-term inhalation toxicity studies were not performed since difenoconazole is not volatile (vapour pressure 0.0000332 mPa [25 °C]) and is not used as a fumigant or an aerosol.

The most sensitive parameter observed was the body weight and reduced body weights were observed in all oral short term toxicity studies performed on rats. A NOAEL of 20 and 21 mg/kg bw in males and females, respectively, was derived from the 90 day study (Suter 1986b). The liver was identified as the target organ with effects expressed mostly as increased relative and absolute liver weights. These changes were however only associated with histological changes in the second 90 day study (Cox, R.H., 1987a) in which an increased incidence and an increased severity of hepatocellular enlargement was noted at doses of ≥ 100/130 mg/kg bw in males and females, respectively. In the first 90 day study (Suter 1986b), the liver findings were reversible and they were therefore not considered to be adverse.

Short term toxicity in the dog

The short term toxicity in dogs was represented by a six month study and a one year study. A 90 day study was not performed since the studies above were considered to cover the effects at three months and there were no indications that dogs were more sensitive to difenoconazole than rats. Similar to rats, the dogs in the 28 day study responded to difenoconazole treatment by reductions in body weights. Increased liver weights were observed in animals administered 3000 and 6000 ppm but they were not associated with pathological changes. However, in females administered 3000 ppm, elevated alkaline phosphatase activity was observed.

The NOAEL was 1000 ppm (31/35 mg/kg bw for males and females respectively) based on the development of cataracts observed in animals administered 3000 ppm.

In the second study, the only treatment related effects observed were increased alkaline phosphatase activity in animals administered 1500 and 500 ppm in diet and a reduced food consumption at 1500 ppm. There were no effects observed on the liver weights and there were no evidence of cataracts. However, the dose levels used in this study was lower compared to those used in the six month study.

Dermal toxicity in rat

Dermal application of difenoconazole to rats resulted in a NOAEL of ≥ 1000 mg/kg/day based on the absence of adverse effects at the highest dose level tested. Similar to the oral short term toxicity studies, the target organ was the liver. In animals administered 1000 mg/kg/day, increased liver weights and decreased bilirubin levels were observed as well as associated pathological changes manifested as centrilobular hepatocellular hypertrophy. These findings were however considered to represent reactions of adaption.

2.3.1.1.4 Genotoxicity

Table 2.3.1.c. Summary of genotoxicity studies with difenoconazole.

Study	Concentrations/ Dose levels	Results
Salmonella/E. coli *in vitro* Ogorek, 1990	0- 5447 µg/plate, +/-activation	negative
Gene mutation in mouse lymphoma L5178Y/TK$^{+/-}$ cells *in vitro* Dollenmeier, 1986a	0-150 µg/ml, - activation 0-50 µg/ml, + activation	negative
Cytogenetic test on Chinese hamster cells *in vitro* Lloyd, 2001	0-105 µg/ml, - activation 0-105 µg/ml, + activation	equivocal and non-reproducible positive response without and with metabolic activation at cytotoxic concentrations
Cytogenetic test on Chinese hamster cells *in vitro* Ogorek, 2001	0-200 µg/ml, - activation 0-200 µg/ml, + activation	non-reproducible positive response with metabolic activation at one concentration
Cytogenetic test in human lymphocytes *in vitro* Strasser, 1985	0- 40 µg/ml, - activation 0-40 µg/ml, + activation	negative
Cytogenetic test in human lymphocytes *in vitro* Fox, 2001	0-75 µg/ml, - activation 0-75 µg/ml, + activation	negative
DNA repair on rat hepatocytes *in vitro* Hertner, 1992	0-50 µg /ml	negative
Micronucleus test mouse bone marrow *in vivo* Ogorek, 1991	0, 400, 800, 1600 mg/kg bw	negative

Difenoconazole was not genotoxic in the bacterial and mammalian cell assays for gene mutations, in the assays of chromosomal damage in isolated human lymphocytes or in the unscheduled DNA synthesis assay**.** *In vivo,* difenoconazole was negative for chromosomal damage in the mouse bone marrow micronucleus assay. Increased chromosomal aberrations were reported in CHO cells treated *in vitro* with difenoconazole, but only at high concentrations inducing cytotoxicity and they were not clearly reproducible either between repeat examinations of the same slides, between experiments or across studies. These observations are not considered to be significant in light of the negative results in the other *in vitro* and *in vivo* genotoxicity assays.

2.3.1.1.5 Long-term toxicity

Table 2.3.1.d. Summary of long-term toxicity studies with difenoconazole.

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
ORAL: **2-year combined chronic toxicity/oncogenicity in rat**					
Cox, 1989a **Report Supplement: Saunders, 1992**	0, 0.5/0.6, 1.0/1.3, 24.1/32.8 and 124/170 mg kg^{-1} day^{-1} (M/F) 0, 10, 20, 500, 2500 ppm	Orally, via the diet	**NOAEL:** **M/F: 1.0/1.3 mg kg^{-1} day^{-1}** **500 ppm** NOEL: M/F: 1.0/1.3 mg kg^{-1} day^{-1} 20 ppm	**LOAEL:** **M/F: 24.1/32.8 mg kg^{-1} day^{-1}** **2500 ppm** LOEL: M/F: 24.1/32.8 mg kg^{-1} day^{-1} 500 ppm	**2500 ppm:** **↓Body weight** **↓Body weight gain** **↓Food consumption (F)** **↓Carcass weight** **500 ppm:** **↓Body weight gain** 2500 ppm: ↓ RBC parameters, ↓ WBC parameters Dysproteinemia Altered clinical chemistry

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
					parameters 2500 ppm 500 ppm: ↓ Body weight (F) ↓ Hb (F) ↓ Platelet count (M) ↑ ALAT (M) Hepatocellular hypertrophy
18 months oncogenicity study in mice					
Cox, 1989b	0, 1.5/1.9, 4.7/5.6, 46.3/57.8 and 423/513 mg kg^{-1} day^{-1} (M/F) and 819 mg kg^{-1} day^{-1} for males at 4500 ppm 0, 10, 30, 300, 2500 (3000 1st two weeks) and 4500 (M) ppm	Orally, via the diet	**NOAEL:** **M/F: <46.3 /57.8 mg kg^{-1} day^{-1}** **30 ppm** NOEL: M/F: 4.7/5.6 mg kg^{-1} day^{-1} 30 ppm	**LOAEL:** **M/F: 46.3 /57.8 mg kg^{-1} day^{-1}** **300 ppm** LOEL: M/F: 46.3 /57.8 mg kg^{-1} day^{-1} 300 ppm	**4500 ppm:** **↑ ALP (M)** **2500 ppm:** **↑ ALAT** **↑ Liver weight** **Hepatocellular carcinoma** **↑Liver weight (F)** **↑Sorbitaldehydrogenas (SDH) (M)** **Hepatocellular necrosis (M, F)** 4500 ppm: ↓ Brain weight (6%) ↓ Testis weight (no dose-response) 2500 ppm: ↑ Carcass weight (not at term.) Altered WBC parameters Macroscopic hepatocellular enlargement Macroscopic hepatocellular masses Bile stasis Hepatocellular fatty change ↓ Body weight ↓ Body weight gain ↑ Liver weight (only females at interim) Hepatocellular hypertrophy Hepatocellular adenoma
M = male; F = female					

The long term oral toxicity was investigated in a combined chronic toxicity/carcinogenicity study on rats and in an oncogenicity study on mice.

Dietary administration of 2 500 ppm difenoconazole technical to rats resulted in decreased absolute body weights (8-23%) and a consistently lower mean food consumption (1-14%). In animals administered 500 and 2 500-ppm, dose-related reductions of body weight gains (6-40%) were observed. The negative effect observed on the red cell mass in females administered 2 500 ppm was not regarded adverse. An increased relative liver weight (14-48%) was observed in animals administered 2 500 ppm that were sacrificed at weeks 53 and 105. This effect was not observed in the recovery animals that were administered the same dose which indicates that the liver enlargement is adaptive during exposure and that the effect is reversible after cessation of exposure. The histopathological examinations showed an increased incidence and severity of hepatocellular hypertrophy in animals administered 500 or 2 500 ppm difenoconazole. There were no treatment-related increases in neoplastic

findings observed during the study. The NOAEL was considered to be 20 ppm (1.0 and 1.3 mg/kg bw in males and females respectively) based on the reduced body weight gains and the reduced absolute body weights observed in animals administered 500 and 2000 ppm.

Dietary administration of difenoconazole technical to mice up to 18 months at dose levels of 0, 10, 30, 300, 2500 and 4500 ppm resulted in 100% mortality/morbidity among the 4500 ppm females and a high mortality among the 4500 ppm males during the first study weeks therefore survival to termination was decreased in the 4500 ppm males. During the first study weeks, a body weight loss was noted in animals administered the highest dose. Thereafter the body weight gains approached control values although the terminal body weights were still reduced. The liver weights were increased in 4 500 ppm males, all 2 500 ppm animals and in the 300 ppm females. The liver enzyme levels were elevated in males administered 4 500 ppm and in animals administered 2 500 ppm. Treatment-related macroscopic findings were seen in the livers of the 4 500 ppm males and the 2 500 ppm animals. Treatment-related microscopic findings in the livers including necrosis, hypertrophy, fatty change and bile stasis were observed in the 4 500-ppm males, the 2 500-ppm animals and in the 300 ppm males. The incidence of hepatocellular adenomas and carcinomas was significantly increased in the 4 500 ppm males and in the 2 500 ppm animals. The NOAEL was considered to be 30 ppm (4.7/5.6 mg/kg bw in males and females respectively). In a supplementary study, difenoconazole was considered to be a reversible barbiturate-type inducer of metabolising enzymes in the mouse liver. In view of the lack of genotoxicity and the finding of tumours only in mice and only at concentrations at which toxicity was observed, the substance is considered not likely to pose a carcinogenic risk to humans.

2.3.1.1.6 Reproductive toxicity

Table 2.3.1.1.6.a: Summary of reproductive and developmental studies with difenoconazole.

Study	Dose levels	Administration way	NOAEL/ NOEL	LOAEL/ LOEL	Target effects
2-generation reproduction Giknis, 1988	0, 25, 250, 2500 ppm	Orally, via diet	250 ppm ≅ 17.3 mg/kg/day	2500 ppm ≅ 178 mg/kg/day	body weight, food consumption
rabbit teratology Hummel et al., 1987	0, 1, 25, 75 mg/kg/day	Orally, by gavage	25 mg/kg/day (maternal) 25 mg/kg/day (foetal)	75 mg/kg/day (maternal)	body weight, food consumption
rat teratology Lochry, 1987	0, 2, 20, 100 or 200 mg/kg	Orally, by gavage	20 mg/kg/day (maternal) 100 mg/kg/day (foetal)	100 mg/kg/day (maternal) 200 mg/kg/day (foetal)	body weight skeletal variations

Dietary administration of 2500 ppm (approximately 178 mg/kg/day) difenoconazole technical to rats over two generations, with one mating in each generation, resulted in a retarded body weight gain and a reduced food consumption in parental animals of both generations. The absolute pup body weights were lower in the 2500 ppm pups than in the control pups in both generations. There were no adverse effects observed on the male and female reproductive organs, mating behaviour, conception, parturition, litter parameters, lactation or weaning by the treatment, at any dose level, in either generation. Sperm parameters were not evaluated. A dose level of 250 ppm ppm (≅ 17.3 mg/kg/day) was considered the NOAEL for both parental animals and pups in this study.

The teratogenic potential of difenoconazole was investigated in rabbits administered 1, 25 and 75 mg/kg/day. Maternal toxicity, manifested as a reduced body weight gain and a reduced food consumption, was observed in animals administered 75 mg/kg/day during the period of organogenesis. Two of the animals administered 75 mg/kg/day aborted and a third animal died of apparent compound related anorexia. A slight increase in resorptions was observed at 75 mg/kg/day, which may have been secondary to maternal toxicity. There were no differences in pregnancy or litter parameters among the treated and control groups. No treatment related external, visceral or skeletal effects were seen. The maternal and foetal NOAEL were both 25 mg/kg/day. There was no evidence of compound related embryotoxic, foetotoxic or teratogenic potential at doses of up to 75 mg/kg/day.

The teratogenic potential of difenoconazole was also investigated in rats administered 2, 20, 100 and 200 mg/kg/day. Similar to rabbits, maternal toxicity, manifested as a reduced body weight gain and food consumption, was seen during the period of organogenesis at 100 and 200 mg/kg/day. Slight increases in resorptions and a reduction in litter size was observed in animals administered 200 mg/kg/day but they did not reach statistical significance and were attributed to maternal toxicity. The increased number of minor skeletal abnormalities at 200 mg/kg/day were considered reversible and/or associated with maternal toxicity. There were no effects observed in dams administered 1 and 20 mg/kg/day or in foetuses from dams treated with 1, 2 or 20 mg/kg/day. The maternal NOAEL was 20 mg/kg bw/day and the foetal NOAEL 100 mg/kg/day. There was no compound related embryotoxic, foetotoxic or teratogenic potential evident at doses of up to 200 mg/kg/day.

2.3.1.1.7 Neurotoxicity

Delayed neurotoxicity studies were not performed because the structure and chemistry of difenoconazole do not resemble chemicals known to induce delayed neurotoxicity. In addition, no effects indicative of nervous system involvement were seen in any of the studies performed with difenoconazole.

2.3.1.1.8 Further studies

The supplementary studies of difenoconazole include an investigation of biochemical and morphological changes in the mouse liver and two cataract studies (performed in chickens and dogs respectively).
The first study was performed in order to further investigate and characterise the increased liver weight, hepatocellular hypertrophy and the adenomas/carcinomas observed in the long term study on mice. Difenoconazole was administered daily to male mice during two weeks and after termination, the liver weights and the activities of various drug metabolising enzymes were analysed. Based on the results of this study, difenoconazole was considered to be a reversible barbiturate-type inducer of metabolising enzymes in the mouse liver and the highest dose of difenoconazole administered that did not induce metabolising enzymes and other parameters in the mouse liver was 10 mg/kg. No peroxisome proliferation was observed.
The cataractogenicity of difenoconazole was investigated in a 56 day study on young chickens and in a 18 week study on dogs in order to evaluate the cataract findings observed in the six month study on dogs. In chickens, cataracts were observed after one month of treatment in some of the animals administered 5000 ppm in diet. Although, the human relevance of these results is difficult to assess, this study is considered to strengthen the suspiscion of difenoconazole as being cataractogenic.

In contrast, treatment of dogs with difenoconazole at concentrations between 3000 and 6000 ppm for 18 weeks did not result in the formation of cataracts. However, since only single animals were tested, the results of this study should be interpreted with caution.

2.3.1.2 Toxicity of metabolites

In plants treated with difenoconazole, one difenoconazole specific metabolite (CGA 205375) and four triazole metabolites (CGA71019, CGA 131 013, CGA 142856 and CGA 205369) were found at levels that exceeded 10% of the TRR. The toxicity of the plant metabolite CGA 205375 that is also formed to a large extent in the mammalian metabolism of difenoconazole is considered to be covered by the toxicity studies performed on the parent compound. The RMS suggests that the toxicity assessment of the other plant metabolites should include studies of acute oral toxicity and genotoxicity[1] as they are only detected at low levels. Since this suggestion is based on the low exposure to metabolites during the representative use, it may be re-evaluated if the use within the EU will expand and include additional applications.

During the conditions of the representative use, the residues of triazole alanine (CGA 131013) and triazole acetic acid (CGA 142856) in plants are considered to be of no concern. The assessment of the toxicological relevance of triazole lactic acid (CGA 205369) and 1, 2, 4-triazole (CGA 71019) residues in plants depends on results from *in vitro* genotoxicity tests that are in progress, thus it cannot be determined at present.

The major metabolites found in the mammalian metabolism of difenoconazole (CGA 205374, CGA 205375 and CGA 189138) were investigated regarding acute oral toxicity and the ability to induce mutations in bacteria. The results raised no concern.

Table 2.3.1.2a. Difenoconazole: Relevant studies for toxicity assessment of plant metabolites

Toxicological Study	Species;administrtion	Dose levels	Results	Reference
CGA71019 (Triazole)				
Acute oral toxicity	Rat gavage	250, 500, 1000, 1250, 1500, 1750 1850 (males only), 2000, 2500 mg/kg	LD_{50} (males): 1650 mg/kg bw LD_{50} (females):1648 Classification: Xn, R22 (harmful if swallowed)	Thyssen, J. and Kimmerle, G.,1976
Bacterial reverse mutation assay	*Salmonella typhimurium* strains: TA98, TA100, TA1535 and TA 1537	10.0, 33.3, 100.0, 333.3, 1000 and 5000 µg/plate.	negative	Poth, A., 1989
CGA 131 013 (Triazole alanine)				
Acute oral toxicity	Rat; gavage/intraperitoneal Mouse; gavage	5000 mg/kg	LD_{50}> 5000mg/kg No classification required	Mihail, F., 1982
Acute oral toxicity	Rat; gavage	2000 mg/kg	LD_{50}> 2000mg/kg No classification required	Henderson, C. and Parkinson, G.R., 1980

[1] *Considered to be represented by a combination of an Ames test, a gene mutation test on mammalian cells and a chromosome aberration test.*

Salmonella / mammalian-microsome mutagenicity test.	*Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537 and TA 102.	20, 78, 313, 1250 and 5000 µg/plate +/-activation	negative	Deparade, E., 1986
Salmonella/E. coli *in vitro*/ liver-microsome test.	*Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537 *Escherichia coli* WP2 uvrA	312.5, 625, 1250, 2500 and 5000 /plate +/-activation	negative	Hertner, Th., 1993
Salmonella/ microsome test	*Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537 and TA 1538	20, 100, 500, 2500 and 12500 µg/plate +/-activation	negative	Herbold, B., 1983
Mutation test on mammalian cells	Chinese hamster cells	500, 1000, 2000, 4000, 6000, 8000 and 10000 µg/ml +/-activation	negative	Dollenmeier, P., 1986
Micronucleus test *in vivo*	Chinese hamster (M/F)	5000 mg/kg bw	negative	Strasser, F., 1986
Micronucleus test *in vivo*	Mouse (M)	2500, 5000 mg/kg bw	negative	Watkins, P.A., 1982
Micronucleus test *in vivo*	Mouse (M/F)	8000 mg/kg bw	negative	Herbold, B., 1983c
CGA 142856 (Triazole acetic acid)				
Acute oral toxicity	Rat; gavage	5000 mg/kg	LD_{50}> 5000mg/kg No classification required	Thevenaz, P., 1984
Salmonella / mammalian-microsome mutagenicity test.	*Salmonella typhimurium* strains: TA98, TA100, TA1535, and TA1537.	20, 80, 320, 1280, and 5120 µg/plate +/-activation	negative	Deparade, E., 1984
In vitro Mammalian Cell Gene Mutation Test	L5178Y mouse lymphoma cells	0.63, 1.25, 2.5, 5, 10 mg/ml +/-activation	negative	Clare, G., 2002
In Vitro Mammalian Chromosome Aberration Test in Human Lymphocytes	Human Lymphocytes	Mitotic index: 0, 0.078, 0.156, 0.313, 0.625, 1.25, 2.5, 5 and 10 mM Metaphase analysis: 2.5, 5 and 10 mM	negative	Pritchard L., 2002
CGA 205374				
Acute Oral Toxicity	Mouse; gavage	5000 mg/kg bw	LD_{50}> 5000mg/kg No classification required	Ohba, K (1991a)
Reverse mutation assay	*Salmonella typhimurium* strains: TA 98, TA 100, TA 1535, TA 1537 and *E. coli* WP2uvrA	156, 313, 625, 1250 and 2500 µg/plate +/-activation	negative	Nakajima, M (1991b)
CGA 205375				

Acute Oral Toxicity	Mouse; gavage	0, 1000, 1300, 1600, 2000, 2500 mg/kg	LD_{50}= 2309 mg/kg No classification required	Ohba, K (1991b)
Reverse mutation assay	*Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537 and *E. coli* WP2uvrA	~2.5-320 µg/plate. depending on strain and presence/absence of metabolic activations	Negative	Nakajima, M (1991c)
CGA-189138				
Reverse mutation assay	*Salmonella typhimurium* strains: TA 98, TA 100, TA 1535 and TA 1537 (histidine-auxotrophic) and *E. coli* WP2 uvrA (tryptophan-auxotrophic)	31.3 (62.5) - 1000 (2000) µg/plate depending on strain and presence/absence of metabolic activations	negative	Nakajima, M (1991a)

2.3.2 ADI

The acceptable daily intake (ADI) is derived from the NOEL in the most susceptible species in long-term toxicity and multi-generation reproduction studies with the application of an appropriate safety factor. Difenoconazole has a low acute toxicity, is not a selective developmental or reproductive toxicant and does not produce neurotoxic effects. Difenoconazole was considered to be a reversible barbiturate-type inducer of metabolising enzymes in the mouse liver and treatment with difenoconazole caused an increased incidence of adenomas/carcinomas in mice. In view of the lack of genotoxicity and the finding of tumours only in mice and only at concentrations at which toxicity was observed, the substance is considered not likely to pose a carcinogenic risk to humans.

A safety factor of 100 is proposed to be sufficient for derivation of the ADI (comprising a factor of 10 for interspecies variations and an additional factor of 10 for intraspecies variations).

The ADI is proposed to be 0.01 mg/kg bw/day based on the 2-year combined chronic toxicity/ oncogenicity in rat study in rats.

Table 2.3.2.a. Difenoconazole: Relevant studies for setting acceptable daily intake (ADI).

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
ORAL: **2-year combined chronic toxicity/oncogenicity in rat**					
Cox, 1989a **Report** **Supplement:** **Saunders, 1992**	0, 0.5/0.6, 1.0/1.3, 24.1/32.8 and 124/170 mg kg^{-1} day^{-1} (M/F)	Orally, via the diet	**NOAEL:** **M/F: 1.0/1.3** **mg kg^{-1} day^{-1}** **20 ppm**	**LOAEL:** **M/F: 24.1/32.8** **mg kg^{-1} day^{-1}** **2500 ppm**	**2500 ppm:** **↓Body weight** **↓Body weight gain** **↓Food consumption (F)** **↓Carcass weight** **500 ppm:** **↓Body weight gain**
	0, 10, 20, 500, 2500 ppm		NOEL: M/F: 1.0/1.3 mg kg^{-1} day^{-1} 20 ppm	LOEL: M/F: 24.1/32.8 mg kg^{-1} day^{-1} 500 ppm	2500 ppm: ↓ RBC parameters, ↓ WBC parameters Dysproteinemia Altered clinical chemistry

Study	Dose levels	Administration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
					parameters 2500 ppm 500 ppm: ↓ Body weight (F) ↓ Hb (F) ↓ Platelet count (M) ↑ ALAT (M) Hepatocellular hypertrophy
18 months oncogenicity study in mice					
Cox, 1989b	0, 1.5/1.9, 4.7/5.6, 46.3/57.8 and 423/513 mg kg^{-1} day^{-1} (M/F) and 819 mg kg^{-1} day^{-1} for males at 4500 ppm 0, 10, 30, 300, 2500 (3000 1st two weeks) and 4500 (M) ppm	Orally, via the diet	**NOAEL:** **M/F: <46.3 /57.8 mg kg^{-1} day^{-1}** **30 ppm** NOEL: M/F: 4.7/5.6 mg kg^{-1} day^{-1} 30 ppm	**LOAEL:** **M/F: 46.3 /57.8 mg kg^{-1} day^{-1}** **300 ppm** LOEL: M/F: 46.3 /57.8 mg kg^{-1} day^{-1} 300 ppm	**4500 ppm:** **↑ ALP (M)** **2500 ppm:** **↑ ALAT** **↑ Liver weight** **Hepatocellular carcinoma** **↑Liver weight (F)** **↑Sorbitaldehydrogenas (SDH) (M)** **Hepatocellular necrosis (M, F)** 4500 ppm: ↓ Brain weight (6%) ↓ Testis weight (no dose-response) 2500 ppm: ↑ Carcass weight (not at term.) Altered WBC parameters Macroscopic hepatocellular enlargement Macroscopic hepatocellular masses Bile stasis Hepatocellular fatty change ↓ Body weight ↓ Body weight gain ↑ Liver weight (only females at interim) Hepatocellular hypertrophy Hepatocellular adenoma
1-year in dogs					
Rudzki et al., 1988	0, 0.71/0.63, 3.4/3.7, 16.4/19.4 and 51.2/44.3 mg kg^{-1} day^{-1} (M/F) 0, 20, 100, 500 and 1500 ppm	Orally via the diet	**NOAEL:** **M/F:** **≥ 51.2/44.3 mg kg^{-1} day^{-1}** **≥ 1500 ppm** NOEL: 51.2/44.3 mg kg^{-1} day^{-1} 100 ppm	**LOAEL:** **Could not be established** LOEL: 51.2/44.3 mg kg^{-1} day^{-1} 500 ppm	1500 ppm: ↓ Food consumption ↓ Body weight gain ↑ ALP (M)
M = male; F = female					

2.3.3 ARfD (acute reference dose)

Due to the degree of acute oral toxicity observed with difenoconazole (based on rat acute oral study by Argus *et al.* (1987) and the early deaths observed in the long term toxicity investigation in mice) it is considered necessary to establish an Acute Reference Dose (ARfD) for this compound. The most sensitive species is rat and thus the ARfD is derived from the 90 day toxicity study in rats. The toxicity profile is similar in the short term and long term toxicity studies with body weight as the most sensitive parameter. Body weight reductions occur already at the first week of treatment (-4%) in the reproduction study at a similar dose as in the 90 day study but is not considered adverse at this time point. However, severe toxicity occurs in the long term toxicity study in mice where deaths occur during the first weeks of study and the LOAEL for deaths is 2500 ppm or 423/513 mg/kg bw.

$$\text{ARfD} = \frac{\text{NOAEL x oral absorption}}{\text{Safety factor}} = \frac{\text{20 mg/kg bw/day}}{100} = 0.2 \text{ mg/kg bw/day}$$

2.3.4 AOEL

According to the guideline of setting the AOEL[1], subchronic toxicity data are appropriate for establishing an AOEL. There are two 90-day studies with rats. The first results in a NOAEL of 250 ppm (20/21 mg/kg bw/day (m/f)) driven by reduced food and water consumptions, reduced body weight, reduced carcass weight, reduced heart weight (Suter, 1986b). The second establishes a NOAEL of 750 ppm (51/66 mg/kg bw/day (m/f)) based on a reduced body weight gain correlated with lower body weight in females (>10%) compared to controls (Cox, 1987a). Body weights were not statistically evaluated in this study by Cox (1987a). In order to provide the most conservative estimate for acceptable operator exposure, it is justified to derive the systemic AOEL from the lower of these two NOAEL values, i.e. 250 ppm (equivalent to 20/21 mg/kg bw/day (m/f)). Due to the high bioavailability of difenoconazole (approximately 90% of the dose being absorbed and excreted in bile and urine) there is no need for a correction factor.

$$\text{AOEL} = \frac{\text{NOAEL x oral absorption}}{\text{Safety factor}} = \frac{\text{20.0 mg/kg bw/day}}{100} = 0.20 \text{ mg/kg bw/day}$$

Table 2.3.4.a. Summary of repeated toxicity studies suitable for setting AOEL.

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
ORAL: 28-day in rat					
Suter, P., 1986a	27/27, 156/166 and 914/841 mg kg^{-1} day^{-1} (M/F) 0, 250, 1 500, 10 000 ppm	Orally via the diet	**NOAEL: M/F:156/166 mg kg^{-1} day^{-1}** **1500 ppm** NOEL: M/F: <27/27	**LOAEL: M/F: 914/841 mg kg^{-1} day^{-1}** **10 000 ppm** LOEL: M/F: 27/27 mg	**↓ Body weight** **↓ Carcass weight** **↓ Organ weight** 10 000 ppm: Altered clinical chemical

[1] *AOEL Guideline for setting of acceptable operator exposure levels (AOELs). Draft. Sanco/xxx/2005 rev 9., 5 July 2005*

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
			mg kg^{-1} day^{-1}	kg^{-1} day^{-1}	parameters
			<250 ppm	250 ppm	Altered blood parameters ↓ PT time Dysproteinemia
90-day in rat					
Suter, P., 1986b ***(Wistar rats)***	0, 3.3/3.5, 19.9/21.4 and 120.9/ 128.5 mg kg^{-1} day^{-1} (M/F) 0, 40, 250 and 1500 ppm	Orally via the diet	**NOAEL:** **M/F: 20/21 mg kg^{-1} day^{-1}** **250 ppm** NOEL: M/F: 3.3/3.5 mg kg^{-1} day^{-1} 40 ppm	**LOAEL:** **M/F: 120.9/ 128.5 mg kg^{-1} day^{-1}** **1500 ppm** LOEL: M/F: 20/21 mg kg^{-1} day^{-1} 250 ppm	**↓ Body weight** **↓ Carcass weight** **↓ Heart weight (11%)** **↓ Food consumption** 1500 ppm: Altered blood parameters Altered clinical chemistry parameters Dysproteinemia ↑ Liver weight ↑ Serum albumin
Cox, R.H., 1987a ***(Sprague Dawley rats)***	0, 1.3/1.7, 13/17, 51/66, 105/131 and 214/275 mg kg^{-1} day^{-1} (M/F) 0, 20, 200,750, 1500 and 3000 ppm	Orally via the diet	**NOAEL:** **M/F: 51/66 mg kg^{-1} day^{-1}** **750 ppm** NOEL: M/F: 1.3/1.7 mg kg^{-1} day^{-1} 20 ppm	**LOAEL:** **M/F: 105/131 mg kg^{-1} day^{-1}** **1500 ppm** LOEL: M/F: 13/17 mg kg^{-1} day^{-1} 200 ppm	**↓ Body weight** **↓ Body weight gain** 1500 ppm: ↓ Carcass weight Altered clinical chemistry parameters Hepatocellular enlargement 750 ppm: ↓ RBC parameters dysproteinemia ↑ Liver weight ↓ Body weight gain (F)
90-day in mouse					
Cox, R.H., 1987b	0, 3.3/4.6, 34.2/45.2 and 440/639 mg kg^{-1} day^{-1} (M/F) 0, 20, 200, 2500, (7500 and 15000) ppm	Orally via the diet	**NOAEL:** **M/F: 34.2/45.2 mg kg^{-1} day^{-1}** **200 ppm** NOEL: M/F: 3.3/4.6 mg kg^{-1} day^{-1} 20 ppm	**LOAEL:** **M/F: 440/639 mg kg^{-1} day^{-1}** **2 500 ppm** LOEL: M/F: 34.2/45.2 mg kg^{-1} day^{-1} 200 ppm	**↓ Ovary weight** **↓ Body weight gain** 2500 ppm: ↑ Liver weight Macroscopic liver enlargement Hepatocellular vaculoization Hepatocellular coagulative necrosis Hepatocellular enlargement
6 months in dog					
O'Connor et al., 1987	0, 3.6/3.4, 31.3/34.8, 96.6/110.6 and 157.8/203.7 mg kg^{-1}day^{-1} (M/F) 0, 100, 1000, 3000 and	Orally via the diet	**NOAEL:** **M/F:** **31.3/ 34.8 mg kg^{-1} day^{-1}** **1000 ppm**	**LOAEL:** **M/F:** **96.6/110.6 mg kg^{-1} day^{-1}** **3000 ppm**	**6000 ppm:** **↓Body weight** **↓Food consumption** **↓Carcass weight** **↓ Prostate weight** **Cataract**

Study	Dose levels	Adminis-tration way	NOAEL/ NOEL	LOAEL/ LOEL	Target organ and effects
	6000 ppm		NOEL: M/F: 3.6/ 3.4mg kg^{-1} day^{-1}	LOEL: M/F: 96.6/110.6 mg kg^{-1} day^{-1}	6000 ppm: ↓ Ovary weight (n.s.) ↓ Uterus weight (n.s.) ↑ Platelet count ↓ Calcium Dysproteinemia 3000 ppm: ↑ Liver weight (F) ↑ ALP (F)
			100 ppm	1000 ppm	↓ Food consumption (M)
1-year in dog					
Rudzki et al., 1988	0, 0.71/0.63, 3.4/3.7, 16.4/19.4 and 51.2/44.3 mg $kg^{-1}day^{-1}$ (M/F)	Orally via the diet	**NOAEL:** **M/F:** **≥ 51.2/44.3 mg kg^{-1} day^{-1}** **≥ 1500 ppm**	**LOAEL:** **Could not be established**	
	0, 20, 100, 500 and 1500 ppm		NOEL: 51.2/44.3 mg $kg^{-1}day^{-1}$	LOEL: 51.2/44.3 mg $kg^{-1}day^{-1}$	1500 ppm: ↓ Food consumption ↓ Body weight gain
			100 ppm	500 ppm	↑ ALP (M)
DERMAL: ***28-day in rat***					
Gerspach, R., 2000	0, 10, 100 or 1000 $kg^{-1}bw$ day^{-1}	Dermal	**NOAEL** **1 000 $kg^{-1}bw$ day^{-1}**	**LOAEL** **>1 000 $kg^{-1}bw$ day^{-1}**	
			NOEL: 100 $kg^{-1}bw$ day^{-1}		1000 ppm: ↑ Liver weight ↓ Bilirubin levels Hepatocellular hypertrophy ↓ Food consumption Hypertrophy of thyroid gland Hyperkeratosis of application site
M = male; F = female					

2.3.5 Drinking water limit

The annex VI of Council Directive 91/414/EEC states that the maximum permissible concentration of pesticide substances in ground water is 0.1µg/L or 10% of the acceptable daily intake (ADI), whichever is lowest.

Assuming a daily average consumption of 2 L water per person and a body weight of 60 kg, the ground water concentration corresponding to 10% of the ADI for difenoconazole would be:

0.01 x 0.1 x 60 / 2 = 0.03 mg/l

According to the discussion above, the drinking water limit for difenoconazole is thus 0.1 µg/L.

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

Table 2.3.6.a. Summary of exposure estimations.

Type of study/estimation	Operator/ bystander/ worker	Crop/application method	Result (% of AOEL) + PPE [1]	– PPE	Section in DAR
UK POEM SCORE® 250 EC (A-7402 T)	Operator	Pome fruit (NEU) Vehicle mounted air blast sprayer	N/E	6.5	B.6.14.1.1.1.1
UK POEM SCORE® 250 EC (A-7402 T)	Operator	Pome fruit (SEU) Vehicle mounted air blast sprayer	N/E	8.5	B.6.14.1.1.1.1
UK POEM SCORE® 250 EC (A-7402 T)	Operator	Carrot Vehicle mounted boom sprayer, hydraulic nozzles	N/E	28	B.6.14.1.1.1.1
UK POEM SCORE® 250 EC (A-7402 T)	Operator	Pome fruit (NEU) Hand-held sprayer	N/E	60	B.6.14.1.1.1.1
UK POEM SCORE® 250 EC (A-7402 T)	Operator	Pome fruit (SEU) Hand-held sprayer	N/E	65	B.6.14.1.1.1.1
German model SCORE® 250 EC (A-7402 T)	Operator	Pome fruit (NEU) Tractor high crops	N/E	2.2	B.6.14.1.1.1.2
German model SCORE® 250 EC (A-7402 T)	Operator	Pome fruit (SEU) Tractor high crops	N/E	2.9	B.6.14.1.1.1.2
German model SCORE® 250 EC (A-7402 T)	Operator	Carrot Tractor field crops	N/E	2.9	B.6.14.1.1.1.2
German model SCORE® 250 EC (A-7402 T)	Operator	Pome fruit (NEU) Hand high	N/E	2.4	B.6.14.1.1.1.2
German model SCORE® 250 EC (A-7402 T)	Operator	Pome fruit (NEU) Hand high	N/E	3.2	B.6.14.1.1.1.2
SEED TROPEX[1] DIVIDEND®030 FS (A-9142 G)	Operator	Seed treatment	N/E	<13%	B.6.14.2.1.1
EURO POEM SCORE® 250 EC (A-7402 T)	Worker	Pome fruit (NEU/SEU) Carrot	N/E	≤10%	B.6.14.1.3.1
Bystander exposure estimation SCORE® 250 EC (A-7402 T)	Bystander	Pome fruit (SEU)	N/E	<1%	B.6.14.1.2
SEED TROPEX[1] DIVIDEND®030 FS (A-9142 G)	Worker	Seed treatment	N/E	2.5%	B.6.14.2.3.1
SEED TROPEX[1] DIVIDEND®030 FS (A-9142 G)	Bystander	Seed treatment	N/E	N/E	B.6.14.2.2

Conclusion: Operator exposure

The operator exposure to **SCORE ® 250 EC A-7402T** using tractor/vehicle mounted airblast sprayers, tractor mounted hydraulic boom sprayers or handheld applications is considered acceptable.

[1] *Since estimates made without the use of PPE resulted in values well below the AOEL, estimates of operator exposure when using PPE were not calculated.*

The estimates of operator exposure to **DIVIDEND®030 FS (A-9142 G)** were calculated by the notifier using the SEEDTROPEX model. The RMS considers that this model requires more extensive data than the two existing studies in order to be accepted as a general model for estimation of exposure during seed treatment. Therefore, results obtained using the SEEDTROPEX model should be interpreted with caution. However, DIVIDEND®030 FS (A-9142 G) is of low acute toxicity and the values obtained using the SEEDTROPEX model are well below the AOEL of difenoconazole. Therefore, the risk of harmful effects in operators handling treated seed is presumed to be low if appropriate protective clothing is worn and basic hygienic rules are observed.

Conclusion: Bystander and worker exposure

Bystander and worker exposure to difenoconazole during the agricultural use of **SCORE ® 250** is considered acceptable.

The worker exposure to **DIVIDEND®030 FS (A-9142 G)** was calculated by the notifier and since it is well below the AOEL of difenoconazole, it is considered acceptable. Bystander exposure in stationary seed treatment facilities is considered to be rare. If an incidental presence of bystanders would occur at a seed treatment facility, it is assumed to be a short duration of exposure and normally lower than that of seed treatment operators who are occupationally exposed longer.Therefore, it is assumed that there will be no risk to persons being incidentally exposed during seed treatment operations with A-9142 G.

2.3.6.2 Consumers

The results of the estimation of the potential exposure of difenoconazole throught the diet are summarised in Table 2.3.6.b. The WHO European model, the German BBA and the UK PSD consumer exposure models lead to low TMDI values and the contribution to the proposed ADI of 0.01 mg/kg bw /day is of maximum 10% for adults, 12% for schoolchildren, 53% for toddlers and 39% of the ADI for infants. Thus it can be concluded that an acceptable safety margin exits for the diet.

Table 2.3.6.b: Estimation of the potential exposure through the diet

Model	Consumer Group	Total TMDI (mg/kg bw/day)	ADI (mg/kg bw/day)	Total TMDI in % of ADI
WHO (1997)	Adult (60 kg bw)	0.00040	0.01	4.0
German BBA (1993)	Girl (13.5 kg bw)	0.001357	0.01	13.6
UK PSD (1999)[a]	Adult (70.1 kg bw)	0.000985	0.01	9.9
	Child (43.6 kg bw)	0.0012147	0.01	12.1
	Toddler (14.5 kg bw)	0.00532	0.01	53.2
	Infant (8.7 kg bw)	0.003873	0.01	38.7

[a]average of extreme consumers

[1] *Estimation made by the notifier.*

2.4 Residues

2.4.1 Definition of the residues relevant to MRLs

Plant metabolism

The plant metabolism of difenoconazole was carried out in four crops, representing four crop groupings – cereals (wheat), root vegetables (potato), pulses/oilseeds (oilseed rape) and fruits (grape and tomato). Because difenoconazole contains both aromatic and triazole ring moieties the studies were performed using two radiolabelled forms of difenoconazole The application methods were seed and foliar treatment for wheat and foliar treatment for potato, grape, tomato and oilseed rape. The representative uses for difenoconazole in the Southern and Northern Europe are on cereals (seed treatment), pome fruit (foliar treatment) and carrots (foliar treatment).

Difenoconazole was extensively degraded in wheat, potato, tomato, grape and oilseed rape with very similar pathways of metabolism in all four crop types. The primary metabolic process in all four crop types involves hydrolysis of the dioxolane ring to form the ketone CGA-205374, which is then reduced to the corresponding alcohol CGA-205375. Oxidation of CGA-205375 occurred resulting in cleavage of the alkyl bridge to form CGA- 189138 and CGA-71019 (≤10% of the TRR). Hydroxylation of parent compound and the metabolites CGA-205374 and CGA-205375 was also observed. Sugar conjugation of parent compound and hydroxylated metabolites, and conjugation of 1,2,4-triazole were observed as a secondary metabolism process. Conjugation of 1,2,4-triazole resulted in the formation of triazole alanine (CGA-131013), which was further degraded to triazole acetic acid (CGA-142856), (See Appendix 1 to section B.7 for an overview of metabolites).

Proposed residue definition (plants, plant products):

Based on the results of the metabolism studies in cereals (wheat), root vegetables (potatoes), fruits (tomatoes, grapevine) and pulses/oilseeds (oilseed rape), the proposed residue definition in plants is difenoconazole alone for both monitoring and risk assessment purposes (see B.7.1). If, however, the intended use within the EU is to expand the use pattern to include foliar application to cereals and/or for use in oilseed rape, this conclusion should be re-evaluated.

Livestock metabolism

Metabolism studies were carried out using [phenyl-^{14}C] and [triazole-^{14}C] difenoconazole in lactating goats and laying hens. The test compound was administered orally in the diet at a concentrations of 5 and 100 mg/kg to the lactating goats and 5, 68 and 121mg/kg to the laying hens.

Difenoconazole was rapidly metabolised, with the majority of the applied radioactivity (up to 96.8% in laying hens and >88% in the lactating goats) excreted in the urine and faeces. Maximum radioactive residue levels were

present in the liver and kidney, at 9.790 and 2.731mg difenoconazole equivalents/kg, respectively, in lactating goats and up to 4.660 and 2.247mg difenoconazole equivalents/kg, respectively, in laying hens.
Maximum residues of parent difenoconazole were detected in the liver and fat of the lactating goats and laying hens, at concentrations up to 0.891mg/kg (9.1% of the TRR) and 1.912 mg/kg (18.4% of the TRR), respectively. In other edible tissues, residues of parent difenoconazole were ≤0.107 mg/kg (2.2% of the TRR). In milk, residues of parent difenoconazole were up to 0.028 mg/kg (8.8% of the TRR) and up to 0.236 mg/kg (5.3% of the TRR) in egg yolk.

CGA-205375 was the major metabolite in the goats and hens, occurring at levels up to 7.127 mg/kg (72.8% TRR) in liver, 1.180 mg/kg (43.2% TRR) in kidney, 0.949 mg/kg (91.7% TRR) in fat, 0.423 mg/kg (91.4% TRR) in muscle and up to 0.130 mg/kg (34.4% TRR) in milk, egg white and egg yolk. 1,2,4-triazole CGA-71019 was transported preferentially to eggs and milk, occurring at levels of 0.182 mg/kg (67.7% TRR) and 0.043 mg/kg (32.3% TRR) in egg white and yolk, respectively and levels up to 0.022 mg/kg (5.8% TRR) in milk. Ring hydroxylated difenoconazole, CGA-205374 and CGA-205375 were observed in the goats at levels up to 0.235 mg/kg (3.9% TRR) in liver and 0.021 mg/kg (15.2% TRR) in milk (See Appendix 1 to section B.7 for an overview of metabolites).

Proposed residue of definition (animals, products of animal origin):
Based on the results of metabolism studies in the lactating goats and laying hens, the proposed definition of the residue in animals and products of animal origin is parent difenoconazole for risk assessment purposes. For the purposes of monitoring, the proposed definition in animals and products of animal origin is parent difenoconazole plus metabolite CGA-205375.

2.4.2 Residues relevant to consumer safety

Estimates of regular dietary intake
The WHO European model, the German BBA and the UK PSD consumer exposure models lead to low TMDI values and the contribution to the proposed ADI of 0.01 mg/kg bw /day is of maximum 10% for adults, 12% for schoolchildren, 53% for toddlers and 39% of the ADI for infants. The potential chronic dietary exposure poses no risk to the consumers. If however, the intended use of difenoconazole will be extended the conclusion may be re-evaluated.

Estimates of acute dietary intake
The ARfD for difenoconazole has been proposed at 0.20 mg/kg bw/day. The UK PSD consumer exposure model lead to low NESTI values with the highest short-term consumption being 8.4% of the ARfD for apples in toddlers. It is therefore concluded that there is negligible acute dietary risk posed by the consumption of difenoconazole residues in treated cereals, pome fruits and carrots.

2.4.3 Residues relevant to worker safety

See section 2.3.6

2.4.4 Proposed EU MRLs and compliance with existing MRLs

On the basis of the residues data submitted, following MRLs can be proposed:

Crop group	Crops	Proposed MRL (mg/kg)	Comments
Cereals	Wheat, Barley, Oat, Triticale, Rye - Grain	0.02	Based on 14 trials conducted in the Northern (8 trials) and Southern (6 trials) regions; LOQ: 0.01-0.02 mg/kg
Root vegetables	Carrot	0.2	Based on 16 trials conducted in the Northern (8 trials) and Southern (8 trials) regions LOD: 0.01-0.03 mg/kg
Fruits	Pome fruit	0.3	Based on 11 trials conducted in the Southern region; LOD: 0.01 mg/kg

2.4.5 Proposed EU import tolerances and compliance with existing import tolerance

No applicable, since no non-EU applications are proposed in the current dossier.

2.4.6 Basis for differences, if any, in conclusion reached having regard to established or proposed CAC

Not applicable, since no Codex MRLs have been established or proposed yet.

2.5 Fate and behaviour in the environment

2.5.1 Definition of residues relevant to the environment

Soil: Difenoconazole and CGA 205375 (1-[2-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-2-1H-[1,2,4]triazol-yl]-ethanol) with the final decision regarding CGA 205375 pending a long-term risk assessment for soil dwelling organisms when studies have been made available.
Groundwater: Difenoconazole
Surface water and sediment: Difenoconazole
Air: Difenoconazole

2.5.2 Fate and behaviour in soil

2.5.2.1 Summary of soil degradation data

The degradation of difenoconazole in soil is principally mediated by micro organisms under aerobic conditions; studies under sterile or anaerobic conditions and soil surface photolysis study demonstrated little or no degradation of difenoconazole. The proposed degradation pathway in soil under aerobic conditions is presented in Figure 2.5.2.1.a.

Two metabolites were observed in quantities >10% of applied radioactivity: CGA 205375 and CGA 71019. CGA 205375 was observed as max. 9.7% (day 84) and this metabolite was also observed in a field study as max. 10-12% of the initial concentration of difenoconazole. CGA 71019 was observed as max. 23.4% (day 271).

In aerobic and anaerobic studies on CGA 205375, the only metabolite measured as >10% of the applied radioactivity was CGA 71019 (max. 32%). The principal fate of CGA 71019 under aerobic conditions was formation of bound residues (max. 62-75% after 30-61 days) and mineralisation (max 15-33% $^{14}CO_2$ at study termination).

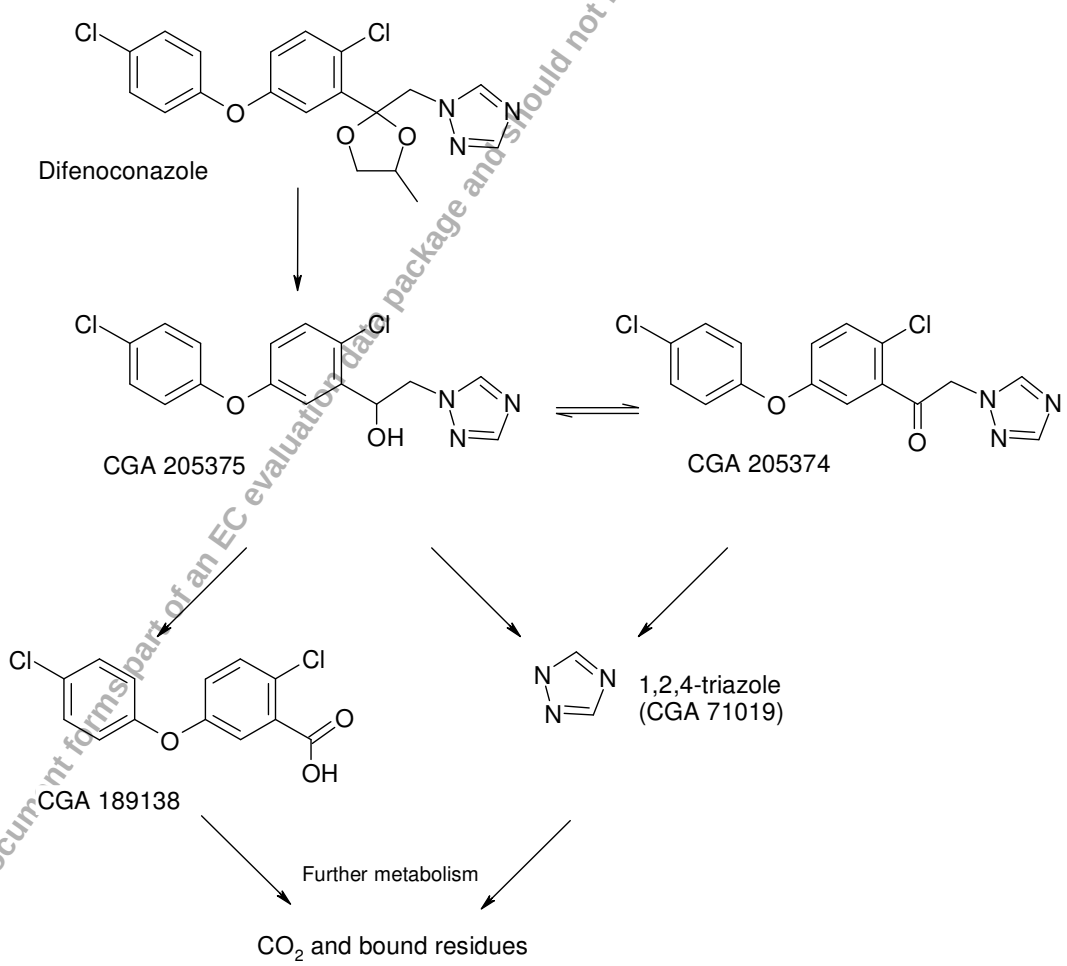


Figure 2.5.2.1.a. Proposed degradation pathway for difenoconazole in soil under aerobic conditions.

In laboratory studies on difenoconazole a significant proportion of the radioactivity was unextractable from soil. The maximum amounts of bound material formed from the chlorophenyl and triazole moieties of the molecule were similar at 48.2 and 54.1% respectively after 238-271 days. As relatively harsh extraction methods were usually employed it can be assumed that this unextracted radioactivity is principally bound or incorporated into the soil organic material. As the main route of breakdown is via bridge cleavage and high amounts of bound residues were rapidly formed in the aerobic study of 1,2,4-triazole (CGA 71019) it is suggested that the identity of at least part of the non-extractable residues is different in samples treated with difenoconazole labelled in different position (this was also supported by other observations, see section B.8.1.8.1).

There was considerable differences between amounts of mineralisation in the two portions of the molecule (chlorophenyl and triazole). Up to 33.4% of the ^{14}C-chlorophenyl radiolabel was evolved as $^{14}CO_2$ after 281 days whereas only max. 4.6% was evolved in the corresponding ^{14}C-triazole treatments after 271 days.

Since degradation appears to be dependent on treatment rate (see below), only the percentages of CO_2, bound residues and metabolites obtained at relevant treatment rates are transferred to the list of endpoints.

Rate of degradation was investigated in six different soils and at different temperature, moisture level and test concentrations. Some of the DT_{50} and DT_{90} values presented are uncertain due to high amounts of difenoconazole remaining at study termination, however, the values are considered acceptable as best available estimates. Median DT_{50} at 20ºC was 120 days (range 53-187 days, n=8), after normalisation with respect to moisture 86 days (see list of endpoints for individual results).

Within the ranges tested there was no indication of influence of organic carbon content, pH or soil type on the rate of degradation. Comparing the rates of degradation at 30ºC and 10ºC to those at 20ºC shows that they give faster or slower rates respectively in line with expectations, i.e. approximately a two-fold change although the data does not allow an exact figure to be estimated.

The results suggests that the rate of degradation of difenoconazole is influenced by treatment rate. In Document M-II it was shown that the increase in degradation rate with increased treatment rate is not linear and it was suggested that the longer half-lives obtained at high treatment rate are more likely to be the result of a gradual saturation of microbial degradative capacity, rather than any toxic effect over the soil concentrations tested. Concentrations from 0.0172 to 1.0 mg/kg were used in the studies, corresponding to 12.8 to 750 g a.s./ha (assuming distribution in 0-5 cm soil layer and density of 1.5 g/cm^3). In the representative use as seed treatment the maximum exposure is 12 g a.s./ha. In the representative uses with spray applications, difenoconazole is applied 1-4 times to pome fruit at 18.75-56.25 g/ha (N EU) or 37.5-75.0 g/ha (S EU) and 1-3 times to carrot at 125 g/ha. Total exposure during one season may hence be maximum 375 g/ha. It therefore seems reasonable not

to use the DT_{50} and DT_{90} derived from samples treated at the highest test concentration (corresponding to 750 g a.s./ha) for calculation of mean and median DT_{50} and DT_{90} - regardless of the mechanism for the slower degradation rate observed at these test concentrations. In addition to values obtained at highest treatment rate, also two values obtained in samples incubated at low moisture conditions (30% FC) and low temperature (10ºC) are excluded from the mean and median because in the same study degradation rate was also investigated on the same loam soil under standard conditions.

The same selection of data based on treatment rate was done for percentages CO_2 and non-extractable radioactivity transferred to the list of endpoint.

Soil degradation studies on the two principle metabolites identified, CGA 205375 and CGA 71019, were available. The degradation of CGA 71019 was rapid in aerobic soil with a mean DT_{50} of 9.5 days. The aerobic degradation rate of CGA 205375 was faster than that of its parent on the same soils, mean DT_{50} was 109 days. For CGA 205375 the DT_{50} and DT_{90} values may however be less certain due to high amounts remaining at study termination but the values are still considered sufficiently reliable for risk assessment. Compared with the maximum amounts formed of CGA 205375 and CGA 71019 in studies on difenoconazole, exaggerated test concentrations were used in the studies in which these compounds were applied as parent material.

Several field dissipation studies were provided due to the persistency of difenoconazole observed under laboratory conditions. Nine studies were considered as main studies, and additional 13 studies were considered as supplementary. Some of the supplementary studies were briefly reported. Others were performed under Canadian conditions (north prairie) with difenoconazole applied as seed treatment. All other studies (supplementary and main) used spray application. All studies (supplementary and main) from which reasonably reliable DT_{50} and DT_{90} values could be obtained are included in the list of endpoint, but mean/median values were based on the set of studies considered as main. The median field DT_{50} was 83 days, median DT_{90} 277 days. For calculation of PECsoil the 90th percentile DT_{50} of 246 days was used (based on the same set of data as the mean/median values).

Timing of application in the field dissipation studies was in May or June except at the location in Freisett where spraying was carried out in October and at the trials in Italy where crops were treated in July-August. The pH of the soils ranged from 5.6 to 8.3 and the % organic carbon from 1.0 to 4.3. Within these ranges there was no obvious influence of these parameters on the rate of dissipation. Neither was the dissipation rate correlated to soil type. In all trials, the majority of the residues were always recovered from the 0-10 cm soil depth but where relevant, measured residues in all soil sections (i.e. including residues below the top layer) were included in the calculations of dissipation rates. The tendency to slower degradation at high test concentrations observed at the laboratory was also indicated in the field studies performed at high treatment rates. However, to provide robust estimates which cover different conditions of use the field data were not selected based on treatment rate. The 90th percentile DT_{50} of 246 days is longer than the DT_{50}s observed in the studies considered as supplementary.

Since field DT_{50} > 3 months and field DT_{90} > 1 year were observed, soil accumulation studies with annual applications were provided: One 3-year study on bare soil and winter wheat in the UK considered as

supplementary, one 10-year study on plot with crop rotation in Switzerland, one 4-year study in an apple orchard in northern Italy, and finally a 4-year study on sugar beet in Italy. None of the studies used application rates equal to the maximum annual application rate (375 g a.s./ha) following the representative uses. Based on the available data, difenoconazole or the two principal metabolites (CGA 205375 and CGA 71019) are not expected to accumulate in soil following normal agricultural practice. No indication of accumulation in soil was indicated by the study in the UK following application to wheat at 75 or 150 g a.s./ha. After application to bare soil low residues (up to 0.05 mg/kg) remaining from the previous season were found but the residues after the 3rd treatment were not different to the first year. However, measurements were limited to the 0-10 cm soil section in this study and the results are only used as support to other studies. The long-term study on field crops in Switzerland, usually with applications of 125 g a.s./ha each year, gave no indication of accumulation of difenoconazole, CGA 205375 or CGA 71019 to a soil depth of 30 cm. In the last year analyses were done on samples to a depth of 60 cm with no residues of these compounds above LOD. However, there was an indication of potential accumulation of total, including bound, 1,2,4-triazole residues since up to 0.009-0.010 mg/kg were found immediately before application of difenoconazole. Since the majority of these residues are likely to be bound to the soil matrix and hence expected to be bioavailable only to a limited degree these residues are not considered as an area of concern. In the Italian study with annual applications of 4 x 62.5 g a.s./ha to an apple orchard, residues remaining from the previous season was only measurable in the second out of four years, at 0.01 mg/kg in soil (inter as well as intra rows). Finally, the Italian study with applications of 3 x 75 g a.s./ha to sugar beets gave no indication of accumulation in soil.

The information provided is considered sufficient and no further studies are considered necessary. Further assessment was done on the two soil metabolites CGA 205375 and CGA 71019.

2.5.2.2 Summary of adsorption, mobility and leaching data

The results from available adsorption/desorption studies indicate that difenoconazole and the metabolite CGA 205375 have a strong sorption and a low potential for mobility in soil, while the metabolite CGA 71019 (1,2,4-triazole) has a weak sorption and is more likely to leach through the soil profile. The mean values for adsorption Kfoc were: 3760 for difenoconazole; 2980 for CGA 205375; 89 for CGA 71019 (see list of endpoint for all individual results).

The extent of adsorption of difenoconazole seemed to depend only on soil organic matter and there was no obvious relationship with other soil parameters, within the range tested.

In the extensive package of field trials, some covering several years of applications, difenoconazole was only rarely detected below 10 cm in soil. Since reliable adsorption/desorption data were available for difenoconazole, CGA 205375 and CGA 71019, "fresh" or "aged" soil column leaching are not formally required. A soil column study with "freshly" applied difenoconazole was however submitted and the result supports the conclusion of low mobility of difenoconazole in soil.

As a conclusion, sufficient information was available on adsorption/desorption and potential mobility in soil of difenoconazole and its two major metabolites in soil CGA 205375 and CGA 71019.

2.5.2.3 Predicted environmental concentrations in soil

Initial, short and long term PECsoil were calculated assuming distribution in the 0-5 cm soil layer, and a value of 1.5 g/cm^3 for bulk density. For calculation of actual and time weighted average (TWA) short and long term PECsoil, a 90th percentile field dissipation DT_{50} of 246 days was used.

For the representative use of DIVIDEND 030 FS the calculation was based on a seed planting rate of 205 kg seed/ha and a seed coating of 6 g a.s./100 kg seeds, resulting in a maximum rate of difenoconazole of 12.3 g a.s./ha. The initial PECsoil was 0.016 mg a.s./kg soil. See list of endpoints for short and long term PECsoil. Initial PECsoil were also calculated for the two principal soil metabolites as:
Max. PECsoil parent x Max. metabolite in soil x Mol. wt fraction.
For CGA 71019 the initial PECsoil was 0.0006 mg/kg, for CGA 205375 it was 0.0014 mg/kg.

For the representative uses of SCORE 250 EC PECsoil were calculated assuming a single application as well as multiple applications to apples and carrots. For the use in apples, application of 4 x 75 g a.s./ha with a minimum spray interval of 7 days and a crop interception of 65% (BBCH 61, flowering) resulted in a initial PECsoil of 0.136 mg/kg. For the use in carrots, application of 3 x 125 g a.s./ha with a spray interval of 14 days and a crop interception of 80% (BBCH 42-43, approx. 20-30% of expected final root diameter) resulted in a initial PECsoil of 0.096 mg/kg. See list of endpoints for short and long term PECsoil. Initial PECsoil were calculated for the metabolites in the same way as for the seed treatment use. For the use in apples the initial PECsoil was 0.0053 mg/kg for CGA 71019, 0.012 mg/kg for CGA 205375. For the use in carrots the initial PECsoil was 0.0038 mg/kg for CGA 71019, 0.0083 mg/kg for CGA 205375.

The RMS also calculated plateau PECsoil for the scenario with 4 annual application of 75 g a.s./ha in apples. Since the orchard scenario was considered with little expected cultivation of the soil, the plateau PECsoil was calculated for a soil depth of only 5 cm. The plateau PECsoil were 0.076 mg/kg just before each annual application (lower part of "saw-teeth" curve) and 0.212 mg/kg just after the annual treatments (upper part of "saw-teeth" curve). These values would theoretically be reached after 7 years of annual treatment. Based on the results of the soil accumulation studies difenoconazole is however not expected to accumulate in soil, and the plateau PECsoil calculated are therefore not used for risk assessment.

2.5.3 Fate and behaviour in water

2.5.3.1 Summary of studies on degradation in surface water

Difenoconazole as well as its metabolites CGA 205375 and CGA 71019 (1,2,4-triazole) were shown to be stable to hydrolytic degradation at environmentally relevant pH values. Studies on direct photochemical degradation in

aqueous solutions and determinations of molar decadic extinction coefficients and quantum yield all showed that difenoconazole as well as CGA 205375 are stable to photolysis.

Difenoconazole was not readily biodegradable in accordance with the OECD criteria. Two water/sediment studies on difenoconazole (^{14}C-chlorophenyl label) were submitted, one carried out at 20ºC, the other at 8ºC. An additional study on the metabolite CGA 205375 (^{14}C-triazole label) was submitted. The conditions in all studies were maintained aerobic in the water phase with more anaerobic conditions in the sediment phase. In the difenoconazole study at 20ºC CGA 205375 was the only metabolite measured as >10 % of the applied radioactivity; max. 4.9% in pond system days 32 and 127, and max. 11.6% in river system on day 90. In the river system, the amounts of CGA 205375 were fairly constant over days 90-183 (11.6-11.4%) and hence seemed to have reached a plateau. Amounts of individual compounds were only presented for the combined water plus sediment system, however, based on the log Pow of 3.81 for CGA 205375, it seems reasonable to assume that it was present mainly in the sediment phase. In the water/sediment study with CGA 205375 added as test item it behaved similarly to difenoconazole, with rapid adsorption to sediment.

The metabolite CGA 71019 (1,2,4-triazole) found in soil studies could not be detected in the water/sediment studies on difenoconazole due to the position of radio labelling. However, in the study on ^{14}C-triazole labelled CGA 205375, 1,2,4-triazole was detected as max. 14.1% of the applied radioactivity in the river system, max. 3.2% in the pond system, both values recorded at study termination (day 148). If it is assumed that CGA 71019 is only formed from difenoconazole via degradation of CGA 205375, the maximum formation of CGA 71019 from difenoconazole would be: 0.116 x 0.141 = 1.6%. However, the amounts of CGA 71019 did not seem to have reached a plateau at study termination and therefore a worst-case rate of formation of CGA 71019 was calculated, assuming that all CGA 205375 remaining at study termination (68.4% in the river system) eventually would be transformed into CGA 71019. Thus, the worst-case max. formation of CGA 71019 from degradation of difenoconazole would be: 0.116 x (0.684 + 0.141) = 9.6%.

Small amounts of $^{14}CO_2$ evolved over the studies; max. 3.9% of the applied radioactivity after 183 days in the study on difenoconazole (^{14}C- chlorophenyl label) at 20ºC, and max. 0.5% after 148 days in the study on CGA 205375 (^{14}C-triazole label) at 20ºC. In the same studies the amounts of bound residues increased over the studies to max. 13.9% of the applied radioactivity after 183 days, and to max. 13.0% after 148 days.

Difenoconazole was very rapidly adsorbed to sediment and was only slowly degraded in that state. Temperature had little effect on the rate of loss of difenoconazole from water to sediment; however, degradation was considerably slowed at 8°C. Similarly to the parent compound, CGA 205375 was only slowly degraded. All degradation rates estimated are uncertain since >50% of the applied test substance remained undegraded at study termination. However, the results are considered acceptable as best available estimates.

Mean DT_{50} for degradation of difenoconazole in the whole systems was 316 days at 20ºC. In the study performed at 8º, DT_{50}s for degradation in the whole systems were estimated to 3 and 2 years, for pond and river system, respectively. This is consistent with calculated DT_{50}s at 8ºC of 2.2-2.3 years using a default Q_{10} of 2.2. Mean DT_{50} for degradation of CGA 205375 in the whole systems at 20ºC was 466 days.

From the results of the studies on water/sediments CGA 205375 is the only metabolite which needs to be considered further. However, due to its presence in soil, also CGA 71019 needs to be further considered for the aquatic environment. No studies on rate of degradation of CGA 71019 in water/sediment systems were submitted but this is considered acceptable since conservative assumptions were used for risk assessment. Hence, sufficient data were submitted.

2.5.3.2 Predicted environmental concentrations in surface water and sediment

For the representative use of DIVIDEND 030 FS in seed treatment PECsw and PECsed were calculated at FOCUS Steps 1 and 2 level of assessment, for the active ingredient and the two metabolites CGA 71019 and CGA 205375. Contamination of surface water via run-off, erosion and drainage was assumed. Sowing of treated seed can take place in the autumn in northern Europe or in spring in both the south and north of Europe. FOCUS Surface Water Step 1 calculations are independent of seasonal and geographic considerations; Step 2 was run with all three scenarios. Application rate of difenoconazole was 12.3 g/ha (based on seed planting rate of 205 kg/ha and seed coating of 6 g a.s./100 kg seed). The "application rates" for the metabolites were calculated internally by FOCUS SW Step 1-2 based on maximum percentage found in soil and molecular weight relative the parent. The initial PECsw and PECsed obtained at Step 1 and Step 2 (N EU autumn planting) are presented in the table below and in the list of endpoints.

For the representative use of SCORE 250 EC in apples and carrots PECsw and PECsed were calculated at FOCUS Steps 1-4 for the active ingredient and at Steps 1-2 for the two metabolites. PEC values following multiple applications were calculated at all steps of assessment, and in addition PEC values resulting from single applications to apples and carrots were provided at Steps 3-4. At Step 2 the region assumed was Southern Europe and the application period assumed was March-May. A crop interception of 70% was used for both apples (late growth stages) and carrot.

The Step 3 scenarios considered were:
Apples: D3, D4, D5, R1, R2, R3 and R4,
Carrot (vegetable root crop): D3, D6, R1, R2, R3 and R4.
For one scenario (R2) modelling of two annual crops was required for vegetable (carrot) use.
Dates for the first application to apples were between early March and early-mid April. In carrots the first application was assumed to take place between early March and early-mid June. At Step 4, a 5 m vegetative buffer strip was assumed for the use in carrots, reducing loading spray drift as well as run-off (50% reduction). For the use in apples, buffer strips of 14 m and 20 m were used to reduce loading by spray drift. No risk mitigation with respect to run-off was assumed for apples.

The maximum PECsw and PECsed calculated at the different steps of FOCUS Surface water assessment are presented in the table below. Additional results are given in the list of endpoints.

Table 2.5.3.2-1. Summary of maximum PECsw and PECsed for difenoconazole and metabolites CGA 71019 and CGA 205375, at the different FOCUS steps run.

Crop	Applications	Compartment	FOCUS Step	Maximum calculated PEC		
				Difenoconazole	CGA 71019	CGA 205375
Seed treatment	12.3 g/ha	Water, µg/L	1	0.693	0.148	0.0679
			2, N EU autumn	0.336	0.0482	0.0327
		Sediment, µg/kg	1	26.0	0.132	2.02
			2, N EU autumn	12.6	0.0429	0.973
Apples	1 x 75 g/ha	Water, µg/L	3	2.93	-	-
			4, 14 m buffer	0.578	-	-
			4, 20 m buffer	0.314	-	-
		Sediment, µg/kg	3	1.90	-	-
			4, 14 m buffer	0.699	-	-
			4, 20 m buffer	0.469	-	-
Apples	4 x 75 g/ha	Water, µg/L	1	32.4	3.76	3.20
			2, S EU	4.23	0.272	0.457
			3	1.943	-	-
			4, 14 m buffer	0.444	-	-
			4, 20 m buffer	0.444	-	-
		Sediment, µg/kg	1	722	3.11	57.8
			2, S EU	128	0.237	11.0
			3	4.033	-	-
			4, 14 m buffer	1.78	-	-
			4, 20 m buffer	1.50	-	-
Carrots	1 x 125 g/ha	Water, µg/L	3	0.783	-	-
			4, 5 m buffer	0.264	-	-
		Sediment, µg/kg	3	67.3	-	-
			4, 5 m buffer	33.9	-	-
Carrots	3 x 125 g/ha	Water, µg/L	1	24.2	4.43	2.38
			2, S EU	2.73	0.176	0.274
			3	0.713	-	-
			4, 5 m buffer	0.392	-	-
		Sediment, µg/kg	1	801	3.89	62.6
			2, S EU	96.5	0.155	7.61
			3	146.6	-	-
			4, 5 m buffer	74.1	-	-

2.5.3.3 Predicted environmental concentrations in groundwater

The simulation model FOCUS PEARL 2.2.2 was used to assess the potential for leaching to groundwater for difenoconazole and its metabolites CGA 205375 and CGA 71019, using the FOCUS groundwater scenarios. The calculations were based on the representative uses of SCORE 250 EC. PECgw were not calculated for the use of difenoconazole in DIVIDEND 030 FS since the calculations done for use in SCORE 250 EC provides a wide margin of safety for the applications as seed treatment.

Nine scenarios were run for the use in apples, and six for carrots. The fate of the parent and the metabolites were simulated in separate model runs with the metabolites applied on the same dates as the parent compound. Application rates for the metabolites were calculated taking the maximum accumulation of CGA 205375 and CGA 71019 in soil degradation studies and differences between molecular weights of the three compounds into account. Each substance was assumed to be applied in each of 26 successive years, with the final 20 years being considered for the assessment.

In the simulations of the use in apples, the first application was made one week after the start of leaf development (from mid March to mid May in the different scenarios), followed by three weekly intervals. In the simulation for use in carrots, two carrot crops were assumed to be grown each season in all six scenarios except Jokioinen. For the scenarios with two carrot crops per season the first application of the year was mid April, followed by two additional fortnightly treatments. For the second crop the first application was made from late July to early September in the different scenarios, followed by two additional fortnightly treatments.

For all FOCUS scenarios run, PECgw was <0.001 µg/L for difenoconazole as well as for CGA 71019 and CGA 205375.

2.5.4 Fate and behaviour in air

Based on low vapour pressure and low value of Henry's law constant, no significant volatilisation of difenoconazole is expected. This was confirmed in two volatilisation chamber studies. In the first study, difenoconazole was applied to bare soil and any volatile radioactivity in effluent air was trapped. Radioactivity in absorption traps accounted for <0.05% of applied over 24 hours. In the second study, pots with soil and wheat plants were sprayed and volatilisation measured as loss of radioactivity from soil and plants. After 24 hours the overall loss was <9%. Photochemical oxidative degradation is expected to be rapid. Hence, PECair is expected to be negligible.

2.6 Effects on non-target species

2.6.1 Effects on terrestrial vertebrates

2.6.1.1 Risk assessment for birds

Studies were available on the active ingredient (acute oral, short term dietary and sub-chronic) and on the plant metabolite CGA 131013 (short term dietary). No studies on the formulations were submitted, since results from mammalian testing indicated that the formulations were not more toxic than the active ingredient.

Table 2.6.1-1: Summary of toxicity endpoints from avian studies with difenoconazole

Species	Exposure duration	Dose range	Results*	Reference
Acute oral toxicity				
Active ingredient				
Anas platyrhynchos (Mallard duck)	acute	1470 – 2150 mg/kg bw	LD_{50}>2150 mg/kg bw	Fletcher (1988a)
Coturnix coturnix japonica (Japanese quail)	acute	125 – 2000 mg/kg bw	LD_{50}>2000 mg/kg/bw	Leopold (1993)
Short-term dietary toxicity				
Active ingredient				
Anas platyrhynchos (Mallard duck)	5 days	312 – 5000 ppm	LC_{50}>5000 ppm (>349 mg/kg bw day)	Fletcher (1988b)

Colinus virginianus (Bobwhite quail)	5 days	312 – 5000 ppm	LC_{50} 4760 ppm (392 mg/kg bw day)	Fletcher (1988c)
MetaboliteCGA 131013				
Anas platyrhynchos (Mallard duck)	5 days	5000 ppm	LC_{50} >5000 ppm (>1342 mg/kg bw day)	Beavers (1983a)
Colinus virginianus (Bobwhite quail)	5 days	5000 ppm	LC_{50} >5000 ppm (>1404 mg/kg bw day)	Beavers (1983b)
Sub-chronic toxicity and reproduction				
Active ingredient				
Anas platyrhynchos (Mallard duck)	18 weeks	25 – 625 ppm	NOEL 625 ppm (81 mg/kg bw day)	Pederson (1990)
Colinus virginianus (Bobwhite quail)	20 weeks	20 – 500 ppm	NOEL 100 mg/kg (9.8 mg/kg bw day)	Frey *et al* (2000)

LD_{50} = median lethal dose (50% mortality); NOEL = no observed effect level

For the major metabolite in plants, CGA 131013, only a short term dietary study was available. However, from these results there are no indications that the metabolite is more toxic than the parent compound. This was also supported by results from mammalian studies, and therefore no further data is considered necessary.

In conclusion, the available studies on birds are considered to fulfil the data requirements in Annex II and II of 91/414, and are sufficient for the risk assessment for birds.

2.6.1.1.1 SEED TREATMENT WITH DIVIDEND 030FS

As difenoconazole is a systemic seed-treatment, birds may be exposed to difenoconazole by direct consumption of treated seed or by eating the shoots of germinated wheat seedlings. Exposure *via* other routes such as dermal, consumption of insects and inhalation is considered to be negligible. Therefore, exposure *via* these routes will not be considered further.

According to the notifier, treated seeds are incorporated into the soil with a seed drill at depths of 2 cm or more and therefore, are not widely available for consumption by **granivorous birds**. Exposure is only considered likely to occur following occasional, accidental spillages and as a result of seed remaining on the soil surface when the drill lifts and turns. When seed does remain on the soil surface, the notifier considers that the seed treatment is expected to dissipate rapidly by dissolution in rain, dew or soil water. Further, as winter wheat seed is typically expected to germinate within 7 days of sowing, treated-seed will only be available for consumption for a short period. Therefore, it was proposed by the RMS that exposure via seed could be limited to 7 days after sowing for the long term assessment.

ETE values were calculated for the standardised realistic worst-case scenario recommended in **SANCO/4145/2000** for seed-treatment, i.e. small 15 g granivorous bird such as the linnet. For the purpose of the first tier risk assessments, it was assumed that there would be no de-husking or avoidance, that birds obtained 100% of their diet within the treated area and that difenoconazole-treated seed represented 100% of the diet. Therefore, the factors AV, DHF, PT and PD were assumed to be 1.

According to the notifier, investigations into the metabolism of difenoconazole in a range of plant species has demonstrated that up to 60% of measurable residues in foliage and grain may exist as the metabolite, triazolyl

alanine (CGA 131013). Therefore, the maximum residue of CGA131013 in grain was assumed to be 60% of the value estimated for parent difenoconazole. However, data to support this assumption was unclear. Therefore, the RMS proposed as a worst case assumption that 100% of the parent compound is transformed to the metabolite (correction for molecular weight, 156 g/mole, compared to 406 g/mole for the parent, or a factor of 0.38 was taken into account). Available data only cover the short term dietary toxicity to birds. These data indicated that the metabolite is less toxic than difenoconazole. This was also the case in short and long term studies on mammals (see Annex B, section 6). In the absence of acute and long term effect data for the metabolite on birds, a reasonable worst case approach is proposed, assuming that the metabolite is of equal toxicity as the parent compound.

The acute and short-term risk of difenoconazole and CGA 131013 to birds following the consumption of DIVIDEND 030FS-treated seed was assessed for a standard granivorous bird, with a body weight of 15 g (FIR/bw 0.38), as proposed in SANCO 4145/2000.

As difenoconazole is systemic, **herbivorous birds** may be exposed by the consumption of residues in plant tissues grown from seeds treated with DIVIDEND 030FS. A significant proportion of active ingredient is considered likely to remain on the seed coat, be lost into soil or taken up into root tissue that would not be available for consumption by birds.

However, for the first tier risk assessments, it was assumed that shoots are consumed by a herbivorous bird. Acute and short-term ETE values were calculated by assuming that 100% of compound present on each seed is taken up into a rapidly-growing wheat shoot that is twice the weight of the seed. For the long term assessment, a shoot weight of 6 times the treated seed was assumed. TER values were calculated for the skylark (FIR/bw 1.06), as proposed by the notifier, and for a medium sized herbivorous bird (FIR/bw 0.76) as proposed by SANCO/4145/2000 for early growth stages of cereals.

For the purpose of the first tier risk assessments, it was assumed that birds obtained 100% of their diet within the treated area and that wheat shoots from difenoconazole-treated seed represented 100% of the diet. Therefore, the factors PT and PD were assumed to be 1. As indicated for exposure *via* consumption of seed treated with DIVIDEND 030FS the maximum residue of CGA131013 in wheat seedlings was assumed to be 100% of the value estimated for parent difenoconazole, with correction for molecular weight (factor 0.38).

The risk of secondary poisoning and biomagnification in terrestrial foodchains and the risk from exposure via contaminated drinking water are considered to be low for difenoconazole and major metabolites in soil and water.

Based on the calculated TER values, the acute and short term risk is concluded to be low. The TER values for long term risk were below the Annex VI trigger of 5 for the active ingredient and the plant metabolite, and hence a refined risk assessment is needed. The risk to both granivorous and herbivorous birds needed to be addressed.

Refinement for **granivorous birds** was based on dehusking, data on dissipation from treated seeds, dietary composition of more relevant focal species compared to the standard species.

Refinement for **herbivorous birds** was based on data on the systemicity of difenoconazole and measured residues in emerging shoots from treated seeds.

The refined long term TER values for granivorous birds and for herbivorous birds feeding on shoots from treated wheat seeds were all above the trigger of 5 for difenoconazole and the plant metabolite CGA 131013, and no further refinement is needed.

2.6.1.1.2 SPRAY APPLICATION WITH SCORE 250EC

The Estimated Theoretical Exposure (ETE) values to difenoconazole for the first tier assessment were estimated according to SANCO/4145/2000, based on the maximum use rate of 4 applications of 75 g as/ha at 7-day intervals in pome fruit and 3 applications of 125 g as/ha at 14 day intervals in carrots as recommended by **SANCO/4145/2000.**

The first tier calculations were based on the standardised realistic worst-case scenarios recommended in the Guidance Document for orchard crops, i.e. small insectivorous bird consuming small insects (FIR/bw 1.04), and for leafy crops, i.e. medium herbivorous bird (FIR/bw 0.76) consuming leafy crops and small insectivorous bird consuming small insects (FIR/bw 1.04). In the case of insects little is known on time-course of contamination and degradation. However, repeated applications are not expected to cause appreciable accumulation of residues, at least in foliage-dwelling insects, particularly as replacement of individuals due to migration and reproduction will contribute to the residue decline in the population. Therefore, Multiple Application (MAF) and time-weighted average factors (f_{TWA}) were not applied for residues in insects.

For the metabolite, CGA 131013, the notifier proposed to assume a maximum of 60% in plant material. This value was not fully justified, since the available residue data was not derived from studies on carrots or grass, and also due to the fact that the number and timing of samples taken was not considered as sufficient to establish a reliable maximum value. Hence, the RMS proposed to assume as a worst case that 100% of the parent compound will be transformed to the metabolite. The ETE was corrected for molecular weight, which was a factor of 0.38 lower than that of the parent (156:406).

No long term assessment was provided for the metabolite, and no long term effect data are available. Based on the lower toxicity in the available short term dietary test (a factor ca 0.3 less toxic compared to the parent), and on the significantly lower short and long term toxicity for mammals, it is considered likely that the metabolite is not more toxic to bird reproduction than difenoconazole. The notifier stated that studies in mammals have shown low toxicity from CGA131013, with acute LD_{50}'s in both rats and mice of >5000 mg as/kg food and a lowest NOAEL of 100 mg as/kg bw/day in reproductive toxicity studies in rats. Again toxicity of the metabolite is significantly lower than for the parent, difenoconazole, which has an acute LD_{50} of 1453 mg as/kg bw/day and long-term NOAEL of 17.3 mg as/kg bw/day in rat.

In the first tier calculations, all acute and short term TER values were above the trigger of 10 for both parent and the plant metabolite, indicating that no further refinement is needed. However, the long term TER values were below the trigger of 5 for herbivores (both parent and metabolite) and insectivors in carrots (parent), and for insectivors in pome fruit (parent) in Southern EU. Hence, refinement was needed.

The risk of secondary poisoning and biomagnification in terrestrial foodchains and the risk from exposure via contaminated drinking water are considered to be low for difenoconazole and major metabolites in soil and water.

In the refinement for herbivorous and insectivorous birds in carrot cultivations a PT factor of 0.5 was proposed, based on that carrot is a minor crop, and that application takes place at a late growth stage when the crop is less palatable to birds. Refinement for insectivorous birds in orchards was based on a PT factor of 0.61 from a radiotracking study in UK (Crocker et al, 1998). These approaches may need further discussions.

To sum up, the acute and short term TER values were above the trigger values for difenoconazole and metabolites in the first tier assessment for all representative use scenarios, and no further refinement is needed.

In the long term assessment, a risk was identified for granivorous birds following seed treatment with DIVIDEND 030FS in the first tier assessment, but based on additional data and proposed refinements all TER values were above the trigger values and no further refinements are considered as necessary. Regarding spray applications with SCORE 250EC, discussions are needed on the acceptability of the proposed refinements of the risk assessment for small insectivores in pome fruit orchards and carrot cultivations and for herbivorous birds in carrot cultivations.

2.6.1.2 Risk assessment for wild mammals

Details of available mammalian toxicity studies with difenoconazole and the plant metabolite CGA 131013 are provided in **Document M-III, Section 3** and in Section B.6 of this DAR. A summary of the endpoints used in the notifier's risk assessment is presented in the table below.

Table 2.6.1-2: Toxicity of difenoconazole and the plant metabolite CGA 131013 to mammals

Study Type	Species	End-point	Value	Reference
Difenoconazole				
Acute oral toxicity	Rat	LD_{50}	1453 mg as/kg bw	Argus *et al* (1987)
2-generation reproduction	Rat	NOAEL	17.3 mg as/kg bw/day	Giknis (1988)
CGA 131013				
Acute oral toxicity	Rat	LD_{50}	>5000 mg as/kg bw	Mihail, F. (1982)
Developmental	Rat	NOAEL	100 mg as/kg bw/day	Clapp *et al*., 1983

The RMS agrees with the proposed endpoints for the acute and long term assessment. In the 2-generation study with difenoconazole on rats, there was a slight (7%) but statistically significant effect on the mean pup weight of males in the F1 generation on day 21 at 17.3 mg as/kg bw per day, but this was not considered to be biologically or ecologically significant. No effects were seen on the F2 generation.

The available studies are considered to fulfil the data requirements of Annex II and III of 91/414, and are considered to be sufficient for the risk assessment for wild mammals.

2.6.1.2.1 SEED TREATMENT WITH DIVIDEND 030FS

According to the notifier, treated seeds are incorporated into the soil with a seed drill at depths of 2 cm or more and therefore, are not widely available for consumption by wild mammals. Exposure is only considered likely to occur following occasional, accidental spillages and as a result of seed remaining on the soil surface when the drill lifts and turns. When seed does remain on the soil surface, the seed treatment is assumed to dissipate rapidly by dissolution in rain, dew or soil water. Further, as winter wheat seed is typically expected to germinate within 7 days of sowing, treated-seed will only be available for consumption for a short period. Therefore, it was proposed by the RMS that exposure via seed could be limited to 7 days after sowing for the long term assessment.

ETE values were calculated for the standardised realistic worst-case scenario recommended in the **EU Guidance Document (SANCO/4145/2000)** for seed-treatment, i.e. 25 g mouse. For the purpose of the first tier risk assessments, it was assumed that there would be no de-husking or avoidance, that mammals obtained 100% of their diet within the treated area and that difenoconazole treated-seed represented 100% of the diet. Therefore, the factors AV, DHF, PT and PD were assumed to be 1. ETE values were calculated for a small, granivorous mammal such as a mouse weighing 25g.

As difenoconazole is systemic, **herbivorous mammals** may be exposed by the consumption of residues in plant tissues grown from seeds treated with DIVIDEND 030FS. According to the notifier, a significant proportion of active ingredient is likely to remain on the seed coat, be lost into soil or taken up into root tissue that will not be available for consumption by mammals. However, for acute and short-term risk assessments, it was assumed that shoots are consumed by a herbivorous mammal, such as a vole, which weighs 25 g. The notifier's assessment was based on a small herbivorous mammal, such as a field vole (standard species according to SANCO 4145/2000). However, it is known that such small mammals are rare visitors on open fields with no vegetation cover, since they want to avoid predators. Therefore, the RMS proposed to include also a larger mammal (ie. rabbit or hare) as focal species for the risk assessment. Acute and short-term ETE values were calculated by assuming that 100% of compound present on each seed is taken up into a rapidly-growing wheat shoot that is twice the weight of the seed. For the long term assessment, a shoot weight of 6 times the treated seed was assumed.

In the assessment of the metabolite, the maximum of 60% of the estimated amount of parent substance was assumed. The same value was also used in the assessment for spray application. However, no data was presented to support this assumption. Therefore, the RMS proposes as a worst case assumption that 100% of the parent compound is transformed to the metabolite (correction for molecular weight, 156 g/mole, compared to 406 g/mole for the parent, or a factor of 0.38 will be taken into account). Based on effect data for the metabolite, an acute oral LD_{50} value of >5000 mg/kg bw and a long term NOAEL value of 100 mg/kg bw per day will be used.

For the purpose of the first tier risk assessments, it was assumed that mammals obtained 100% of their diet within the treated area and that wheat shoots from difenoconazole-treated seed represented 100% of the diet. Therefore, the factors PT and PD were assumed to be 1. The ETE values for the metabolite CGA 131013 was assumed to be 100% of that estimated for the parent difenoconazole, with correction for molecular weight (factor 0.38).

The risk of secondary poisoning and biomagnification in terrestrial foodchains and the risk from exposure via contaminated drinking water are considered to be low for difenoconazole and major metabolites in soil and water.

In conclusion, the acute TER values were above the trigger of 10 in Annex VI of 91/414, and the refined long term TER for herbivorous mammals was above the trigger of 5. However, for the granivorous mammal, the long term TER values were below the trigger of 5, and therefore a refined assessment was needed for this scenario.

Refinement for granivorous mammals was based on data on dietary composition of wood mouse. The refined long-term TER value for wood mouse proposed by the notifier is 6.7 which is above the trigger value of 5 and indicates acceptable long-term risk to granivorous mammals from Dividend-treated seed. This risk assessment is still conservative since no allowance has been made for dissipation of difenoconazole residues on seeds due to weathering and other dissipation processes.

Refinement for herbivorous mammals was based on data on systemicity of difenoconazole and measured residues in shoots. The refined long term TER values for herbivorous mammals feeding on shoots from treated wheat seeds were all above the trigger of 5 for difenoconazole and the plant metabolite CGA 131013, and no further refinement is needed.

2.6.1.2.2 SPRAY APPLICATION WITH SCORE 250EC

The exposure of wild mammals to difenoconazole was assumed to be predominantly dietary, through the consumption of dry residues on food items. Exposure to difenoconazole *via* dermal and inhalation routes is considered unlikely, since at the time of application and for a short period thereafter, the notifier stated that most wild mammals will leave the immediate vicinity of spray operations in response to the human disturbance.

The Estimated Theoretical Exposure (ETE) values to difenoconazole for the first tier assessment were estimated according to **EU Guidance Document SANCO/4145/2000**, based on the maximum use rates of 4 applications of 75 g as/ha at 7-day intervals in pome fruit and 3 applications of 125 g as/ha at 14 day intervals in carrots.

The first tier ETE values were calculated by the notifier for the following scenarios: (1) orchard crop, i.e. small herbivorous mammal consuming short grass (FIR/bw 1.39) and (2) leafy crops, i.e. medium herbivorous mammal consuming leafy crops (FIR/bw 0.28). For orchard crops, the Guidance Document SANCO 4145/2000 assumes that for a fungicide such as SCORE 250EC 60% of the applied amount will reach ground vegetation

due to interception by the crop (pome fruit, medium crop cover). In the first tier risk assessment, this was allowed for by using correspondingly reduced RUD values.

The risk of secondary poisoning and biomagnification in terrestrial foodchains and the risk from exposure via contaminated drinking water are considered to be low for difenoconazole and major metabolites in soil and water.

In the first tier calculations, the acute TER values are above the trigger for all representative use scenarios, and the long term TER values were above the trigger for the use in carrots (parent and metabolite). However, refinement is still needed for the long term toxicity to small herbivorous mammals in pome fruit.

Refinement for herbivorous mammals in pome fruit was based on crop interception data from FOCUS and on data on dietary composition of field voles. The refined long-term TER for vole was 6.0 which is above the relevant trigger value of 5 and indicates that no further refinement is needed.

To sum up, the acute and short term TER values were above the trigger values for difenoconazole and metabolites in the first tier assessment for all representative use scenarios, and no refinement is needed.

In the long term assessment, the TER values were below the trigger values for difenoconazole following seed treatment with DIVIDEND 030FS and spray applications with SCORE 250EC in pome fruit. However, based on additional data and proposals provided by the notifier and accepted by the RMS, the TER_{lt} values were above the trigger values for all representative use scenarios. Hence, no further refinement is needed.

2.6.2 Effects on aquatic organisms

Descriptions of aquatic toxicity studies conducted with difenoconazole and the metabolites CGA 205375 and CGA 71019 are provided in **Document M-II, Section 6**.

Toxicity studies with fish, daphnia and algae were conducted with two precursor formulations (A-7402 H and A-7402 A) that are similar to A-7042 T (SCORE 250EC), and a *Chironomus* study was conducted with A-7042 G. Descriptions of these studies are provided **Document M-III for SCORE 250EC, Section 6**.

The acute toxicity studies with fish, *Daphnia* and algae were also conducted with A-9142 G (DIVIDEND 030FS). Descriptions of these studies are provided **Document M-III for DIVIDEND 030FS, Section 6.**
A summary of all endpoints is provided in the table below.

Table 2.6.2-1: Toxicity of difenoconazole, its major metabolites in water/sediment systems and the representative formulations DIVIDEND 030FS and SCORE 250EC to aquatic organisms.

Study type Test substance	Species	Endpoint	Value (mg as/L)	Reference
FISH ACUTE TOXICITY				
Difenoconazole	Rainbow trout	96 h LC_{50}	1.1(0.98-1.1)	Surprenant (1990a)
	Bluegill sunfish	96 h LC_{50}	1.3 (1.0-1.8)	Bowman (1988)
	Sheepshead minnow	96 h LC_{50}	1.1(0.86-1.5)	Machado (1993)
CGA 71019	Rainbow trout	96-h LC_{50}	498 (378-657)	Rufli (1983)
CGA 205375	Rainbow trout	96-h LC_{50}	0.74 (0.58-0.95)	Swarbrick (2001a)
DIVIDEND 030FS	Rainbow trout	96-h LC_{50}	0.70 (0.43-1.2)	Gries (1999a)
SCORE 250EC	Rainbow trout	96-h LC_{50}	**0.65** (0.56-1.1)	Voigt (1990a)
SCORE 250EC	Rainbow trout	96-h LC_{50}	0.38 – 0.92	Volz (2004a)
FISH PROLONGED TOXICITY				
Difenoconazole	Rainbow trout	21-day NOEC	0.023	Grade (1993a)
CGA 71019	Rainbow trout	28-d NOEC	3.2	Dorgerloh and Sommer (2002)
CGA 205375	No data available	not needed		
DIVIDEND 030FS	No data available	not needed		
SCORE 250EC	Rainbow trout	21-day NOEC	0.15	Voigt (1991)
FISH EARLY LIFE STAGE TOXICITY				
Difenoconazole	Fathead minnow (ELS)	NOEC	**0.0076**	Surprenant (1987b)
	Fathead minnow (ELS)	NOEC	0.0087	Surprenant (1990b)
BIOCONCENTRATION IN FISH				
Difenoconazole (20 ug/L)	Bluegill sunfish	BCF (whole fish)	320±32 (no unit)	Forbis (1987)
Difenoconazole (1 ug/L)	Bluegill sunfish	BCF (whole fish)	330 (no unit)	Fackler (1992)
INVERTEBRATES ACUTE				
Difenoconazole	*Daphnia magna*	48 h LC_{50}	0.77 (0.59-0.95)	Forbis (1988a)
	*Mysidopsis bahia**	96 h LC_{50}	**0.15** (0.11-0.22)	Suprenant (1990b)
	*Crassostrea virginica**	96 h LC_{50}	>0.3	Surprenant (1990c)
CGA 71019	*Daphnia magna*	48-h EC_{50}	>100	Bell (1995)
CGA 205375	*Daphnia magna*	48 h LC_{50}	1.4 (1.2-1.7)	Swarbrick (2001b)
DIVIDEND 030FS	*Daphnia magna*	48 h LC_{50}	0.43 (0.3-0.6)	Gries (1999b)
SCORE 250EC	*Daphnia magna*	48 h LC_{50}	0.62 – 1.38	Volz (2004b)
INVERTEBRATES CHRONIC				
Difenoconazole	*Daphnia magna*	21-day NOEC	**0.0056**	Forbis (1988b)
	Chironomus riparius	28-d NOEC	0.015 (*via* water)	Van der Kolk (1999)
	Chironomus riparius	28-d NOEC	50 mg as/kg sediment	Van der Kolk (1999)
CGA 71019	No data available	not needed		
CGA 205375	*Chironomus riparius*	28-d NOEC	0.4 (via water)	Grade (2001)
	Chironomus riparius	28-d NOEC	10 mg/kg (via sediment)	Grade (2001)
SCORE 250EC	*Chironomus riparius*	28-day NOEC	0.075 (*via* water)	Neumann (1997)
DIVIDEND 030FS	No data available	not needed		
ALGAE				
Difenoconazole	*Scenedesmus subspicatus*	72-h E_bC_{50}/E_rC_{50}	1.2/3.8 (3.3-4.5)	Rufli (1989)
	Scenedesmus subspicatus	72-h E_bC_{50}/E_rC_{50}	**0.032** (0.026-0-039)	Grade (1993b)
CGA 71019	*Pseudokirchneriella subcapitata*	72-h E_bC_{50}/E_rC_{50}	13 (11-15)	Palmer *et al* (2001)
CGA 205375	*Pseudokirchneriella subcapitata*	72-h E_bC_{50}/ E_rC_{50}	1.2(1.2-1.3)/ 3.1(3.0-3.2)	Swarbrick (2001b)
DIVIDEND 030FS	*Scenedesmus subspicatus*	72-h E_bC_{50}/ E_rC_{50}	1.8(1.3-2.6)/ >3.0(2.8->3.0)	Gries (1999c)
SCORE 250EC	*Scenedesmus subspicatus*	96-h E_bC_{50}/E_rC_{50}	1.6/2.5	Peters (1992)
SCORE 250EC	*Scenedesmus subspicatus*	72-h E_bC_{50}/E_rC_{50}	0.29 (0.22 – 0.60)/ 0.96 (0.62 – 1.75)	Volz (2004c)
AQUATIC PLANTS				
Difenoconazole	No reliable data	not required		

[a] *LC_{50} = median lethal concentration (50% mortality); EC_{50} = median effect concentration (50% effects); E_bC_{50} = effective concentration for 50% biomass reduction; NOEC = no observed effect concentration*
**marine species*

For the metabolite CGA 71019, long term data was available for fish, although the acute test on invertebrates did not include concentrations high enough to conclude which species (fish or invertebrates) were the most sensitive. However, since the risk assessment resulted in very high TER values for the metabolite (acute as well as long term for fish), there is a sufficient safety margin and no further data is considered to be necessary.

Regarding the metabolite CGA 205375, fish was slightly more sensitive that invertebrates in acute studies. However, since the major part of this compound has been concluded to be situated in the sediment (see Annex B.8), the RMS considers that it is justified to focus the long term assessment on the sediment dwelling invertebrate *Chironomus*.

No long term data was available for DIVIDEND 030FS, and this is not needed since this is a seed treatment formulation that will not directly reach surface waters, and continued or repeated exposure will not occur.

In conclusion, the available studies are considered to fulfil the data requirements of Annex II and III of 91/414 and are sufficient for the risk assessment for aquatic organisms.

2.6.2.1 Risk assessment for aquatic organisms

2.6.2.1.1 SEED TREATMENT WITH DIVIDEND 030FS

The PEC_{sw} values were slightly corrected based on the RMS assessment in Annex B.8, and the calculated TER values are given in Appendix 3 of this document.

From the TER values calculated using initial PEC from FOCUS Step 1 (see Annex B.8), it was concluded that no refinement was needed for the short term and long term assessment for fish and sediment dwelling species or short term assessment for aquatic invertebrates, or for algae regarding the active ingredient, or for any trophic level regarding the major metabolites. Further refinement was needed for the long term risk from difenoconazole to aquatic invertebrates. However, based on FOCUS Step 2 PECsw, all TER values are above the trigger values in Annex VI of 91/414, and no further refinement is needed.

2.6.2.1.2 SPRAY APPLICATION WITH SCORE 250EC

The PEC_{sw} values were slightly corrected based on the RMS assessment in Annex B.8. The calculated TER values are given in Appendix 3 of this document. Based on the FOCUS Step 1 PECsw values, the TER triggers were higher than the trigger values in Annex VI of 91/414 for the major metabolites. However, for difenoconazole refinement was needed for all trophic levels at the representative use in carrots and pome fruit. Based on the FOCUS Step 2 PECsw values for the representative use in carrots, the TER values were higher than the trigger values in Annex VI of 91/414 for short term effects on fish and for algae. Refinement was still

needed for long term risk to fish, for aquatic invertebrates and for sediment dwelling organisms. For pome fruit, the TER values were higher than the trigger values in Annex VI of 91/414 for short term effects on fish. Refinement was needed for long term risk to fish, for short and long term risk to aquatic invertebrates and for sediment dwelling organisms and for algae.

The most sensitive species tested was *Daphnia magna*, and it is considered that the refined assessment based on this NOEC value will cover also the other trophic levels which failed the lower tier assessments. Chronic TERs for the most sensitive species based on the maximum PEC from FOCUS Step 3 still fall below relevant triggers for pome fruit (all scenarios) and carrots (3 out of 6 scenarios), indicating the need for further refinement.

The notifier claimed that the use of maximum PEC_{sw} values for assessing chronic risk of difenoconazole is very conservative, since in natural aquatic systems difenoconazole will rapidly dissipate from the water column (DT_{50} up to 2 days in the water phase in water-sediment studies). The test designs used in algal, chronic *Daphnia* and chronic fish tests did not allow for dissipation of the compound that would occur under more realistic exposure conditions, and therefore the notifier proposed that the chronic assessments for fish and invertebrates should be based on data from 34-day and 21-day flow-through studies, combined with time-weighted average (TWA) PEC_{sw} values.

In an additional submission in May 2006, the notifier provided further justification for using the time weighted average PEC_{sw} for the risk assessment for fish and aquatic invertebrates. A summary of the argumentation is given in Annex B.9. From the RMS point of view, the available chronic studies on fish and invertebrates do not give sufficient information on the exposure time needed for the onset of the observed effects. The chronic risk assessment for fish was based on the fish early life stage (ELS) study (**Surprenant, 1987b**), where NOEC was derived from effects on larval weight that was recorded only at the end of the study after 34 days exposure. For invertebrates, the assessment was based on number of young per adult in a 21 day study (**Forbis, 1988b**) where effects were clearly observed at an early stage of the test period. Therefore, since the relevant exposure time window for reproductive effects is unknown, it is the RMS opinion that TER values should be based on maximum PEC_{sw} values. The use of global maximum or time weighted average PEC_{sw} for the risk assessment needs to be further discussed.

Since the RMS was not convinced that time weighted average PECsw values should be used for refinement, also FOCUS Step 4 calculation was required in order to establish appropriate risk mitigation levels. These were submitted in May 2006. Recalculated TER values based on the global maximum values for each scenario are given in Appendix 3. Based on the maximum PEC_{sw} calculated according to FOCUS Step 4 scenarios including risk mitigation measures, all long term TER values were above the trigger of 10. In conclusion, no further refinement is needed.

2.6.3 Effects on bees and other arthropod species

Descriptions of honey-bee acute oral and contact toxicity studies conducted with difenoconazole were provided in **Document M-II, Section 6**. In addition, acute oral studies were conducted with the formulation, A-7402 A,

which is similar to A-7402 T. A summary of acute and contact oral toxicity endpoints from all studies is provided in the table below. For the use of difenoconazole for seed treatment in wheat, exposure is considered to be negligible.

Table 2.6.3-1: Acute toxicity of difenoconazole to honey bees

Test substance	Endpoint	LD_{50} (µg as/bee)	Reference
Difenoconazole ai	48-h contact LC_{50}	>100	Hoxter and Jaber (1989)
	48-h contact LC_{50}	>100	Grieg- Smith (1990)
	48-h oral LC_{50}	>177	

In addition, two semi-field tests conducted under realisitic conditions were submitted by the notifier. The results indicated that no significant effects on bee mortality, foraging behaviour, flight activity or brood health are expected at the representative use of difenoconazole by spray application.

The available data fulfils the requirements of Annex II and III of 91/414 and are considered to be sufficient for the risk assessment for honey bees.

A summary of the results from available studies on non-target arthropods is given in the table below.

Table 2.6.3-2: Summary of results from non-target arthropod studies with difenoconazole and representative formulations.

Species	Test type	Rate (g as/ha)	Result	Reference
LABORATORY STUDIES				
ACTIVE INGREDIENT				
Aphidius rhopalosiphi	fresh residues on glass plates.	18, 36, 72, 144, 288	LR_{50} 178 g as/ha	Kleiner (2000a)
Typhlodromus pyri	fresh residues on glass plates.	18, 36, 72, 144, 288	LR_{50} 112 g as/ha	Kleiner (2001)
DIVIDEND 030FS				
Aleochara bilineata	treated seeds in moistened sand	23.2 g as/ha (60 mg as/kg seed and seed density of 379 kg/ha	LR_{50} >23.2 g as/ha	Grimm (1999a)
Poecilus cupreus	treated seeds in moistened sand	18.8 g as/ha (60 mg as/kg seed and seed density of 307 kg/ha	LR50 >18.8 g as/ha	Grimm (1999b)
Poecilus cupreus	treated seeds in moistened sand	56.4 g as/ha (60 mg/kg seed and seed density of 937 kg/ha	LR50 >56.4 g as/ha	Reber (1999)
SCORE 250EC				
Aphidius rhopalosiphi	fresh residues on glass plates.	5, 127, 253	ER_{50} 127 – 253 g as/ha	Nienstedt (1999a)
Typhlodromus pyri	fresh residues on glass plates.	5, 127, 253	ER_{50} 127 – 253 g as/ha	Nienstedt (1999b)
Chrysoperla carnea	fresh residues on glass plates	4, 100, 200	ER_{50} >200 g as/ha	Kleiner (2000b)
Pardosa spp.	direct spray over adults, food and substrate (sand).	4, 100, 200	ER_{50} >200 g as/ha	Kleiner (1999)
Poecilus cupreus	direct spray over adults, food and substrate (sand).	6, 30, 150, 300	ER_{50} >300 g as/ha	Reber (1999b)
EXTENDED LABORATORY STUDIES				

Species	Test type	Rate (g as/ha)	Result	Reference
SCORE 250EC				
Typhlodromus pyri	fresh residues on bean leaves	6, 30, 150, 300	ER_{50} 152 – 303 g as/ha	Grimm (1999)
Chrysoperla carnea	fresh residues on bean leaves	14, 28, 75, 125, 202, 288	ER_{50} >288 g as/ha	Walker (2001)
Orius laevigatus	fresh residues on maize plants	6, 30, 150, 300	ER_{50} >300 g as/ha	Reber (1999a)
SEMI-FIELD STUDIES				
SCORE 250EC				
Aphidius rhopalosiphi	fresh and 14-day old residues on broad beans.	75, 125, 288	ER_{50} >288 g as/ha.	Longley (2001a)
Trichogramma cacoeciae	fresh and 14-day old residues on broad beans.	15, 75, 125, 288	ER_{50} >288 g as/ha	Longley (2001b)
Coccinella septempunctata	fresh and 14-day aged residues on broad beans.	4 applications of 125 g as/ha at 14-day intervals	ER_{50} >4 x 125 g as/ha	Engelhard (1997b)
Episyrphus balteatus	14-day aged residues on broad beans.	15, 75, 125, 288	ER_{50} >288 g as/ha for aged residues based on mortality. Results from fresh residues not reliable due to high control mortality.	Longley (2001c)
Episyrphus balteatus	fresh residues on broad beans.	288	62% effect on number of viable eggs per female when an outlier was excluded. Aged residues not tested for reproduction. Potential for recovery is considered likely.	Longley (2001c)
FIELD STUDIES				
SCORE 250EC				
Predatory mites	Field study on in apple orchards in Italy.	4 applications of 79.5 g as/ha at intervals of 10 or 11 days	No significant effect on the population density of predatory mites up to 28 days after the last application, except for an increased population on day 28 after the last application.	Muther (2000a)
Predatory mites	Field study in apple orchards in Italy.	4 applications of 59.6 g as/ha at intervals of 10 or 11 days	No significant effect on the population density of predatory mites up to 28 days after the last application.	Muther (2000b)

The available studies are considered to fulfil the data requirements of Annex II and III of 91/414, and are sufficient for the risk assessment for non-target arthropods.

2.6.3.1 Risk assessment for honey bees

2.6.3.1.1 SEED TREATMENT WITH DIVIDEND 030FS

As difenoconazole is systemic, honey-bees may potentially be exposed to by ingestion of nectar and pollen containing residues in crops grown from DIVIDEND 030FS treated seed. The maximum concentration of difenoconazole in nectar and pollen was assumed to be equivalent to the proposed seed-treatment rate, *i.e.*12.3 g as/ha. This assumption is extremely conservative, as degradation of difenoconazole in the soil or dilution due to uptake, translocation and metabolism within the crop plant, have not been taken into account. Furthermore, exposure is also likely to be limited as the proposed uses of DIVIDEND 030FS are on cereals, which are not particularly attractive to bees.

The HQ for DIVIDEND 030FS was calculated by the notifier using an acute oral LD_{50} of 177 µg as/bee as shown in the table below. The resulting value is much lower than the trigger value of 50, indicating a negligible risk to bees.

2.6.3.1.2 SPRAY APPLICATION WITH SCORE 250EC

A risk assessment was provided by the notifier in **Document M-III, Section 6.** Applications of SCORE 250EC could result in exposure of honey-bees either by direct over-spray or by contact with residues on plants whilst bees are foraging for food. For this assessment, the maximum single application rate for each representative use pattern will be used to represent the worst-case scenario.

Hazard quotients for difenoconazole were calculated by the notifier using the highest single application rate of 125 g as/ha and the lowest acute toxicity endpoint for each exposure route. The hazard quotients for bees based on acute toxicity values are below the trigger value of 50. Furthermore, cage tests conducted with A-7402 A indicate that exposure to spray applications at 2 L formulation/ha (500 g as/ha), does not have any significant effects on bee mortality, foraging behaviour, flight activity or brood health.

2.6.3.2 Risk assessment for other arthropod species

2.6.3.2.1 SEED TREATMENT WITH DIVIDEND 030FS

Non-target arthropods living in the crop may be exposed to seed-treatments, such as DIVIDEND 030FS, through direct contact with residues in the soil or on treated seed, or by feeding on crop plants containing difenoconazole residues. The maximum residual concentration of difenoconazole in soil and foliage was assumed to be equivalent to the proposed seed-treatment rate of 6g as/100 kg seed at a seed density of 205 kg wheat seed/ha (equivalent to 12.3 g as/ha).

As DIVIDEND 030FS is a seed-treatment that is applied directly to the crop seed prior to sowing, non-target arthropods living in off-crop areas are unlikely to be exposed to this pesticide and will not be considered in this risk assessment.

HQ values were calculated using LR_{50} values from glass-plate, dose response tests conducted with the standard sensitive species *Aphidius rhopalosiphi* and *Typhlodromas pyri*. All HQ values fall below the ESCORT 2 trigger value of 2 for Tier 1 studies on inert substrates thus indicating that difenoconazole poses a low risk to non-target arthropods within the crop following the proposed use for seed treatment.

Non-target arthropod tests were also conducted with representative ground-dwelling species (*Aleochara bilineata* and *Poecilus cupreus*) exposed to wheat seeds treated with DIVIDEND 030FS at 2 mL/kg seed at seed

densities up to 937 kg/ha (equivalent to a maximum of 56.4 g as/ha). Exposure to DIVIDEND 030FS did not cause a significant effect on the mortality or fecundity of those species tested, at rates up to 4.5-fold greater than the maximum predicted exposure rate of 12.3 g as/ha.

In conclusion, the risk for non-target arthropods is considered to be low at the use of difenoconazole for seed treatment. No further refinement is needed.

2.6.3.2.2 SPRAY APPLICATION WITH SCORE 250EC

A risk assessment for non-target arthropods at spray application with SCORE 250EC was provided by the notifier in **Document M-III, Section 6.**

In-field

Non-target arthropods living in the crop may be exposed to SCORE 250EC by direct over-spray during spray operations, through contact with residues on plants and soil, or by feeding on exposed food items. HQ values were calculated using LR_{50} values from glass-plate, dose response tests conducted with the standard sensitive species *Aphidius rhopalosiphi* and *Typhlodromus pyri,* based on the PER values corrected by the RMS. All HQ values fell below the ESCORT 2 trigger value of 2 for Tier 1 studies on inert substrates thus indicating that SCORE 250EC poses a low risk to non-target arthropods within the crop.

Off field

Non-target arthropods living in off-crop areas may be exposed to SCORE 250EC by spray drift from field applications. Off-crop areas are assumed to be densely vegetated and thus spray drift is unlikely to reach bare ground. Therefore, evaluation of exposure *via* soil residues in off-crop areas was not considered. Off-crop foliar PER values were calculated from in-crop foliar PERs in conjunction with BBA drift values (cited in ESCORT 2; 10.12% at 3 m distance for 4 applications to pome fruit and 2.01% at 1 m distance for 3 applications to field crops (carrots).

The model used to estimate spray drift was developed for drift onto a two-dimensional water surface and, as such, does not account for interception and dilution by three-dimensional vegetation in off-crop areas. Therefore, a vegetation distribution or dilution factor of 10 is incorporated into the equation when calculating PERs to be used in conjunction with toxicity endpoints derived from two-dimensional, glass plate or leaf disc studies. Maximum off-crop foliar PERs for each use pattern were calculated at distances of 1m for carrots and 3 m for pome fruit. PERs were estimated assuming 65% foliar interception for pome fruit.

When calculating HQs using toxicity data from Tier 1 lab studies with the standard two species, a correction factor of 10 is incorporated to allow for extrapolation to the species diversity expected in off-crop areas. HQ values were calculated using LR_{50} values from glass-plate, dose response tests conducted with the standard sensitive species *Aphidius rhopalosiphi* and *Typhlodromus pyri,* and based on the off-field PER-values corrected by the RMS. All HQ values fell below the ESCORT 2 trigger value of 2 for Tier 1 studies on inert substrates thus indicating that SCORE 250EC poses a low risk to non-target arthropods in off-crop areas.

Further support of low risk to non-target arthropods was provided by additional laboratory and semi-field studies with a range of species including parasitoids, predatory mites, foliage-dwellers and ground-dwellers. In lab tests, effects on mortality or fecundity of >50% were not reported following a single application of 125 g as/ha. Similarly, results from semi-field studies where four applications of A-7402 G at 125 g as/ha were made at 14-day intervals, indicated that exposure to dried residues after four applications, did not cause >50% effect on mortality or fecundity in those species tested. As stated in the **Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002, October 2002)**, effects of <50% seen in higher-tier studies are considered acceptable provided that the test covered the appropriate field rate. Therefore, SCORE 250EC is considered to pose low risk to non-target arthropods when applied in accordance with proposed representative use patterns in pome fruit and carrots.

2.6.4 Effects on earthworms and other soil non-target macro-organisms

2.6.4.1 Risk assessment for earthworms

A summary of available studies on earthworms is given in the table below.

Table 2.6.4-1: Summary of earthworm toxicity endpoints for difenoconazole, the soil metabolites CGA 71019 and CGA 205375, and the representative formulations DIVIDEND 030FS and SCORE 250EC.

Test substance	Endpoint	Value (mg as/kg soil)	Reference
SHORT TERM			
Difenoconazole	14-day LC_{50}	>610	Surprenant (1987c)
CGA 71019	14-day LC_{50}	>1000	Heimbach (1986)
CGA 205375	14-day LC_{50}	312 (284 – 343)	Batscher (2002)
DIVIDEND 030FS	no short term data		
SCORE 250EC	14-day LC_{50}	40 (36 – 44)	Thun (1993)
LONG TERM			
Difenoconazole	no reliable data		Nienstedt (1999c)
CGA 71019	28-day NOEC	0.0708 (reproduction)	Ehlers (2000)
CGA 205375	no long term data	ongoing study	
DIVIDEND 030FS	56-day NOEC	0.2 (reproduction)	Friedrich (2002)
SCORE 250EC	56-day NOEC	1.7 (reproduction)	Nienstedt (2001)

**this value was not fully reliable, and should be treated with caution. The formulation data will be used for the risk assessment. However, the study is considered to fulfil the data requirement.*

Only one of the major metabolites in soil (CGA 71019) was tested for effects on reproduction, although for this metabolite this was not required since the DT_{90} in soil was <100 days. For CGA 205375, the trigger of DT_{90}>100 days was exceeded, and based on the acute tests on earthworms this metabolite was shown to be more toxic than the parent compound. Therefore, the long term toxicity needs to be addressed. A study is ongoing, and the final report will be submitted in July 2006, and will be evaluated in an Addendum to this DAR.

Further, the available long term study on the active ingredient was not considered as reliable due to a very high variability in control and treated groups. Based on recommendations in the Guidance Document On Terrestrial Ecotoxicology Under Council Directive 91/414/EEC (SANCO/10329/2002), certain study types (for example non-target arthropod studies, the earthworm reproduction test and the soil micro-flora test) may be conducted

with a formulated product instead of the active substance. Hence, it is considered appropriate to use the more reliable NOEC from available formulation studies (0.2 mg as/kg dw for DIVIDEND 030FS and 1.7 mg as/kg dw for SCORE 250EC) for the risk assessment as proposed by the notifier.

It should be kept in mind that since the worms were fed with untreated cattle manure during the tests, it could be argued that only the contact route of exposure was included, and the total exposure levels were probably under-estimated compared to field conditions. However, this is a normal procedure for this type of test, and was also in accordance with the recommendations in the referred guidelines.

2.6.4.1.1 SEED TREATMENT WITH DIVIDEND 030FS

Calculations of the predicted soil concentrations of difenoconazole and its metabolites, CGA 71019 and CGA 205375 at the use of the representative seed treatment formulation, are described in **Document MIII Section 5,** and evaluated by the RMS in Annex B.8. In order to evaluate the potential risk of difenoconazole and its soil metabolites to earthworms following the proposed uses of DIVIDEND 030FS, acute and long term toxicity exposure ratios (TER_A and TER_{LT}) have been calculated considering the toxicity data and the maximum predicted environmental concentrations in soil (PEC_S). As the log P for difenoconazole and CGA 205375 are greater than 2 (log P_{ow} = 4.4 and 3.8, respectively), the 14 day LC_{50} and NOEC values were reduced by a factor of 2 to account for the relatively high organic matter content of the artificial test soil compared to agricultural soils. Log P_{ow} values for the soil metabolite CGA 71019 is less than 2 and does not require adjustment. The TER values for earthworms exceeded the short and long-term Annex VI triggers of 10 and 5, respectively, indicating that no further refinement is needed.

2.6.4.1.2 SPRAY APPLICATIONS WITH SCORE 250EC

The potential short term risk of difenoconazole to earthworms was evaluated by calculation of a toxicity exposure ratio (TER) between soil PEC and the 14-day $LC_{50.}$ For compounds with a log P_{OW} value greater than 2, the LC_{50} is reduced by a factor of 2 in order to account for the relatively high organic matter content of the artificial test soil compared to agricultural soils.

The potential long-term risk of difenoconazole to earthworms was assessed by calculation of a long-term TER (TER_{LT}) between the maximum PEC and the 28-day reproduction NOEC as shown below. As for the acute risk assessment, the NOEC is reduced by a factor of 2 to account for the relatively high organic matter content of the test soil.

Short and long-term TER values for difenoconazole were calculated using an LC_{50} of 40 mg/kg and a 28-day NOEC of 1.7 mg/kg, respectively, based on a study with the formulation. The resulting values provided by the notifier (based a study with the representative spray formulation) exceed the relevant Annex VI triggers.

Short and long-term TER values for the difenoconazole metabolite, CGA 71019, were calculated using an LC_{50} of 1000 mg/kg and a 56-day NOEC of 0.0708 mg/kg, respectively. The resulting values exceed the relevant Annex VI triggers, indicating that CGA 71019 poses low acute risk to earthworms.
The acute risk of CGA 205375 was assessed from a toxicity exposure ratio between the 14-day LC_{50} of 312 mg/kg and the maximum soil PEC. The resulting acuteTER values are greater than the trigger of 10 and indicate negligible acute risk to earthworms.

In general, the RMS agrees with the risk assessment provided by the notifier. However, the possible impact of the observed increase in weight gain on field populations of earthworms may need further discussion.

2.6.4.2 Risk assessment for other soil non-target macro-organisms

Since the DT_{90} value of difenoconazole was >365 days, further data was needed to address the possible effects on organic matter decomposition in soil under field conditions. In a litter bag test with the SCORE 250EC formulation applied at a rate corresponding to 0.506 kg as/ha, with direct overspray of the litter bags before burrowing into the soil, a 17% reduction in decomposition was observed after 168 days compared to the control. In the report from the EPFES workshop, an effect of 10 – 25% was proposed as trigger. The notifier argued that the EPFES workshop was held after the field phase of this study had been completed and published after the study had been reported, and that prior to the EPFES workshop, the guidance (edited version issued as BBA, 2001[1]) stated that expert judgement was needed in cases where reduction in decomposition compared to the control was between 15 and 30%. In this case the effects were within this interval (max 17% effect), and therefore the ecological significance of the effects may need to be further discussed. It should be kept in mind however, that the exposure situation in the available study was probably more "worst case" (higher dose and litter bags directly exposed) compared to the representative use of difenoconazole in carrots, pome fruit and as a seed treatment.

In conclusion, the available studies are not considered to completely fulfil the data requirements in Annex II and III of 91/414, since the metabolite CGA 205375 still remains to be tested on Collembola. A study is ongoing and will be submitted in July 2006 in order to complete the assessment. Based on the single species tests with difenoconazole and CGA 71019 on Collembola, the risk was concluded to be low at the representative uses of difenoconazole. However, the ecological significance of the observed effects in the litter bag study compared to more realistic exposure conditions at the representative uses of difenoconazole may need further discussions.

2.6.5 Effects on soil micro-organisms

The available studies on effects of difenoconazole, metabolites in soil and the representative formulation SCORE 250EC are summarised in the table below. No study was submitted on the representative seed treatment formulation, DIVIDEND 030FS.

[1] *BBA, 2001. Minutes of a meeting on the requirement of data according to Council Directive 91/414/EEC, Annex III, point 10.6.2, organised by the BBA (Braunschweig), 27-28 November, 2000; Minutes edited by C. Kula and S. Guske, March 2001.*

Table 2.6.5-1: Effects of difenoconazole on nitrogen transformation and carbon mineralization

Type of study and time scale	Test soils	Dose range tested	Results	Reference
Nitrogen transformation				
ACTIVE INGREDIENT				
28 days	loamy sand silty loam	1.67 and 16.7 mg as/kg	Ca 60% increased NO_3 in Lucerne-amended loamy sand at both treatment levels at 28 d, less pronounced in NH_3SO_4-amended soil. <25% effect in silty loam	Ellgehausen (1990)
METABOLITE CGA 71019				
28 days	sandy loam	0.035 and 0.353 mg/kg	<25% effect after 28 days	Völkel (2000)
METABOLITE CGA 205375				
28 days	sandy loam	0.09 and 0.22 mg/kg	<25% effect after 28 days	Seyfried (2002)
DIVIDEND 030FS				
No data available.				
SCORE 250EC				
28 days	two field soils	0.33 and 1.67 mg as/kg	<25% effect after 28 days	Maas (1990)
Carbon mineralization				
ACTIVE INGREDIENT				
28 days	silty loam	1.67 and 16.7 mg as/kg	<25% effect in silty loam	Ellgehausen (1990)
METABOLITE CGA 71019				
28 days	sandy loam	0.035 and 0.353 mg/kg	<25% effect after 28 days	Völkel (2000)
METABOLITE CGA 205375				
28 days	sandy loam	0.09 and 0.22 mg/kg	<25% effect after 28 days	Seyfried (2002)
DIVIDEND 030FS				
No data available.				
SCORE 250EC				
28 days	two field soils	0.33 and 1.67 mg as/kg	<25% effect after 28 days	Maas (1990)
Single species test				
ACTIVE INGREDIENT				
Marasmius oraede (6d),	loamy sand	0.05 – 16.4 mg as/kg soil	6 d NOEC 1.64 mg as/kg	Grade (2000)
Mucor circinelloides (3d)	loamy sand	0.05 – 16.4 mg as/kg soil	3 d NOEC 4.9 mg as/kg	Grade (2000)
Paecilomyces marquandii (17d)	loamy sand	0.05 – 16.4 mg as/kg soil	17 d NOEC 16.4 mg as/kg	Grade (2000)
Phytophtora nicotianae (17d)	loamy sand	0.05 – 16.4 mg as/kg soil	17 d NOEC 16.4 mg as/kg	Grade (2000)

The notifier claimed that treatment with difenoconazole at 16.7 mg as/kg caused <25% effect on respiration or nitrification processes in soil while exposure to 4.9 mg/kg caused <25% effect on the growth of soil fungi. Therefore, difenoconazole was considered to have no biologically significant effect on soil micro-organisms at concentrations 35-fold greater than the maximum soil PEC of 0.136 mg/kg. Therefore, it was considered that difenoconazole would pose a low risk to soil micro-organisms.

Treatment with the soil metabolites CGA 71019 at 0.353 mg/kg caused <25% effect on soil respiration processes. Therefore, CGA 71019 had no biologically significant effect on soil micro-organisms at concentrations approximately 70-fold greater than the worst case maximum soil concentration of 0.005 mg/kg. Treatment with CGA 205375 at 0.22 mg/kg caused <25% effect on soil respiration processes. Therefore, CGA 205375 had no biologically significant effect on soil micro-organisms at concentrations approximately 20-fold greater than the maximum soil PEC of 0.012 mg/kg.

For DIVIDEND 030FS, no data was submitted. However, the RMS agrees with the notifier that the effects from this formulation can be considered to be covered by the data on the active ingredient where a low risk was concluded.

Available studies are considered to fulfil the data requirements of Annex II and III of 91/414, and no further studies are needed for Annex I inclusion.

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

A summary of available data on the effects of difenoconazole on non-target plants is given in the table below.

Table 2.6.6-1: Summary of results from non-target plant studies with difenoconazole and SCORE 250EC.

Species	Test type	Rate (g as/ha)	Result	Reference
LABORATORY STUDIES				
ACTIVE INGREDIENT				
Avena sativa	soil incorporation	0.1, 0.3, 1.0, 3.0 and 10 mg as/kg soil, equivalent to between 75 g and 7.5 kg as/ha	21 day ER_{50} >10 mg as/kg dw soil based on fresh biomass	**Balluff (2004)**
Brassica napus	soil incorporation	0.1, 0.3, 1.0, 3.0 and 10 mg as/kg soil, equivalent to between 75 g and 7.5 kg as/ha	21 day ER_{50} >10 mg as/kg dw soil based on fresh biomass	**Balluff (2004)**
Glycine max.	soil incorporation	0.1, 0.3, 1.0, 3.0 and 10 mg as/kg soil, equivalent to between 75 g and 7.5 kg as/ha	21 day ER_{50} >10 mg as/kg dw soil based on fresh biomass	**Balluff (2004)**
DIVIDEND 030FS	**no data available**			
SCORE 250EC				
Brassica napus	spray application	12.5, 25, 50, 100, 200 and 400 g formulation/ha	21 day ER_{50} >100 g as/ha based on seedling emergence 14 day ER_{50} >100 g as/ha based on vegetative vigour	**Walder (2000)**
Avena fatua	spray application	12.5, 25, 50, 100, 200 and 400 g formulation/ha	21 day ER_{50} >100 g as/ha based on seedling emergence 14 day ER_{50} >100 g as/ha based on vegetative vigour	**Walder (2000)**
Beta vulgaris	spray application	12.5, 25, 50, 100, 200 and 400 g formulation/ha	21 day ER_{50} >100 g as/ha based on seedling emergence 14 day ER_{50} >100 g as/ha based on vegetative vigour	**Walder (2000)**
Zea mays	spray application	12.5, 25, 50, 100, 200 and 400 g formulation/ha	21 day ER_{50} >100 g as/ha based on seedling emergence 14 day ER_{50} >100 g as/ha based on vegetative vigour	**Walder (2000)**
Glycine max	spray application	12.5, 25, 50, 100, 200 and 400 g formulation/ha	21 day ER_{50} 100 g as/ha based on seedling emergence 14 day ER_{50} >100 g as/ha based on vegetative vigour	**Walder (2000)**
Allium cepa	spray application	12.5, 25, 50, 100, 200 and 400 g formulation/ha	21 day ER_{50} >100 g as/ha based on seedling emergence 14 day ER_{50} >100 g as/ha based on vegetative vigour	**Walder (2000)**

Non-target plants and seeds present in off-crop areas may be exposed to SCORE 250EC by spray drift onto their foliage. Alternatively, non-target plant seed, that has been shed, may be exposed by spray drift onto the soil. For risk assessment purposes, the maximum exposure concentrations were estimated using BBA drift values at varying distances from the crop edge. For effects on seed, the total drift rate was assumed to be deposited on soil and for effects on emerged vegetation, the total drift rate was assumed to be intercepted by the vegetation as a worst case.

In glasshouse tests with A-7402 G, applications of 400 g formulation/ha (95.7 g as/ha assuming a formulation density of 1.045 kg/L) caused <25% effect on seedling emergence or vegetative vigour in five of the six species tested. In the case of soyabean (*Glycine max*), treatment with 400 g formulation/ha caused <50% in the vegetative vigour test but had approximately 50% effect in the seedling emergence test. Effects from this study were expressed in terms of reduction in visual score based on observations of plant health and size following exposure to pre-emergence applications of A-7402 G. However, in a further germination study where technical difenoconazole was incorporated into the soil before the seed was sown (Balluff, 2004), rates up to 10 mg as/kg (equivalent to 7.5 kg as/ha) caused a maximum 35% (i.e. <50%) effect in soya bean. This effect was estimated from assessments of fresh weight, which according to the notifier are considered a better indicator of effects on plant growth than visual scores. Nevertheless, for the purposes of risk assessment, the minimum EC_{50} for vegetative vigour and seedling emergence was considered to be 100 g as/ha.

According to **SANCO/10329/2002,** risk to terrestrial plants is considered acceptable provided that the maximum single application rate causes <50% effect on plant growth. TER values were calculated using the minimum EC_{50} of 95.7 g as/ha estimated from seedling emergence and vegetative vigour tests conducted with 6 test species.

Vegetative vigour and seedling emergence TER values exceed the recommended trigger of 5, indicating that SCORE 250EC poses low risk to the vegetative growth and seedling emergence of off-crop non-target terrestrial plants.

In conclusion, the risk to off-crop non-target terrestrial plants is assessed to be low at the representative uses of difenoconazole for seed treatment in cereals and at spray application in pome fruit and carrots. No further data is needed.

2.6.7 Effects on biological methods of sewage treatment

For the proposed uses of difenoconazole contamination of sewage treatment plants is not considered likely. Further, with a NOEC of 32 mg as/L and an EC_{50} of >100 mg/L, the risk for harmful effects on biological methods of sewage treatment is considered to be acceptable.

Appendix 1: Standard terms and abbreviations

A1.1 Technical Terms

A	ampere
Ach	acetylcholine
Ache	acetylcholinesterase
ADI	Acceptable Daily Intake
ADP	adenosine diphosphate
AE	acid equivalent
AFID	alkali flame-ionization detector or detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD50	approximate median lethal dose 50%
ALT	alanine aminotransferase (SGPT)
AOEL	Acceptable Operator Exposure Level
AMD	automatic multiple development
ANOVA	analysis of variance
AP	alkaline phosphatase
approx	approximate
ARC	anticipated residue contribution
ARfD	acute reference dose
as	active substance
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	adenosine triphosphate
BCF	bioconcentration factor
bfa	body fluid
BOD	biological oxygen demand
bp	boiling point
BSAF	biota-sediment accumulation factor
BSE	bovine spongiform encephalopathie
BSP	bromosulfophthalein
Bt	bacillus thuringiensis
Bti	bacillus thuringiensis israelensis
Btk	bacillus thuringiensis kurstaki
Btt	bacillus thuringiensis tenebrionis
BUN	blood urea nitrogen
bw	body weight
c	centi-(x 10^{-2}
°C	degree celsius (centigrade)
CA	controlled atmosphere
CAD	computer aided design
CADDY	computer aided dossier and data supply (an electronic dossier interchange and archiving format)
cd	candela
CDA	controlled drop(let) application
cDNA	complementary DNA
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CL	confidence limits
cm	centimetre
CNS	central nervous system
COD	chemical oxygen demand

CPK	creatinine phosphatase
cv	coefficient of variation
Cv	ceiling value
CXL	Codex Maximum Residue Limit (Codex MRL)
d	day
DES	diethylstilboestrol
DFR	dislodgeable foliar residue
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic Acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days pot inoculation
DRES	dietary risk evaluation system
DT	disappearance time
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
dw	dry weight
DWQG	drinking water quality guidelines
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
ECD	electron capture detector
ECU	European currency unit
ED_{50}	median effective dose
EDI	estimated daily intake
ELISA	enzyme lined immunosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EPMA	electron probe micro analysis
ERC	environmentally relevant concentration
ERL	extraneous residue limit
F	field
F_o	parental generation
F_1	filial generation, first
F_2	filial generation, second
FIA	fluorescence immuno assay
FID	flame ionization detector
FOB	functional observation battery
fp	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
g	gram
G	glasshouse
GAP	Good Agricultural Practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionization detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase
GI	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
GMO	genetically modified organism

GMM	genetically modified micro-organism
GPC	gel-permeation chromatography
GPPP	good plant protection practice
GPS	global positioning system
GSH	glutathion
GV	granulosevirus
h	hour(s)
H	Henry's Law constant (calculated as a unitless value) (see also K)
ha	hectare
Hb	haemoglobin
HCG	human chorionic gonadotropin
Hct	haematocrit
HDT	highest dose tested
hL	hectolitre
HEED	high energy electron diffraction
HID	helium ionization detector
HPAEC	high performance anion exchange chromatography
HPLC	high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography - mass spectrometry
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gas chromatography
H_s	Shannon-Weaver index
Ht	haematocrit
I	indoor
I_{50}	inhibitory dose, 50%
IC_{50}	median immobilisation concentration
ICM	integrated crop management
ID	ionization detector
IEDI	international estimated daily intake
IGR	insect growth regulator
im	intramuscular
inh	inhalation
ip	intraperitoneal
IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
iv	intravenous
IVF	*in vitro* fertilization
k	kilo
K	Kelvin or Henry's Law constant (in atmospheres per cubic meter per mole) (see also H)[13]
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
K_{oc}	organic carbon adsorption coefficient
K_{om}	organic matter adsorption coefficient
kg	kilogram
L	litre
LAN	local area network
LASER	light amplification by stimulated
LBC	loosely bound capacity
LC	liquid chromatography
LC-MS	liquid chromatography - mass spectrometry
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dose letalis media
LCA	life cycle analysis
LC_{Lo}	lethal concentration low
LC-MS-MS	liquid chromatography with tandem mass spectrometry

LD_{50}	lethal dose, median; dosis letalis media
LD_{Lo}	lethal dose low
LDH	lactate dehydrogenase
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of determination
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counter
LSD	least squared denominator multiple range test
LSS	liquid scintillation spectrometry
LT	lethal threshold
m	metre
M	molar
MAC	Moult accelerating compound
µm	micrometer (micron)
MC	moisture content
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase
µg	microgram
mg	milligram
MHC	moisture holding capacity
min	minute(s)
mL	millilitre
MLT	median lethal time
MLD	minimum lethal dose
mm	millimetre
mol	Mol
MOS	margin of safety
mp	melting point
MRE	maximum residue expected
mM	Milimoles
MRL	maximum residue level
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
n	normal (defining isomeric configuration)
NAEL	no adverse effect level
nd	not detected
NEDI	national estimated daily intake
NEL	no effect level
NERL	no effect residue level
ng	nanogram
nm	nanometer
NMR	nuclear magnetic resonance
no	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intent to suspend
NPD	nitrogen-phosphorus detector or detection

NPV	nuclear polyhedrosis virus
NR	not reported
NTE	neurotoxic target esterase
OC	organic carbon content
OCR	optical character recognition
ODP	ozone-depleting potential
ODS	ozone-depleting substances
OM	organic matter
op	organophosphorus pesticide
Pa	pascal
PAD	pulsed amperometric detection
2-PAM	2-pralidoxime
pc	paper chromatography
PC	personal computer
PCV	haematocrit (packed corpuscular volume)
PEC	Predicted Environmental Concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PED	plasma-emissions-detector
pH	pH-value
PHED	pesticide handler's exposure data
PHI	pre-harvest interval
PIC	prior informed consent
pic	phage inhibitory capacity
PIXE	proton induced X-ray emission
pKa	negative logarithm (to the base 10) of the dissociation constant)
PNEC	predicted no effect concentration
po	by mouth
P_{ow}	partition coefficient between n-octanol and water
POP	persistent organic pollutants
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
ppp	plant protection product
ppq	parts per quadrillion (10^{-24})
ppt	parts per trillion ($10^{-12)}$
PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	prothrombin time
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r	correlation coefficient
r^2	coefficient of determination
RBC	red blood cell
REI	restricted entry interval
Rf	retardation factor
RfD	reference dose
RH	relative humidity
RL_{50}	median residual lifetime
RNA	ribonucleic acid
RP	reversed phase
rpm	rotations per minute
rRNA	ribosomal ribonucleic acid
RRT	relative retention time
RSD	relative standard deviation

s	second
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship
SBLC	shallow bed liquid chromatography
sc	subcutaneous
sce	sister chromatid exchange
SD	standard deviation
se	standard error
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
SOP	standard operating procedures
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
spp	subspecies
sq	square
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STMR	supervised trials median residue
t	tonne (metric ton)
$t_{½}$	half-life (define method of estimation)
T_3	tri-iodothyroxine
T_4	thyroxine
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TC_{Lo}	toxic concentration, low
TID	thermionic detector, alkali flame detector
TD_{Lo}	toxic dose low
TDR	time domain reflectrometry
TER	Toxicity Exposure Ratio
TER_1	toxicity exposure ration for initial exposure
TER_{ST}	toxicity exposure ration following repeated exposure
TER_{LT}	toxicity exposure ration following chronic exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGGE	temperature gradient gel electrophoresis
TIFF	tag image file format
TLC	thin layer chromatography
Tlm	median tolerance limit
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit
TOC	total organic carbon
Tremcard	Transport emergency card
tRNA	transfer ribonucleic acid
TSH	Thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UV	ultraviolet

v/v	volume ratio (volume per volume)
WBC	white blood cell
wk	week
wt	weight
w/v	weight per volume
w/w	weight per weight
XRFA	X-ray fluorescence analysis
yr	year
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

A1.2 Organisations and Publications

ACPA	American Crop Protection Association
ASTM	American Society for Testing and Materials
BA	Biological Abstracts (Philadelphia)
BART	Beneficial Arthropod Registration Testing Group
CA	Chemical Abstracts
CAB	Centre for Agriculture and Biosciences International
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Food
CE	Council of Europe
CIPAC	Collaborative International Pesticides Analytical Council Limited
COREPER	Comite des Representants Permanents
EC	European Commission
ECB	European Chemical Bureau
ECCA	European Crop Care Association
ECDIN	Environmental Chemicals Data and Information Network of the European Communities
ECDIS	European Environmental Chemicals Data and Information System
ECE	Economic Commission for Europe
ECETOC	European Chemical Industry Ecology and Toxicology Centre
ECLO	Emergency Centre for Locust Operations
ECMWF	European Centre for Medium Range Weather Forecasting
ECPA	European Crop Protection Association
EDEXIM	European Database on Export and Import of Dangerous Chemicals
EHC (number)	Environmental Health Criteria (number)
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMIC	Environmental Mutagens Information Centre
EPA	Environmental Protection Agency
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organisation
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
EU	European Union
EUPHIDS	European Pesticide Hazard Information and Decision Support System
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organisation of the UN
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FRAC	Fungicide Resistance Action Committee
GATT	General Agreement on Tariffs and Trade
GAW	Global Atmosphere Watch
GIFAP	Groupement International des Associations Nationales de Fabricants de Produits

	Agrochimiques
GCOS	Global Climate Observing System
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GEDD	Global Environmental Data Directory
GEMS	Global Environmental Monitoring System
GIEWS	Global Information and Early Warning System for Food and Agriculture
GRIN	Germplasm Resources Information Network
HRAC	Herbicide Resistance Action Committee
IARC	International Agency for Research on Cancer
IATS	International Academy of Toxicological Science
IBT	Industrial Bio-Test Laboratories
ICBB	International Commission of Bee Botany
ICBP	International Council for Bird Preservation
ICES	International Council for the Exploration of the Seas
ICPBR	International Commission for Plant-Bee Relationships
ILO	International Labour Organisation
IMO	International Maritime Organisation
IOBC	International Organisation for Biological Control of Noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Resistance Action Committee
IRC	International Rice Commission
ISCO	International Soil Conservation Organisation
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JECFA	FAO/WHO Joint Expert Committee on Food Additives
JFCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
JMP	Joint Meeting on Pesticides (WHO/FAO)
JMPR	Joint Meeting on the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
NATO	North Atlantic Treaty Organisation
NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute (USA)
NCTR	National Centre for Toxicological Research (USA)
NGO	non-governmental organisation
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Co-operation and Development
OLIS	On-line Information Service of OECD
PAN	Pesticide Action Network
RNN	Re-registration Notification Network
RTECS	Registry of Toxic Effects of Chemical Substances (USA)
SCPH	Standing Committee on Plant Health
SETAC	Society of Environmental Toxicology and Chemistry
SI	Systeme International d'Unites
SITC	Standard International Trade Classification
TOXLINE	Toxicology Information On-line
UN	United Nations
UNEP	United Nations Environment Programme
WCDP	World Climate Data Programme
WCP	World Climate Programme
WCRP	World Climate Research Programme
WFP	World Food Programme
WHO	World Health Organisation
WTO	World Trade Organisation
WWF	World Wildlife Fund

Appendix 2: Specific terms and abbreviations

A2.1 Technical Terms

ADME	adsorption, distribution, metabolism and excretion
ADR	European agreement concerning the international carriage of dangerous goods by road
AR	applied radioactivity
AR	application rate
AUC	area under curve
ALP	alkaline phosphatase
a.i.	active ingredient
a.s.	active substance
Bq	becquerel
b.w.	body weight
CHO	chinese hamster ovary
Chol	cholesterol
DM	dry matter
EC	emulsifiable concentrate
E_bC_{50}	median effective concentration for biomass
E_rC_{50}	median effective concentration for growth rate
FS	flowable concentrate
FOMC	first order multicompartment kinetic model (Gustafson & Holden)
GLDH	glutamate dehydrogenase
HCl	hydrochloric acid
HQ	hazard quotient
K_F	freudlich coefficient
K_{OH}	hydroxyl radical rate constant
K_{OW}	octanol water partition coefficient
K_p	permeability konstant
LAI	leaf area index
LH	luteinizing hormone
LSC	liquid scintillation counting
MAC	maximum allowable concentration
MATC	maximum Acceptable Toxic Concentration
MMAD	mass median aerodynamic diameter
MS	Member State
MWHC	maximum water holding capacity
n.a.	not analysed
n.d.	not determined
N/A	not applicable
N/E	Not evaluated
NCE	normochromaric erythrocytes
NEDI	national estimated daily intake
NESTI	national estimate of short term intake
NEU	Northern EU
N/R	not required
NTA	non-target arthropods
OM	organic matter
PCE	polychromatic erythrocytes
PDE	potential dermal exposure
PEARL	pesticide leaching model
PEC_a	predicted environmental exposure in air
PEC_{gw}	predicted environmental exposure in ground water
PEC_s	predicted environmental exposure in soil
PEC_{sw}	predicted environmental exposure in surface water
PIE	potential inhalatory exposure
pKa	dissociation constant

POEM	predictive Operator Exposure Model
Pow	octanol water partition coefficient
PPE	personal protective equipment
QA	quality assurance
r^2	coefficient of determination
RPE	respiratory protective equipment
RSD	relative standard deviation
s	second
SE	Sweden
SEU	Southern EU
SFO	single first-order kintic model
SMS	Southern Member State
SSD	species sensitivity distribution
TC	transfer coefficient
TLC	thin layer chromatography
TRR	total radioactive residue
UDS	unscheduled DNA synthesis
UK	United Kingdom

A2.2 Organisations and Publications

BBA	Federal Biological Research Centre for Agriculture and Forestry (Germany)
EPA	Environmental Protection Agency (USA)
ESCORT	European Standard Characteristics of Non-Target Arthropod Regulatory Testing
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
KemI	Swedish Chemicals Inspectorate (SE)
SYN	Syngenta Ltd.
PSD	Pesticide Safety Directorate, UK

Appendix 3: Listing of endpoints

The List of endpoints for Difenoconazole is attached as a separate document.

Level 3

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

3.1 Background to the proposed decision

Difenoconazole is a systemic triazole fungicide that controls a broad-spectrum of foliar, seed and soil-borne diseases, caused by Ascomycetes, Basidiomycetes and Deuteromycetes, in cereals, soya, rice, grapes, pome fruit, stone fruit, potatoes, sugar beet and several vegetable and ornamental crops. It is applied by foliar spray or seed treatment. The representative uses evaluated are seed treatment to cereals (60 mg as/kg seed, formulation DIVIDEND 030FS) and spray application to pome fruit and carrots (3 x 125 g as/ha and 4 x 75 g as/ha, respectively, formulation SCORE 250EC).

Data submitted on the active substance show no evidence of adverce physical and chemical properties. There are no indications of problems associated with the physical, chemical or technical properties of the product when used as recommended.

Acceptable methods of analysis were available for the active substance as manufactured (GC-FID) and for difenoconazole in the representative formulations (Score 250 EC: GC-FID; Dividend: 030 FS: HPLC-UV). Moreover, acceptable monitoring methods were available for analysis of residues of difenoconazole in food/feed of plant origin and animal origin (HPLC-MS/MS), soil (HPLC-MS/MS, GC-ECD, GC-AFID or GC-NPD), drinking and surface water (GC-ECD) and air (HPLC-MS/MS). Analytical methods for the determination of residues of difenconazole in body fluids and tissues were not required.

In addition to the above mentioned methods data on several pre-registration methods used in the residue, fate and ecotox sections was submitted. The methods were in general considered acceptable and the quality of the data generated from methods considered not fully validated should not have been affected.

Difenoconazole is of moderate acute oral toxicity, with a LD_{50} value of 1453 mg/kg bw, and should be classified as Xn; R22 according to the Commission Directive 67/548/EEC. The acute dermal and inhalation toxicities are low with LD_{50} and LC_{50} values above 2010 mg/kg and 3.3 mg/dm^3 air/4 hours respectively. Difenoconazole did not cause skin or eye irritation and was not a skin sensitiser. The critical effect observed in repeated dose studies on both rats and dogs was a reduced body weight and the liver was identified as the target organ. The liver effects were mostly expressed as increased relative/absolute liver weights and were in some studies accompanied by histological changes or elevated ALP levels. Cataract development was observed in a six month study on dogs administered approximately 100 mg/kg bw of difenoconazole.

According to the results from the *in vitro* and *in vivo* tests performed, difenoconazole is not a genotoxic substance. Difenoconazole was considered to be a reversible barbiturate-type inducer of metabolising enzymes in the mouse liver and treatment with difenoconazole caused an increased incidence of adenomas/carcinomas in mice. In view of the lack of genotoxicity and the finding of tumours only in mice and only at concentrations at which toxicity was observed, the substance is considered not likely to pose a carcinogenic risk to humans. There were no evident signs of reproductive toxicity observed in the two-generation reproduction study or in the developmental studies conducted. An ADI of 0.01 mg/kg bw/day was proposed based on the reductions in body weight gain and absolute body weights observed in a 2-year combined chronic toxicity/oncogenicity study in rats. The AOEL and ARfD values were based on the effects (reduced food and water consumptions, reduced body weight, reduced carcass weight and reduced heart weights) observed in a 90 day study in rats. In plants treated with difenoconazole, one difenoconazole specific metabolite (CGA 205375) and four triazole metabolites (CGA71019, CGA 131 013, CGA 142856 and CGA 205369) were found at levels that exceeded 10% of the TRR. However, during the conditions of the representative use, the levels of these residues in plants are low thus only studies of acute oral toxicity and genotoxicity are considered necessary. CGA 131 013, CGA 142856 and CGA 205369 residues in plants is considered to be of no concern. CGA 205369 (triazole lactic acid) and CGA 71019 (1, 2, 4-triazole) residues in plants is considered to be of no concern **provided** that the *in vitro* genotoxicity tests that are in progress show negative results.

The operator exposure to difenoconazole (SCORE ® 250 EC A-7402T) in orchards with tractor mounted airblast sprayers or hand-held applications and in field crop scenarios with tractor mounted hydraulic boom sprayers or hand-hels applications is considered acceptable. The predicted levels of exposure of bystanders and re-entry workers do not give rise to concern.
The estimates of operator exposure to DIVIDEND®030 FS (A-9142 G) were calculated by the notifier using the SEEDTROPEX model. The RMS considers that this model requires more extensive data than the two existing studies in order to be accepted as a general model for estimation of exposure during seed treatment. Therefore, results obtained using the SEEDTROPEX model should be interpreted with caution. However, DIVIDEND®030 FS (A-9142 G) is of low acute toxicity and the values obtained using the SEEDTROPEX model are well below the AOEL of difenoconazole. Therefore, the risk of harmful effects in operators handling treated seed is presumed to be low if appropriate protective clothing is worn and basic hygienic rules are observed. The predicted levels of exposure of bystanders and re-entry workers do not give rise to concern.

From assessment of the potential exposure of difenoconazole through the diet it can be concluded that an acceptable safety margin exits. The WHO European model, the German BBA and the UK PSD consumer exposure models lead to low TMDI values and the contribution to the proposed ADI of 0.01 mg/kg bw /day is of maximum 10% for adults, 12% for schoolchildren, 53% for toddlers and 39% of the ADI for infants. The acute dietary risk posed by the consumption of difenoconazole residues in treated cereals, pome fruits and carrots was concluded to be negligible. The calculated NESTI values are all considerably lower than the ARfD of 0.20 mg/kg bw/day, with the highest short-term consumption being 8.4% of the ARfD for apples in toddlers.

For the representative area of use, the proposed residue definition in plants is difenoconazole alone for both monitoring and risk assessment purposes. The proposed definition of the residue in animals and products of animal origin is parent difenoconazole for risk assessment purposes but for the purposes of monitoring both parent difenoconazole and the metabolite CGA 205375.

Difenoconazole is slowly degraded in soil under aerobic conditions, and stable under anaerobic conditions. High treatment rate appears to result in slower degradation. Laboratory studies carried out at relevant treatment rates resulted in DT_{50}s in the range 53 to 187 days (n=8) with a median value of 120 days. Two metabolites (CGA 205375 and CGA 71019) were identified close to or above 10% of the applied radioactivity. Both metabolites were addressed further. Under field conditions with a wide range of application rates difenoconazole disappeared with DT_{50}s of 22-265 days (median 83 days), with DT_{90}s in the range 72-879 days (median 277 days). From the results of soil accumulation studies carried out over 3-10 years on various crops and bare soil difenoconazole or the two principal metabolites are not expected to accumulate in soil following normal agricultural practice. In one of the studies, there was an indication of potential accumulation of total, including bound, 1,2,4-triazole residues since up to 0.009-0.010 mg/kg were found immediately before application of difenoconazole. Since the majority of these residues are likely to be bound to the soil matrix and hence expected to be bioavailable only to a limited degree these residues are not considered as an area of concern.

Difenoconazole and the metabolite CGA 205375 adsorbs strongly to soil but the metabolite CGA 71019 (1,2,4-triazole) showed only a weak sorption. None of the substances are expected to leach to groundwater at levels close to or above 0.1 µg/L.

Difenoconazole is expected to rapidly disappear from the water column in aquatic environments due to adsorption to sediments. Degradation of difenoconazole is expected to be slow. Mean DT_{50} for degradation of difenoconazole in two water/sediment systems at 20ºC was 316 days (whole systems). CGA 205375 and CGA 71019 were the only metabolites identified at significant amounts and both were included in the risk assessment for aquatic environments.

Difenoconazole is not expected to volatilise and photochemical oxidative transformation is rapid. The predicted environmental concentrations in air is therefore expected to be negligible.

For seed treatment, standard bird species for the assessment were granivorous birds, medium sized herbivorous birds and small herbivorous birds feeding on treated seeds and shoots emerging from treated seeds, respectively. No acute or short-term risks to birds were identified in the initial standard risk assessment for seed treatment. A long term risk was identified for granivorous birds, however the refined assessment based on dissipation data of difenoconazole from treated seeds and diet composition of a relevant focal species (skylark) indicate that the TER values were above the trigger values in Annex VI of 91/414.

For the use in carrots, the standard species were medium sized herbivorous birds and insectivorous birds, and for pome fruit insectivorous birds only. No acute or short-term risks to birds were identified in the initial standard

risk assessment for spray application. Although a long term risk to birds was identified in the initial standard risk assessment for spray application, based on the refinements of the PT factors (percent of time spent in treated areas) the TER values were above the trigger values in Annex VI of 91/414.

Standard mammalian species for the assessment of the seed treatment use were granivorous mammals and herbivorous mammals. No acute risks to mammals were identified in the initial standard risk assessment for seed treatment. Although a long term risk was identified for granivorous mammals, the refined assessment based on diet composition data for the relevant focal species (wood mouse), the TER values were above the trigger values in Annex VI of 91/414.

For the use in carrots, the standard mammalian species were medium sized herbivorous mammals, and for pome fruit small herbivorous mammals. No acute or long term risks to mammals were identified in the initial standard risk assessment for carrots. A long term risk was identified for small herbivorous mammals in pome fruit in the initial standard risk assessment, however refined assessment based on diet composition data for the relevant focal species (field vole), the TER values were above the trigger values in Annex VI of 91/414.

For aquatic organisms, no short- or long term risks were identified at Step 2 at the representative seed treatment use. At spray application in carrot and pome fruit, risk was identified for fish, aquatic invertebrates and algae at Step 2, and at Step 3 there was still a risk for the most sensitive species in 3 out of 6 scenarios for carrots and all scenarios for pome fruit using the global maximum concentrations. However, refinement based on FOCUS Step 4 scenarios indicated that with appropriate risk mitigation measures, the TER values are all above the trigger values in Annex VI of 91/414.

No risks were identified for honey bees and other non-target arthropods. This result of the initial standard risk assessment for non-target arthropods was supported by further laboratory studies and semi-field studies.

No acute or long-term risks were identified for earthworms at the representative use as seed treatment and in pome fruit and carrot cultivations. Long term data was missing for one major metabolite in soil.

No risk was identified for soil micro organisms. The result of a litter bag study did not give reason for concern.

No risk was identified for non-target terrestrial plants.

In the definition of the residues relevant to the environment, difenoconazole was included as the sole compound in the surface water, sediment and air compartments. In soil, the metabolite CGA 205375 may be relevant, pending new long term data for earthworms and Collembola. In groundwater, no residues were included in the definition.

3.2 Proposed decision concerning inclusion in Annex I

[redacted]

3.3 Rationale 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

[redacted]

The information in sections 3.2 and 3.3 has been removed upon request by the European Commission as it relates to risk management recommendations or proposals.

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 Annex I

4.1 Identity of the active substance

The information supplied is sufficient for a decision to be made on Annex I inclusion for difenoconazole.

4.2 Physical and chemical properties of the active substance

The information supplied is sufficient for a decision to be made on Annex I inclusion for difenoconazole.

4.3 Data on application and further information

The information supplied is sufficient for a decision to be made on Annex I inclusion for difenoconazole.

4.4 Classification, packaging and labelling

The information supplied is sufficient for a decision to be made on Annex I inclusion for difenoconazole.

4.5 Methods of analysis

The information supplied is sufficient for a decision to be made on Annex I inclusion for difenoconazole.

4.6 Toxicology and metabolism

The RMS considers that the assessment of the toxicological relevance of the plant metabolites 1,2,4-triazole (CGA 71019) and triazole lactic acid (CGA 205369) requires additional *in vitro* data on genotoxicity (section B.6.8.2). The notifier has announced (April 2006) that additional studies to determine the genotoxicity of 1,2,4-triazole (CGA 71019) and the genotoxicity and acute toxicity of triazole lactic acid (CGA 205369) have been initiated or are planned. The RMS suggests that additional data and assessment on the toxicological relevance of 1,2,4-triazole (CGA 71019) and triazole lactic acid (CGA 205369), will be included in an Addendum to this DAR.

4.7 Residue data

The information supplied is sufficient for a decision to be made on Annex I inclusion for difenoconazole.

4.8 Environmental fate and behaviour

The information supplied is sufficient for a decision to be made on Annex I inclusion for difenoconazole.

4.9 Ecotoxicology

Birds and mammals:

No further data is needed for Annex I inclusion.

Aquatic organisms:

No further data is needed for Annex I inclusion.

Bees and other non-target arthropods:

No further data is needed for Annex I inclusion.

Earthworms:

The long term effects of the soil metabolite CGA 205375 needs to be addressed, since the trigger of DT_{90}>100 days was exceeded, and since this metabolite was shown to be more toxic than the parent compound. The notifier has announced that a study is ongoing, and will be submitted in July 2006.

Other soil macro-organisms:

The long term effects of the soil metabolite CGA 205375 needs to be addressed, since the trigger of DT_{90}>100 days was exceeded. The notifier has announced that a study is ongoing, and will be submitted in July 2006.

Soil non-target micro-organisms:

No further data is needed for Annex I inclusion.