LEVEL 1

Metalaxyl-M

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

1.1 Purpose for which the monograph was prepared (Document A)

This monograph is submitted to support the application for the first inclusion of the new active substance metalaxyl-M in Annex I to Directive 91/414/EEC.

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

Not applicable as metalaxyl-M is a new active substance with only one applicant.

1.3 Identiy of the active substance (Annex IIA 1)

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

Applicant : **NOVARTIS Crop Protection AG**

CH-4002 Basle
Switzerland

Contact person : ir. Johan Henken
Manager Regulatory affairs
NOVARTIS Agro Benelux B.V.
Crop Protection Sector
Postbus 1048
NL-4700 BA Roosendaal

Tel. No. : 00 31 (0) 165-574 741
Tfx. No. : 00 31 (0) 165-559 605

1.3.2 Manufacturer of the active substance (Annex IIA 1.2)

Manufacturer : **Säurefabrik Schweizerhall**

CH-4133 Schweizerhalle
Switzerland

Location of plant : **CH-4133 Schweizerhalle**
Switzerland

Contact point : **NOVARTIS Crop Protection AG**
Niklaus Burkhard
R-1058.8.14
CH-4002 Basle

Tel. No. : 00 41 (0) 61 697 25 94
Tfx. No. : 00 41 (0) 61 697 49 66

1.3.3 ISO common name and synonyms (Annex IIA 1.3)

Common name : Metalaxyl-M (ISO-approved), Mefenoxam (unofficial)

1.3.4 Chemical name (Annex IIA 1.4)

IUPAC nomenclature : mixture of
(R)-2-[(2,6-dimethyl-phenyl)-methoxyacetylamino]-propionic acid methyl ester (min. 97 %)
(S)-2-[(2,6-dimethyl-phenyl)-methoxyacetylamino]-propionic acid methyl ester (max. 3 %)

CA nomenclature : mixture of
N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-D-alanine methyl ester (min. 97 %)
N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-L-alanine methyl ester (max. 3 %)

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

Code number of CIBA-GEIGY for the a.s. : CGA 329351 (R) + CGA 351920 (S) (since January 1994)
CGA 76539 (before January 1994)

Throughout the dossier, the notifier used CGA 329351 to refer to metalaxyl-M, as well as to indicate the R-enantiomer as such, which was rather confusing.

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

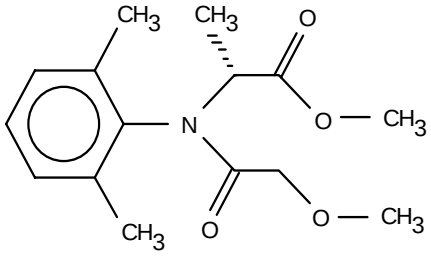
CAS number : 70630-17-0 (R)
69516-34-3 (S)
EEC number : not available
CIPAC number : 580

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

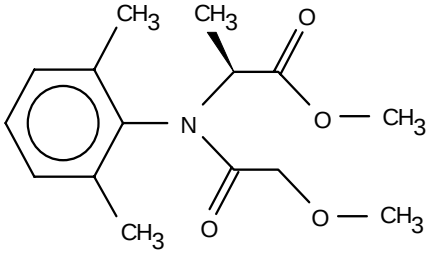
Molecular formula : $C_{15}H_{21}NO_4$

Structural formula:

R- ***enantiomer (CGA 329351) :***



S- ***enantiomer (CGA 351920) :***



Molecular mass: 279.3

1.3.8 Method or methods of manufacture (Annex IIA 1.8)

Confidential information, see Annex C

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

The minimum purity of the a.s. as manufactured, as stated by the notifier, is 940 g/kg;

i.e. the technical a.s. contains :	**min.**	**940 g/kg**	**sum of CGA 329351 and CGA 351920**
	min.	**910 g/kg**	**CGA 329351**
	max.	**40 g/kg**	**CGA 351920**

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

Confidential information, see Annex C

1.3.11 Analytical profile of batches (Annex IIA 1.11)

Confidential information, see Annex C

1.4a Identity of the plant protection product RIDOMIL GOLD 480 EC(Annex IIA 3.1; Annex IIIA 1)

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

Trade name : RIDOMIL GOLD 480 EC
Code number : A-9408 B

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

Applicant : **NOVARTIS Crop Protection AG**
CH-4002 Basle
Switzerland

Contact person : Dr. F. Meier-Manz
R-1058.7.54
CH-4002 Basle

Tel. No. : 00 41 (0) 61 697 27 21
Tfx. No. : 00 41 (0) 61 697 23 00

Location of plant : **NOVARTIS**
Usine de Monthey
CH-1870 Monthey

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

Emulsifiable concentrate, EC

1.4.4a Function (Annex IIIA 1.6)

Fungicide

1.4.5a Composition of the preparation (Annex IIIA 1.4)

Table 1.4.5a-1 : Composition of RIDOMIL GOLD 480 EC

Component	Content		Function
	g/l	% w/w	
Metalaxyl-M **- pure a.s.** **- T.C. (purity min. 94 %)**	 **(480)** **480-511**	 **(46.2)** **46.2-49.1**	**Active substance**
Other components	**Confidential information, see Annex C**		

1.4b Identity of the plant protection product RIDOMIL GOLD MZ 68 WP (Annex IIA 3.1; Annex IIIA 1)

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

Trade name : RIDOMIL GOLD MZ 68 WP
Code number : A-9407 A

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

Applicant : **NOVARTIS Crop Protection AG**
CH-4002 Basle
Switzerland

Contact person : Dr. F. Meier-Manz
R-1058.7.54
CH-4002 Basle
Tel. No. : 00 41 (0) 61 697 27 21
Tfx. No. : 00 41 (0) 61 697 23 00

Location of plant : **Dr. R. Maag AG**
Postfach 233
CH-8157 Dielsdorf

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

Wettable powder, WP

1.4.4b Function (Annex IIIA 1.6)

Fungicide

1.4.5b Composition of the preparation (Annex IIIA 1.4)

Table 1.4.5b-1 : Composition of RIDOMIL GOLD MZ 68 WP

Component	Content % w/w	Function
Metalaxyl-M **- pure a.s.** **- T.C. (purity min. 94 %)**	 **(4)** **4.0-4.3**	**Active substance**
Mancozeb **- pure a.s.** **- Mancozeb 80 WP**	 **(64)** **80**	**Active substance**
Other components	**Confidential information, see Annex C**	

1.5 Uses of the plant protection products RIDOMIL GOLD 480 EC and RIDOMIL GOLD MZ 68 WP

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

Metalaxyl-M is used in agriculture, horticulture and forestry as

- Foliar spray to control airborne disease
- Stem paint against crown rots and trunk cankers

→ RIDOMIL GOLD MZ 68 WP is representative of these types of uses

- Soil treatment against soilborne diseases

→ RIDOMIL GOLD 480 EC is representative of this type of use

- Seed treatment against seedborne or systemic airborne diseases
- Post-harvest dip or drench to control fruit diseases

→ **no Annex III dossier was submitted in order to support these types of uses**

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

Metalaxyl-M inhibits mycelial growth and spore formation. Foliar pathogens are inhibited only after they have penetrated the leaves.
Metalaxyl-M is taken up very rapidly following root, stem or leaf application. Translocation of the compound is primarily acropetal (xylem) and this is a gradual and continuous process, thus providing additional fungicide activity and disease control as new plant growth occurs, or several weeks (or months) after soil treatment. Limited basipetal (phloem) transport was also observed.

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

Table 1.5.3-1 : List of pests controlled and crops protected

Crop	**Pathogen**
Avocado	***Phytophthora spp.***
Beans	***Pythium spp., Peronospora spp.***
Berries	***Phytophthora spp.***
Carrots	***Phytophthora spp., Pythium spp., Plasmopara nivea***
Citrus	***Phytophthora spp.***
Cucurbits	***Pseudoperonospora spp.***
Fruiting vegetables	***Phytophthora spp., Pythium spp., Peronospora spp.***
Grapes	***Plasmopara viticola***
Hops	***Pseudoperonospora humuli***
Kiwi fruit	***Pythium spp., Phytophthora spp.***
Leafy vegetables	***Pythium spp., Phytophthora spp., Bremia lactucae, Peronospora spp.***

Crop	Pathogen
Maize	***Sclerophthora spp., Pythium spp.***
Oilseed rape	***Peronospora spp.***
Ornamentals	***Pythium spp., Phytophthora spp., Peronospora spp.***
Peas	***Peronospora spp., Pythium spp.***
Pome fruit	***Phytophthora spp., Pythium spp.***
Potatoes	***Phytophthora infestans, Pythium spp.***
Stone fruit	***Phytophthora spp., Pythium spp.***
Sugar beet	***Phytophthora schachtii, Pythium spp.***
Sunflower	***Plasmopara halstedii, Pythium spp., Peronospora spp.***
Tobacco	***Peronospora tabacina, Pythium spp., Phytophthora spp.***
Tomatoes	***Phytophthora infestans***

Table 1.5.3-2 : Intended uses of metalaxyl-M in the EU - Foliar Application/Stem paint (RIDOMIL GOLD MZ 68 WP)

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
Apple **(stem paint)**	**Italy**	**3.5 g a.s. per tree (a few trees/ha)**	**7 g a.s. per tree**	**2**		**14 -28**
Artichoke **(foliar spray)**	**Italy**	**0.1 kg a.s./ha**	**0.3 kg a.s./ha**	**3**		**20**
Beans **(foliar spray)**	**Italy**	**0.12 kg a.s./ha**	**0.24 kg a.s./ha**	**2**	**first sign of symptoms**	**14 - 28**
Beans, field & broad **(foliar spray)**	**Italy, UK**	**0.075 - 0.117 kg a.s./ha**	**0.15 - 0.234 kg a.s./ha**	**2**	**first sign of symptoms**	**14 - 56**
Beans, field **(foliar spray)**	**Ireland**	**0.1 kg a.s./ha**	**0.3 kg a.s./ha**	**3**	**preventative program**	**14**
Brassicas (**foliar spray)**	**Portugal**	**0.1 kg a.s./ha**	**0.3 kg a.s./ha**	**3**	**after transplanting & 6 -8 leaves**	**14**
Broccoli **(foliar spray)**	**Italy**	**0.1 kg a.s./ha**	**0.3 kg a.s./ha**	**3**		**20**
Brussels sprouts **(foliar spray)**	**UK, Ireland**	**0.1 kg a.s./ha**	**0.3 kg a.s./ha**	**3**	**at first sign of disease**	**14**

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
Cabbage **(foliar spray)**	**Italy**	**0.1 kg a.s./ha**	**0.3 kg a.s./ha**	**3**		**14 - 20**
Cauliflower **(& calabrese in UK) (foliar spray)**	**Italy, UK, Ireland**	**0.075 - 0.1 kg a.s./ha**	**0.15 - 0.3 kg a.s./ha**	**2 - 3**		**14 - 21**
Cherry **(stem paint)**	**Italy**	**3.5 g a.s. per tree (a few trees/ha)**	**7 g a.s. per tree**	**2**		**30**
Citrus **(stem paint)**	**Italy**	**3.5 g a.s. per tree (about 10% of the surface/ha is treated)**	**7 g a.s. per tree**	**2**		**30**
Citrus **(skirt spray)**	**Spain**	**0.35 g a.s. per tree (5-15-50% surface/ha treated)**	**0.7 g a.s. per tree**	**2**		**15**
Cucumber **(foliar spray)**	**Austria, France, Greece, Italy Portugal, Spain**	**0.04 - 0.15 kg a.s./ha**	**0.6 kg a.s./ha**	**3 - 4**		**3 - 14**
Grapes **(foliar spray)**	**Austria, France, Germany, Greece, Italy, Portugal, Spain**	**0.12 kg a.s./ha**	**0.42 kg a.s./ha**	**2 - 4**	**pre and post flowering**	**15 - 56**
Hops **(foliar spray)**	**Germany**	**0.15 kg a.s./ha**	**1.2 kg a.s./ha**	**6**	**from first shoots onwards**	**10 (7 - 14)**
Leek **(foliar spray)**	**(Belgium), UK**	**0.075 (- 0.085) kg a.s./ha**	**0.225 (- 0.255) kg a.s./ha**	**3**	**at first sign of disease**	**14**
Lettuce **(foliar spray)**	**Belgium, Luxemburg, Germany, Italy, Netherlands**	**0.1 - 0.125 kg a.s./ha.**	**0.3 - 0.32 kg a.s./ha.**	**3**		**14 - 28**
Melon (foliar spray)	**France, Italy,**	**0.094 - 0.12**	**0.28 - 0.36**	**3**		**3 - 21**

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
	Portugal					
Onion (foliar spray)	Austria, France, Germany, Italy, Spain, UK	0.075 - 0.15 kg a.s./ha	0.225 -0.45 kg a.s./ha	3	first sign of disease	14 - 28
Ornamentals (foliar spray)	Netherlands	0.036 - 0.14 kg a.s./ha	0.42 kg a.s./ha	3		
Pea (foliar spray)	Italy	0.117 kg a.s./ha	0.234 kg a.s./ha	2	first sign of disease	21
Peach (stem paint)	Italy	3.5 g a.s. per tree	7 g a.s. per tree	2		20
Pepper (foliar spray)	Portugal	0.1	0.3	3	after transplanting	14
Potato (foliar spray)	Austria, Belgium, Finland, France, Germany, Ireland, Italy, Luxembourg ,Netherland, Portugal, Spain, Sweden, UK	0.075 - 0.113 kg a.s./ha	0.375 - 0.4 kg a.s. / /ha	2 - 5	from start of disease development until before desiccation	7 - 28
Horse Radish (foliar spray)	Austria	0.1 kg a.s./ha	0.3 kg a.s./ha	3		30
Soybean (foliar spray)	Italy	0.1 kg a.s./ha	0.3 kg a.s./ha	3		35
Spinach (foliar spray)	Italy	0.1 kg a.s./ha	0.2 kg a.s./ha	2		20
Strawberry (foliar spray)	Italy	0.35 kg a.s./ha	0.7 kg a.s./ha	2	after transplanting or at end of growing period	14 - 40
Tobacco (foliar spray)	Austria, France, Greece, Italy, Portugal	0.08 - 0.15 kg a.s./ha	0.9 kg a.s./ha	2 - 6	active growth stage	7 - 28
Tomato (foliar spray)	France, Greece,	0.04 - 0.15 kg a.s./ha	0.6 kg a.s./ha	3 - 4	from start of first disease	3 - 28

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
	Italy, Portugal, Spain					
Watermelon (foliar spray)	France, Italy	0.094 - 0.12	0.28 - 0.36	3		3 - 21

Table 1.5.3-3 : Intended uses of metalaxyl-M in the EU - Soil Application (RIDOMIL GOLD 480 EC)

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
Apple (soil application)	Italy, Spain	1 g a.s. /m^2	2 g a.s. / m^2	2	during autumn or March, beginning of vegetative growth	15 - 28
Apple (soil application)	Spain	via drip irrigation 1 g a.s. / tree in 0.5 m diameter circle	via drip irrigation 2 g a.s. / tree in 0.5 m diameter circle	2	during autumn or March	15 - 28
Avocados (soil application)	Italy	1 g a.s. / m^2	2 g a.s. / m^2	2	autumn	15
Beans (soil application)	Italy	0.05 - 0.1 g a.s. / m^2	0.1 - 0.2 g a.s. / m^2	2	at sowing or pre-planting	3 - 14
Broccoli (soil application)	Italy	0.05 - 0.1 g a.s. / m^2	0.1 - 0.2 g a.s. / m^2	2	at sowing or pre-planting	14
Cabbage (soil application)	EU countries	0.05 - 0.1 g a.s. / m^2	0.1 - 0.2 g a.s. / m^2	2	at sowing or pre-planting	14
Carrot (soil application)	France, Ireland, UK	0.24 - 0.6 kg / ha	0.6 kg / ha	1 - 2	4 - 6 weeks after drilling	30
Cauliflower (soil application)	Italy	0.05 - 0.1 g a.s. / m^2	0.1 - 0.2 g a.s. / m^2	2	at sowing or pre planting	14

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
Cherry **(soil application)**	**Italy**	**0.5 - 1 g a.s. / m ^{2}**	**1 - 2 g a.s. / m ^{2}**	**2**	**root growth flushes**	**30**
Chicory **(root treatment)**	**Belgium**	**10 g a.s./ 100 l water for 5 tons of roots**	**10g a.s./ 100 l water for 5 tons of roots**	**1**	**before conservation and forcing**	**14 - 28**
Citrus **(soil application)**	**Italy, Spain**	**1 g a.s. / m ^{2} in tree root zone.**	**2 g a.s. / m ^{2} in tree root zone.**	**2**	**root growth flushes, vegetative growth begins**	**15 - 30**
Citrus **(soil application)**	**Spain**	**drip irrigation 1 g a.s. / m ^{2} in tree root zone.(0.576 kg a.s./ha)**	**drip irrigation 2 g a.s. / m ^{2} in tree root zone. (1.152 kg a.s./ha)**	**2**	**root growth flushes, vegetative growth begins**	**15 - 30**
Grass, turf **(soil application)**	**Italy**	**0.725 - 1 kg a.s./ha**	**2.25 - 3 kg a.s./ha**	**3**		
Hops **(soil application)**	**Belgium**	**0.4 kg a.s./ha**	**0.4 kg a.s./ha**	**1**	**beginning of plant growth**	**7 - 14**
Kiwifruit **(soil application)**	**Italy**	**0.5 - 1 g a.s. / m ^{2}**	**1 - 2 g a.s. / m ^{2}**	**2**	**root growth flushes**	**180**
Lettuce **(soil application)**	**Italy**	**0.1 g a.s. / m ^{2}**	**0.2 g a.s. / m ^{2}**	**2**	**at sowing or pre planting**	**14 - 28**
Melon **(soil application)**	**Italy**	**0.1 g a.s. / m ^{2}**	**0.2 g a.s. / m ^{2}**	**2**		**3 - 20**
Ornamentals **(soil application)**	**Germany, Italy, Netherlands**	**12 g a.s. /m ^{3} soil in potting mix, 0.1 g / m ^{2} and up to 7.5 kg a.s. / ha (containers greenhouses only)[1]**	**12 g a.s. /m ^{3} soil in potting mix, 0.1 g / m ^{2} and up to 7.5 g a.s. / ha (containers greenhouses only)**	**1**		
Ornamentals -Flowers **(soil application)**	**Italy**	**0.05 - 1 g a. I. / m ^{2}**	**3 g a.s. / m ^{2}**	**1 - 3**	**at sowing**	

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
Ornamentals Forestry (soil application)	Italy, Netherlands	4 g a.s. / m^2 / 7.25 g per m^3 soil in potting mix)	4 g a.s. / m^2 / 7.25 g per m^3 soil in potting mix)	1	at sowing	
Peach (= Stone Fruit in Spain) (soil application)	Italy, Spain	0.5 - 1 g a.s. / m^2	1 - 2 g a.s. / m^2	2	root growth flushes	15
Peach (=Stone Fruit) (soil application)	Spain	via drip irrigation 1 g a.s. / m^2	via drip irrigation 2 g a.s. / m^2	2	during autumn or March	15 - 28
Pear (soil application)	Spain	1 g a.s. / m^2	2 g a.s. / m^2	2	during autumn or March, begining of vegetative growth	15 - 28
Pear (soil application)	Spain	via drip irrigation 1 g a.s. / tree in 0.5 m diameter circle	via drip irrigation 2 g a.s. / tree in 0.5 m diameter circle	2	during autumn or March	15 - 28
Peppers (soil application)	Italy, Spain (mainly greenhouses in Spain)	0.1 g a.s. /m^2 0.480 kg a.s./ha	0.3 g a.s. /m^2 1.44 kg a.s./ha	3	pre and post transplanting	15
Soybean (soil application)	Italy	0.25 - 0.5 kg a.s./ha	0.25 - 0.5 kg a.s./ha	1	at sowing	35
Stone fruit (soil application)	EU countries	1 g a.s. per m^2 at base of tree	2 g a.s. per m^2 at base of tree	2	begin and end of vegetation period	15
Strawberry (soil application)	Belgium, France, Italy, Netherlands, Spain	0.18 - 1 kg a.s./ha	1 kg a.s./ha	1 - 2	pre and post planting	15 - 60
Tobacco (soil application)	Greece, Italy	0.48 - 0.69 kg a.s./ha	0.48 - 0.69 kg a.s./ha	1	pre plant (in transplant water)	21
Watermelon (soil	Italy	0-05 - 0.1 g a.s. / m^2	0.2 g a.s. / m^2	2	at sowing or pre planting	3

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
application)						

Table 1.5.3-4 : Intended uses of metalaxyl-M in the EU - Seed treatment application

Crop	Country	No. of appl., type	Rate (kg a.s./100 kg seed)	PHI days
Beans	EU	1, seed	8.75 g - 35 g/100 kg seed	-
Beets	EU	1, seed	8.75 g - 17.5 g/100 kg seed	-
Brussel sprout	EU	1, seed	8.75 g - 70 g/100 kg seed	-
Cabbage	EU	1, seed	17.5 g - 70 g/100 kg seed	-
Carrot	EU	1, seed treatment	17.5 g - 35 g/100 kg seed	-
Cauliflower	EU	1, seed	8.75g - 70 g/100 kg seed	-
Cotton	EU	1, seed treatment	8.75 g -17.5 g/100 kg seed	-
Eggplant	EU	1, seed	8.75 g -17.5 g/100 kg seed	-
Lettuce	EU	1, seed	17.5 g - 35 g/100 kg seed	-
Maize	EU	1, seed treatment	1g - 52.5 g/100 kg seed	-
Melon	EU	1, seed treatment	8.75 g -35 g/100 kg seed	-
Onion	EU	1, seed treatment	17.5 g -35 g/100 kg seed	-
Pea	EU	1, seed treatment	8.75 g -35 g/100 kg seed	-
Peppers	EU	1, seed treatment	17.5 g - 35 g/100 kg seed	-
Radish	EU	1, seed treatment	17.5 g - 35 g/100 kg seed	-
Rape	EU	1, seed treatment	8.75 g - 70 g/100 kg seed	-
Sorghum	EU	1, seed treatment	8.75 g -52.5 g/100 kg seed	-
Spinach	EU	1, seed treatment	17.5 g - 70 g/100 kg seed	-
Sugarbeet	EU	1, seed treatment	17.5 g - 105 g/100 kg seed	-
Sunflower	EU	1, seed treatment	17.5 g - 105 g/100 kg seed	-
Tomato	EU	1, seed treatment	17.5 g - 35 g/100 kg seed	-

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

See Annex B, Appendix A - Authorizations and registrations

LEVEL 2

Metalaxyl-M

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

2.1.1 Identity

Metalaxyl-M is a mixture of the R-enantiomer CGA 329351 (min. 97%) and the S-enantiomer CGA 351920 (max. 3%) of the racemic compound metalaxyl, a fungicide which has been used in a large number of applications world-wide for many years.

The minimum purity of the a.s. as manufactured, as stated by the notifier, is 940 g/kg; i.e. the technical a.s. contains min.940 g/kg of the sum of CGA 329351 and CGA 351920 and min. 910 g/kg of CGA 329351. These purity values, as well as the proposed impurity profile, were confirmed by an acceptable analytical profile of batches.
As the impurity 2,6-dimethylaniline is considered to be of toxicological significance, its maximum content (0.5 g/kg) should be included in the proposed technical specification for metalaxyl-M.

2.1.2 Physical and chemical properties

Active substance :

The physico-chemical properties of the active substance can be summarized as follows :

Appearance :	**purified a.s. : clear, pale yellow, viscous liquid with weak odour** **a.s. as manufactured (TC) : clear, light brown, viscous liquid with weak odour**
Freezing point :	**- 38.7°C (glass transition temperature)**
Boiling point :	**not determinable due to thermal decomposition**
Temperature of decomposition :	**approx. 270°C**
Relative density (20°C) :	**1.125**
Vapour pressure (25°C) :	**$3.3\ 10^{-3}$ Pa**
Henry's law constant (25°C) :	**$3.5\ 10^{-5}$ Pa.m^3/mol**
UV/VIS absorption (λ_{max}) :	**266 nm (512 l.mol^{-1}.cm^{-1}) and 274 nm (477 l.mol^{-1}.cm^{-1})** **no absorption between 290 and 750 nm**
Solubility in water (25°C) :	**26 g/l**
Solubility in organic solvents (TC) (25°C) :	**n-hexane : 59 g/l** **toluene : completely miscible** **dichloromethane : completely miscible** **methanol : completely miscible** **n-octanol : completely miscible** **acetone : completely miscible** **ethyl acetate : completely miscible**
Partition coefficient (log P_{ow}) (25°C) :	**1.71**
Hydrolysis (20°C) :	**hydrolytical stability up to pH 7** **pH 9 : DT_{50} = 216 d**
Direct phototransformation (25°C) :	**not significant**

Quantum yield :	**not determined (ε < 1 l.mol^{-1}.cm^{-1} at 290 nm)**
Dissociation constant :	**no pKa in an accesible pH-range**
Stability in air :	**estimated DT_{50} in the atmosphere = between 4 and 6 h**
Flammability/auto-flammability (TC) :	**auto-ignition temperature : 410°C**
Flash point (TC) :	**179°C (1013 mbar)**
Explosive properties (TC) :	**not explosive**
Oxidizing properties (TC) :	**not corrosive**
Surface tension (TC) (20°C) :	**σ = 57.6 - 57.8 mN/m (1 g/l)**

Metalaxyl-M is readily soluble in water and in a range of organic solvents. Its octanol/water partition coefficient indicates no significant potential for bioaccumulation.
Metalaxyl-M is slightly volatile and very slightly volatile from water, meaning that exposure of users through volatilization is not expected to present a significant problem but nevertheless needs to be taken into consideration, as well as off-target movement by transport in air.

Metalaxyl-M is hydrolytically stable up to pH 7 and only slightly hydrolyzing under basic conditions, indicating that hydrolysis should not play a significant role in the environmental dissipation of the molecule. Direct photodegradation is not significant either.

The a.s. exhibits no explosive or corrosive properties and its flash point and auto-ignition temperature present no safety hazard.

Formulations :

Two formulation types were selected by the notifier as the representative formulated products :
- an emulsifiable concentrate (EC) containing 480 g/l metalaxyl-M (RIDOMIL GOLD 480 EC)
- a wettable powder (WP) containing 4% metalaxyl-M and 64% mancozeb (RIDOMIL GOLD MZ 68 WP)
Summary tables of the physico-chemical properties of RIDOMIL GOLD 480 EC and RIDOMIL GOLD MZ 68 WP are given in Annex B, point 2.2.

In the case of RIDOMIL GOLD 480 EC, all data requirements have been met, with the exception of <u>oxidizing properties</u> for which a study report was promised by July 1998. The formulated product was found to be not explosive and its flash point and auto-ignition temperature are not critical.

In the case of RIDOMIL GOLD MZ 68 WP, all data requirements have been met. The formulated product was found to be not explosive, not oxidizing and not highly flammable, but it should be classified as a self-heating substance.

The technical properties of both formulations indicate that no particular problems are to be expected when they are used as recommended and their stability allows storage under practical conditions.

2.1.3 Details of uses and further information

Uses of the formulations containing metalaxyl-M :

Metalaxyl-M inhibits mycelial growth and spore formation by selectively interfering with the synthesis of ribosomal RNA. Metalaxyl-M itself is the active ingredient : no fungicidally active metabolites of the parent compound have

been found.
The intended uses of metalaxyl-M formulations are restricted to foliar spray applications to control airborne diseases (mainly on grapes, potatoes and tomatoes; also in vegetable crops), stem paint applications against crown rots and trunk cankers (fruit trees) and soil treatment against soilborne diseases (in orchards, on a wide variety of field crops and also in confined areas). Foliar spray formulations contain metalaxyl-M in association with another a.s.
The notifier submitted no data to support the use of metalaxyl-M for seed treatment (against seedborne or systemic airborne diseases) and as post-harvest dip or drench (to control fruit diseases).

The uses supported by available data are the foliar spray uses on the following crops : grapes, potatoes and vegetables (mainly tomatoes, bulb vegetables, cucumber, melon, broccoli, lettuce, spinach, globe artichoke). The risk evaluation (operator exposure, consumer exposure, impact on the environment and on the non-target species) will be based on these 3 crop types. The application rates for other crops (foliar spray as well as soil treatment) are in the same range and can be covered , at least partially, by these 3 crop scenarios.

	foliar use (grape)	foliar use (potatoes)	foliar use (tomatoes)	foliar use (vegetables)	soil uses (high use on a localized area)
Toxicology - operator/ worker/bystander exposure	**X**	**X**	**X**	**covered by potato and tomato scenarios**	
Residue - consumer exposure	**X**	**X**	**X**	**X**	
Fate and behaviour in the environment - soil	**X**	**X**	**covered by potato scenario**	**covered by potato scenario**	**X**
- surface water	**X**	**X**	**covered by potato scenario**	**covered by potato scenario**	**X**
- groundwater	**X**	**X**	**covered by potato and grape scenarios**	**covered by potato and grape scenarios**	**covered by potato and grape scenarios**
Ecotoxicology	**X**	**X**	**covered by potato scenario**	**covered by potato scenario**	**X**

Packaging :

The available packaging material was described and stated to have been approved according to ADR-methods 3552 to 3555. Reports describing the results of aforementioned tests were not submitted.

Resistance of the packaging material to its contents was demonstrated.

Procedures for cleaning application equipment and protective clothing :

The spray equipment is cleaned immediately after use by draining the system completely and rinsing spray tank, boom and nozzles 2 to 3 times with clean water. The effectiveness of the cleaning procedure was demonstrated.

No specific recommendations were given regarding the cleaning of protective clothing.

Re-entry intervals, waiting periods and other precautions to protect man, livestock and the environment

PHI : pre-harvest intervals as proposed for the intended uses are included in Tables 1.5.3-2 and 1.5.3-3 of this document.

Re-entry periods :

Re-entry period (in days) for livestock to areas to be grazed :	**A waiting period of one week is considered to be adequate**	
Re-entry period (in hours or days) for man to crops, buildings or spaces treated :	**Soil treatment :**	**not necessary to define a particular re-entry period for workers**
	Foliar spray :	treated areas should not be entered before the spray deposit on leaf surfaces has dried, unless protective clothing is worn. Further definition of a re-entry period for workers is not necessary
Withholding period (in days) for animal feedingstuffs :	***More information is required***	
Waiting period (in days) between application and handling treated products :	***More information is required***	
Waiting period (in days) between last application and sowing or planting succeeding crops :	***More information is required***	

Recommended methods, precautions and handling procedures to minimize the risks relating to warehouse storage, user level storage, transport, fire :

- Handling : Avoid contact with skin, eyes and clothing. Avoid inhalation of dust, resp. fog and vapours. Do not eat, drink or smoke while working. In addition to dustproof, resp. splashproof filling and measuring equipment, further personal protection measures are recommended to avoid possible contact with the product.
Personal protective equipment : gloves (hand protection), goggles or face shield (eye protection), heavy duty cotton or synthetic fabric working clothes, e.g. overalls (body protection). In case of heavy exposure, wear dust mask or face shield, resp. gas mask (breathing protection). Change working clothes daily.

- Storage : Store the product in closed original containers, protected from light and humidity and from temperatures below -10 °C and above 35 °C.
Store separately from feed, food and stimulants. Do not store together with highly flammable products.

- Transport : **Use unbreakable containers, make sure they cannot fall. Label in accordance with regulations.**
For details : see Material Safety Data Sheets (Appendix B in Annex B)

- Fire-fighting measures :

Extinguishing media : Powder, foam, carbon dioxide or waterspray (do not use direct jet of water)

Combustion gases : In the event of fire, the formation of hydrogen cyanide, sulfur oxides, sulfuric acid, carbon monoxide and nitrogen oxides must be anticipated.
Combustion products are toxic and irritant.

Special hazards : Measures have to be taken to prevent the contaminated extinguishing agent from seeping into the ground or from spreading uncontrollably.

Protective equipment : Use respirator to protect from fumes.

Procedures for use in the event of an accident during transport, storage or use :

- Environmental precautions : Keep away from sources of ignition. Do not contaminate waters and sewers. Dampen solid material carefully to prevent it being blown away. Cover up liquid product with absorptive material such as sand, soil, diatomaceous earth etc. Prevent material from spreading, e.g. by damming in with absorptive material. Collect material in specially marked, tightly closing containers.
Place damaged containers is specially marked larger ones.
Clean dirty areas with carbonated or soapy water. Put washing water in containers too, to avoid any contamination of surface and ground water, water supplies and drains. Hose down the area for a prolonged period. Heavily contaminated soil layers have to be dug out down to clean soil.
Spilled product cannot be used further and must be disposed of. If safe disposal is not possible, contact the manufacturer, the dealer or the local representative and dispose of in an incinerator approved for chemicals.

- Personal precautions : first-aid measures : see also points B.5.9.4 and B.5.9.5

General : Remove the affected person from the danger zone to a well-ventilated room or to fresh air, and protect from undercooling.
In case of suspected poisoning : immediately call a physician.

Ingestion : Repeatedly administer medicinal charcoal in a large quantity of water.
Note : Never give anything by mouth to an unconscious person. Do not induce vomiting.

Skin contact : Remove contaminated clothing and thoroughly wash the affected parts of the body with soap and water, inclusive hair and under finger nails.

Eye contact : Rinse eyes with clean water for several minutes and immediately call a physician.

Procedures for destruction or decontamination of the formulations and their packaging :

Neutralization procedures for use in the event of accidental spillages are not considered to be suitable. Empty (rinsed) packages should be disposed of according to government recommended practices. Metalaxyl-M formulations can be disposed of safely by controlled incineration in a licensed incinerator; no other methods are proposed. Information on pyrolytic behaviour is not required as the active substance contains no halogens.

2.1.4 Classification and labelling

Classification and labelling of metalaxyl-M made by the Rapporteur

Classification	Xn, R22 Xi, R41, R52/53	
Labelling:		
Hazard symbol:	Xn, R22-41 , R52/53	
Indication of danger:	harmful	
Risk phrases:	R22	harmful
	R41	risk of serious damage to eyes
	R52/53	harmful to aquatic organisms, may cause long-term adverse effect in the aquatic environment
Safety phrases	S2	keep out of reach of the children
	S26	in case of contact with eyes, rinse immediatly with plenty of water and seek medical advice
	S39	wear eye/face protection

Justification for the proposal made by the Rapporteur concerning the classification and labelling of metalaxyl-M.

Proposed classification	**Justification**
Xn, R22	LD_{50} oral, rat : 669 mg/kg bw
Xi, R41	severe irritant to rabbit eyes
R52	Eb_{50} (*Scenedesmus subspicatus*) = 36 mg a.s./l
R53	the biodegradation of the a.s. is 0% in 29 days

2.2 Methods of analysis

2.2.1 Analytical methods for analysis of the active substance as manufactured

The methods submitted allow to determine the purity (sum of 2 enantiomers, as well as separate enantiomers) and the impurities of the technical a.s.

2.2.2 Analytical methods for formulation analysis

The methods submitted allow to determine the a.s. content (sum of 2 enantiomers) of formulations (EC and WP). Methods that allow to determine the enantiomer ratio in formulations were not submitted, but they are required to enable the a.s. in the formulation to be distinguished from metalaxyl.

Validated analytical methods for the determination of 2,6-dimethylaniline in formulations also remain to be provided, as this impurity is considered to be of toxicological significance.

2.2.3 Analytical methods for residue analysis

The submitted analytical methods were developed for determination of residues of the racemate metalaxyl, detecting metalaxyl as a single response signal (not enantiomer-selective). Since metalaxyl-M exhibits the same analytical properties as metalaxyl under these conditions, the developed methods are also suitable for the determination of metalaxyl-M residues.
Consequently the submitted methods do not permit to distinguish between both compounds, which implies that residues resulting from the use of metalaxyl formulations cannot be distinguished from those resulting from the use of metalaxyl-M preparations.

Feed and food of plant origin :

The GC-methods submitted for the analysis of *parent compound* in food matrices of plant origin allow to determine parent metalaxyl/metalaxyl-M. Methods REM 181.01, REM 181.02 and REM 181.03, fully validated for use in tomatoes, grapes, potatoes, wine and must (LOQ 0.02 mg/kg) and tobacco (LOQ 0.1 mg/kg for green leaves and 0.2 mg/kg for dried leaves), can be recommended for enforcement.
This is not the case for the GC- and HPLC (2-column switch)-methods submitted for the determination of *total residues*, i.e. parent compound and metabolites containing the 2,6-dimethylaniline (DMA) moiety. As these methods are based on hydrolysis of the residues and subsequent determination of the DMA formed, they are not specific for metalaxyl/metalaxyl-M and their metabolites but will also detect other compounds containing the DMA-moiety.

Feed and food of animal origin :

The GC- methods submitted **for the determination of *total residues* in food matrices of animal origin** are also common-moiety methods determining DMA and the aforementioned comment with respect to specificity is equally valid for these methods.

Soil, water, air :

GC-methods REM 16/76 and REM 7/77 submitted for *soil analysis* both allow the determination of parent metalaxyl/metalaxyl-M, while REM 7/77 also determines acid metabolite CGA 62826. Both methods can be recommended for enforcement, provided that the proposed LOQ of 0.05 mg/kg is confirmed by additional validation data and precision data are submitted for the acid metabolite.

HPLC-methods REM 2/86 and REM 12/87 submitted for *water analysis* allow to determine parent metalaxyl/metalaxyl-M and major soil metabolite metalaxyl acid, resp. as single compounds or as the sum of both. Both methods can be recommended for enforcement where drinking water is concerned (LOQ 0.1 µg/l), but data demonstrating the applicability of the methods to surface water remain to be provided.

GC-method REM 143.02 submitted for the determination of residues in *air* allows the determination of parent metalaxyl/metalaxyl-M and can be recommended for monitoring, provided that the proposed LOQ of 10 µg/m^3 is confirmed by additional validation data.

Body fluids and tissues :

The GC- method submitted for the determination of residues in *urine*, being based on hydrolysis and subsequent determination of the 2,6-dimethylaniline (DMA) formed, is not specific for metalaxyl/metalaxyl-M and their metabolites forming DMA upon hydrolysis, but it also detects other compounds containing the DMA-moiety.
However, as metalaxyl-M is not classified as toxic or highly toxic, analytical methods for residue analysis in body fluids and tissues are not required.

2.3 Impact on human and animal health

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

Metabolism :
- After oral low dose administration, during the first 24 h after metalaxyl, 71% (males) and 65.8% (females) of the radioactivity was excreted via bile and 31.3 % (male) and 49 % (female) were excreted via urine ; after metalaxyl-M, 40.5% (male) and 49% (female) was excreted in urine.
Urinary excretion after metalaxyl or metalaxyl-M is quite similar suggesting that the apparent extent of absorption is important, in the same range of magnitude and rapid for both compounds.
- After high oral dose of metalaxyl, 69.4% (male) and 54.5% (female) were excreted via bile and 45.6% (male) and 53.5% (female) in urine, while 30.6% (male) and 35.6% (female) were excreted in urine after metalaxyl-M.
If it is assumed that the amount of excreted radioactivity via bile and urine represents the bioavailable amount of metalaxyl, then a *resorption rate* of 100 % can be calculated for the low and for the high dose male and female.
Similar kinetic parameters were observed for metalaxyl-M and metalaxyl confirming that absorption, which is most frequently a passive process , does not differentiate between isomers.

Both compounds translocate easily to almost all tissues except brain, and especially high concentrations in liver, kidney, thyroid, fat and adrenal were observed. The concentrations in organs were somewhat higher in tissues of female rats, decreased as time elapsed, and were relatively low in all tissues 72 h after administration.
Metalaxyl-M and metalaxyl do not accumulate.

From the *metabolism* study, it appears that metalaxyl and metalaxyl-M are metabolized at different rates but along the same routes.
The metabolic pathways were subdivided into three major pathways : demethylation of the ether, oxidation of the aromatic methyl, demethylation of the ester and the minor pathway, hydroxylation at the meta position on the phenyl ring.
All metabolites isolated undergo Phase II conjugation reactions and are present as glucuronide and sulfate conjugates.
For both compounds, faecal and urinary *excretions* were rapid reaching 73-80% within 24 h. For both compounds, urinary excretion was more important in females. Increasing the dose of metalaxyl-M lowered the urinary excretion for both sexes with a simultaneous increased faecal excretion. The quantitative difference in excretion route may result from differences in biliary excretion.
The metabolites found in rats, goats and hens indicate that the major metabolic pathway in these species are qualitatively equivalent. Quantitative differences between species are explained by faster metabolic rate of the hen and its greater tendency for oxidative transformations of metalaxyl.
In plants, the detected metabolites suggest phase I oxidation followed by phase II conjugation with sugars.
Metalaxyl-M and metalaxyl are bioequivalent.

Acute toxicity :
Metalaxyl-M has been studied for systemic toxicity in the rat at doses from 200 to 2000 mg/kg bw orally, 2000 mg/kg bw dermally, and 2.29 mg/m^3 by inhalation. It was estimated that the exposure by inhalation to 2.29 mg/m3 during 4 h is equivalent to a systemic dose of 192 mg/kg bw. At this inhalation dose, similar signs are observed as after oral administration of 200 mg/kg bw, but of lesser intensity. From the effects observed it can be concluded that metalaxyl-M is toxic for the nervous system, producing central, neuromuscular and autonomic signs, and respiratory insufficiency. It has to be classified as harmful by ingestion.

Metalaxyl-M is not a skin irritant or sensitizer, but has to be classified as an eye irritant.

As far as systemic toxicity is concerned, data from Ciba Geigy indicate that the racemic substance, metalaxyl, produced a qualitatively and quantitatively similar effects.

Summary of acute toxicity of metalaxyl-M

Type of test; test species	Test substance purity	Results	Classification	References
Rat, acute oral	**97.9%**	**_ : 953 mg/kg bw _ : 375 mg/kg bw**	**Xn, R22**	**Schoch, 1994a**
Rat, dermal, semi-occluded	**97.3%**	**_ :>2000 mg/kg _ : > 2000 mg/kg**	**-**	**Schoch, 1994b**
Rat, nose only inhalation, 4 hours (aerosol)	**97.1%**	**_ _:> 2.29 g/m^3 (> 192 mg/kg bw)**	**-**	**Arts, 1995**
Rabbit, skin irritation	**97.3%**	**3 _: not irritant**	**-**	**Marty, 1994a**
Rabbit, eye irritation	**97.3%**	**irritant**	**R41**	**Marty, 1994b**
Guinea pig, M&K test	**97.3%**	**not sensitizer**	**-**	**Marty, 1994c**
Guinea pig, Buehler test	**96.6 %**	**not sensitizer**	**-**	**Glaza, 1995**

***Genotoxicity*:**
Genotoxicity testing of the enantiomer metalaxyl-M were confined to point mutation and chromosome aberration tests. No increased number of back mutations were found in any strain or at any concentration of metalaxyl-M in the Ames test. In Chinese hamster ovary cells, none of the experiments revealed biologically significant increased incidences of specific chromosomal aberrations. A weak cell cycle arresting activity was detected.
Metalaxyl-M is devoid of mutagenic and clastogenic potential *in vitro*, under the conditions of the tests .

The racemate metalaxyl was tested for its mutagenic potential in a variety of different tests covering both , eukaryotes and prokaryotes *in vivo* and *in vitro*.
Although not all of the studies were conducted according to current standards, the aspect of mutagenicity is considered to be adequatly investigated.
No induction of point mutations were observed in bacterial cells and in mouse lymphoma cells. No evidence of mitotic crossing-over, gene conversion or reverse mutation or chromosome loss were observed.
In Chinese hamster ovary cells, in the absence of metabolic activation, metalaxyl increased the frequency of chromosomal aberrations. However, in this study, the purity of the compound was not specified. These effect was confirmed in the open literature using human peripheral lymphocytes. This effect was not reported for metalaxyl-M.
Metalaxyl did not induce clastogenic or aneugenic effects *in vivo*. Interference with DNA primary structure was negative in cells with high (rat hepatocytes) and with low (human fibroblasts) metabolic activity.

Finally, a dominant lethal study did not reveal adverse effects on implantations or embryonic deaths .

In conclusion, metalaxyl-M is devoid of genotoxic effects *in vivo*.

Summary of genotoxicity of metalaxyl-M/metalaxyl

Type of test Cell/Test species	Test substance; purity	Conditions	Results	References
In vitro gene mutation test				
Salmonella/ mammalian microsome test	metalaxyl-M: 97.3%; b.n°.KGL 4634/6	TA98, 100, 102, 1535, 1537 and WP2uvrA +/- S9 mix, DMSO; 312.5, 625, 1250, 2500, 5000 µg/plate	negative	Hertner, 1994a
Salmonella/	metalaxyl : 95.7%;	TA98, 100, 102, 1535, +/- S9 mix,		Deparade and

Type of test Cell/Test species	Test substance; purity	Conditions	Results	References
mammalian microsome test	b.n°P503119	acetone; 20, 78, 313, 1250, 5000 µg/plate	negative	Arni, 1985
Mouse lymphoma cells L5178Y TK+/-	metalaxyl : 94.1%; b.n°EN32212	- S9 mix: 0.0625, 0.125, 0.25, 0.5 mg/ml +S9 mix:0.125, 0.25, 0.5, 1mg/ml ; DMSO	negative	Strasser and Muller, 1982
In vitro chromosome assays				
- Chromosome aberrations - Cell cycle effect	**metalaxyl-M** 97.3% ; b.n°. KGL 4634/6	Chinese hamster ovary cells DMSO ; - S9 mix: 18 h treatment: 126.88, 253.75, 507.5, 1015 µ g/ml 42 h treatment: 253.75, 507.5, 1015 µg/ml + S9 mix: 3 hr (15 or 39 h recovery) : 253.75, 507.5, 1015, 2030 µg/ml	-negative -weak arresting activity	Hertner, 1994b
In vitro DNA repair assays				
- UDS	metalaxyl, 94.1%; b.n°.EN32212	human fibroblasts CRL 1121 ; 4, 20, 100, 500 µg/ml in DMSO ; - S9 mix	negative	Puri and Muller, 1982
	metalaxyl, 95.7%; b.n°.P.503119	rat hepatocytes; 16, 80, 400, 2000 µg/ml in DMSO	negative	Puri and Muller, 1985
In vitro assays for other effects				
Mitotic crossing-over, gene conversion, reverse mutation	metalaxyl , 94.1%; b.n°. EN32212	*Saccharomyces cerevisiae* D7; DMSO; +/- S9 mix	negative	Arni and Muller, 1982
In vivo genotoxicity test				
Micronucleus assay	metalaxyl, 96.1%; b.N.°603107	mouse, 312.5, 156.3, or 78.1 mg/kg bw, by gavage in oleum arachis	negative	Hertner and Arni, 1992
Nucleus anomalies in bone marrow cells	metalaxyl; 98%; b.n°.P2/2.76	mouse bone marrow; 595, 1190, 2380 mg/kg bw/d in aqueous CMC for 2 days	negative	Langauer and Muller, 1979
Dominant lethal assay	metalaxyl; 99.4%; b.n°P3	**mouse, oral dose, 65, 195 mg/kg bw in in aqueous CMC**	**negative**	**Fritz, 1978a**

***Short-term toxicity* :**

Metalaxyl-M was administered orally in rats in doses from 2 to 300 mg/kg bw/d, and in dogs in doses from 1.5 to 80 mg/kg bw/day. Minimal effects were noted on body weight gain and food consumption.
Effects that were considered to be treatment related include reversible liver weight increases , accompanied by centrilobular hepatocellular hypertrophy in the rat and the increases in plasma AP and ALT in dogs . The target organ is the liver, showing minimal changes, probably adaptative, due to an increased metabolic activity after short-term exposure, leading to small necrotic effects after long-term exposure.
Metalaxyl increased the level of cytochrome P450 , and PNOD (CYP IIB1 marker) and UDP glucuronyl transferase activities after 7 days treatment with 80 mg/kg bw/day.
Quantitatively and qualitatively similar changes were observed with the racemic compound metalaxyl.
At the higher doses studied, metalaxyl did also produce in the rat extramedullary hematopoiesis and in the dog anemia, increased albumin and renal weight.
Dermal administration of metalaxyl to rabbits or metalaxyl-M to rats did not result in local or systemic effects even at limit dose level of 1000 mg/kg bw/d. Comparison of the results with oral data also point to a quite low dermal absorption of 10% or less.
A NOAEL of 7.5 mg/kg bw/d can be derived from these repeated dose, subchronic experiments.
The bridging study suggests that metalaxyl-M does not exhibit any greater toxicity than metalaxyl and hence studies on metalaxyl may be assessed in place of metalaxyl-M.

Summary of short term-toxicity of metalaxyl-M/metalaxyl

Type of test Test species	Compound and test substance purity	Results			References
		NOAEL (mg/kg bw /day)	LOAEL (mg/kg bw/day)	Critical endpoints	
Rat, oral, 28 day	metalaxyl-M; 97.3%; B.n°.KGL-4634/6	50	150	hypoactivity	Gerspach, 1994
	metalaxyl; 96.1%; b.n°.EN 603107	50	150	⇗spleen weight and extramedullary hematopoiesis	
Rat, oral, 90 day	metalaxyl-M; 97.1%; B.n°OP.4	16.8	45	hepatic hypertrophy	Gerspach, 1995
Rat, oral, 90 day	metalaxyl; 99%; b.n°P3	17	82.5	liver cell hypertrophy; ovarian cysts	Drake, 1977
Dog, oral, 90 day	metalaxyl-M; 97.1%; b.n°.OP-4	7.25	38.6	⇗AP; ⇗liver weight	Altmann, 1995
Dog, oral, 6 mth.	metalaxyl; 92%; b.n°.FL-800050	7.25	29	⇗liver weight; ⇗AP	Beck and De Ward, 1981
Dog, oral, 1 and 2 year	metalaxyl; 92.7%; b.n°.EN31653	8	80	⇗AP and ALT; ⇗liver , kidney weight; anemia	Harada, 1984
Rat, dermal, 21 day	metalaxyl-M : 97.1%; batch n°OP.4	1000	-	-	Gerspach, 1998
Rabbit, dermal , 21 day	**metalaxyl; 92% ; B.n°. ?**	**1000**	-	-	**Calkins, 1980**

Long-term toxicity studies :

Metalaxyl-M was not tested in long-term, repeated dose experiments.
Because of the similarity between the D-enantiomer metalaxyl-M and the racemic metalaxyl in acute, sub-chronic and genotoxicity tests, the test results with metalaxyl are accepted for the evaluation of the potential long-term toxicity of metalaxyl-M.

Metalaxyl was administered in doses from 2 to 55 mg/kg bw/day to rats and from 5 to 150 mg/kg bw/day to mice. It produced very mild liver toxicity. No treatment related increase in the incidence of tumours was observed.

A NOAEL of 2 mg/kg bw/day can be derived from these repeated dose, chronic experiments.

Summary of long-term toxicity and carcinogenicity of metalaxyl

Type of test Test species	Test substance purity	Results			References
		NOAEL (mg/kg bw/ day)	LOAEL (mg/kg bw/day)	Critical endpoints	
Rat, 104 week	metalaxyl: 93%, b.n°. P14: week 1-70 ; 94.6%, b.n°.EN32212: week71-105	2	9.43	↗ liver weight; periacinar fatty vacuolation	Ashby and Witney, 1980
Mice, 104 week	Metalaxyl: week 1 to 75 : b.n°. P14: 93%; week 76 to 105 : EN32212 , 94.1 %	25	129	↘ bodyweight gain (week 11-30)	McSheely et al., 1980

Neurotoxicity:

Except for some unspecific symptoms observed in the acute toxicity studies at dose levels at or above the LD_{50}, the acute, short- and long-term studies outlined above revealed neither clinical signs nor any biochemical or histopathological changes, which might point to a neurotoxic potential of metalaxyl or its enantiomer metalaxyl-M. Additional studies on neurotoxicity are therefore, not necessary.

Reproductive toxicity:

In a bridging developmental study in rats, metalaxyl-M induced maternal toxicity at 50 mg/kg bw/d. There was no evidence for embryotoxic or teratogenic potential in rats, up to doses of 250 mg/kg bw/d.

Metalaxyl, at doses as high as 58 mg/kg bw/d, induced hepatomegaly but did not affect reproductive performances. Offspring development remained unaffected in a three generation study in rats.
Metalaxyl in rats, depressed bodyweight gain in dams at 60 mg/kg bw/d and onwards.
In rabbits, adverse effects on maternal weight and food consumption were observed at 300 mg/kg bw/d.
The developmental studies with metalaxyl gave no indication of a teratogenic or embryotoxic potential even when the compound was administered at dose close to maternal lethality.

In the bridging study with metalaxyl-M, there was no evidence of foetotoxicity or teratogenicity confirming the reproductive toxicity profile of metalaxyl-M to be similar to that of metalaxyl.

Summary of reproductive toxicity and teratogenicity of metalaxyl-M / metalaxyl

Type of test Test species	Test substance purity	Results			References
		NOAEL (mg/kg b w/ day)	LOAEL (mg/kg b w /day)	Critical endpoints	
rat, 3 generation study	Metalaxyl : b.n°. P7/WSH, 93.5%	reprotox: > 58 syst.tox = 13	- 58	- hepatomegaly in adult F2B generation females	Cozens et al., 1980
rat, developmental	Metalaxyl-M: b.n°.OP.4; 97.1%	mat. tox = 10 develop > 250	-50 -	↘ bw gain and food consumption -	Khalil, 1994
rat, developmental	Metalaxyl b.n°.FL840049 97.2%	mat. tox= 50 develop >400	250 -	clinical signs, ↘ bw -	Leng and Schardein, 1985
rat, developmental	Metalaxyl : b.n°.P3 ; 99.4%	mat. tox= 20 develop > 120	-60 -	-↘ bodyweight gain -	Fritz, 1978b
Rabbit, developmental	Metalaxyl technical, unknown purity b.n°.FL 840049	mat. tox = 150 develop. > 300	300 -	↘ bodyweight change and food consumption -	Laughlin and Schardein, 1984

Toxicity studies on metabolites CGA 108906, CGA 62826 and CGA 107905:

The transformation of metalaxyl-M in soil starts with the cleavage of the ester bond to form the main soil metabolite CGA 62826. The first metabolite is further degraded to several minor metabolite fractions, i.e. CGA 108906, CGA 107955. Under anaerobic conditions, degradation of the parent compound stops at the stage of CGA 62826.
Several studies were performed in order to evaluate the mobility of the a.s./metabolites and the possible contamination of groundwater at level > 0.1 µg/l
- The columns leaching studies indicated the high mobility of both metalaxyl-M and metalaxyl. The mobility of the metabolite CGA 62826 was even higher.
- 2 lysimeter studies were performed with metalaxyl. Metalaxyl was recovered in the combined leachate of one year at concentrations of < 0.01 to 0.05 µg/l. The metabolite CGA 62826 was recovered at the concentration of 0.25-4.12 µg/l. The metabolite CGA 108906 was recovered at the concentration of 0.16-1.11 µg/l.
Therefore, the toxicological relevance of the major metabolites found in groundwater (CGA 62826 and CGA 108906) needed to be evaluated.

The toxicity of CGA 62826 or metalaxyl acid (detected in lysimeter leachate and soil, primary metabolite of metalaxyl detedcted in rat urine), CGA 108906 (detected in lysimeter leachate and potato ; not identified in rats) and CGA 107955 (major urinary and faecal metabolite of metalaxyl in rats) was more throroughly investigated.

Toxicity profiles for CGA 62826 and CGA 108906 have been established by determination of acute oral and dermal toxicity in the rat, subchronic (28 days) oral toxicity in the rat and the mutagenic potential in bacteria.
The two metabolites are clearly less toxic after single oral application than metalaxyl or metalaxyl-M. No significant systemic toxicity was noted with the metabolites.
After dermal application, metabolites CGA 62826 or CGA 108906 caused no systemic toxicity at the test limit dose of 2000 mg/kg bw. Repeated oral administration for 28 days essentially confirmed the lower toxicity of these metabolites observed after single administration. Both metabolites caused only minimal effects which were all fully reversible. They were all considered non-adverse. The NOAEL was fixed at 1000 mg/kg bw For CGA62826 and at 200mg/kg bw/d for CGA108906. No mutagenic effect was found in bacteria up to the test limit concentration of 5000 µg/ml.

Summary of acute toxicity studies of metabolites of metalaxyl-M

Type of test **Test species**	**Test substance** **purity**	**Results**	**References**
Rat, acute, oral	metalaxyl-M 97.9%	LD_{50} _ : 953 mg/kg bw LD_{50} _ : 375 mg/kg bw	Schoch, 1994a
Rat, acute, oral	metalaxyl	LD_{50} : 633 mg/kg bw	
Rat, acute, oral	**CGA 108906** B.n°. 5817.1 ; 99%±2%	LD_{50} combined >2000 mg/kg bw.	Hartmann, 1994
Rat, acute, oral	**CGA 62826**; 100%; b.n° RV-1592/4	LD_{50} >2000 mg/kg bw	Winkler, 1996a
Rat, acute, oral	**CGA 62826** batch and purity not specified	LD_{50} combined >1000 mg/kg bw.	Loosli, 1979
Rat, acute, oral	**CGA107'955** B.n°. RV-1553/4 ; 95 %	LD_{50} combined > 3000 mg/kg bw	Sarasin et al., 1986

Summary of short-term and genotoxicity studies of metabolites of metalaxyl-M

Type of test Test species	Test substance	NOAEL mg/kg bw/d	LOAEL mg/kg bw/d	Critical endpoints	References
28 day, oral rat	metalaxyl-M	50	150	↗ adrenal w. ↗ blood urea	Gerspach, 1994
28 day, oral, rat	metalaxyl	50	150	↘ blood Ca^{2+} and Na^{+}, ↗ spleen w.	Gerspach, 1994
28 day, oral, rat	CGA62826	1000	-	-	Fankhauser, 1997
28 day, oral, rat	CGA108906	200	1000	↗ blood glucose and K^{+}; ↗ heart w.	Gerspach, 1997
Ames test	CGA 62826	negative			Deparade, 1997
Ames test	CGA 108906	negative			Ogorek, 1997

2.3.2 Establishment of an Acceptable Daily Intake (ADI)

An ADI can be calculated from a NOAEL of 2 mg/kg bw/d (lowest NOAEL), identified in the 2 year rat study. Applying an assessment factor of 100 (10 for interspecies variation x 10 for intraspecies variation), the acceptable daily intake becomes :

ADI = 0.02mg/kg bw/day.

The same ADI was proposed by the notifier.

2.3.3 Establishment of an Acute Reference Dose (ARfD)

- Not applicable

2.3.4 Establishment of an Acceptable Operator Exposure Level (AOEL)

The AOEL short-term for man is calculated on the basis of an internal NOAEL from a sub-chronic animal experiment, taking into account the apparent degree of absorption, and applying an assessment factor, chosen in function of the critical effect observed in the animal experiments.

It appears from the dog experiment that a subchronic exposure to 7.25 mg/kg bw/d (lowest NOAEL, taken from the 90 day and 6 months studies in dog) of metalaxyl-M will not result in any toxic effect. A much longer , 2 year study in dog, but with metalaxyl, gave 8 mg/kg bw/d just at the limit of toxicity. A dose of 7.5 mg/kg bw/d represents a mean between the 2 dog studies. The oral absorption seems to be 100%, which means that the absorbed NOAEL is also 7.5 mg/kg bw/d. Applying an assessment factor of 100 for extrapolation to man. The acceptable operator exposure level, expressed as an internal, systemic dose becomes:

AOEL systemic = 0.075 mg/kg bw/d

A short-term dermal test exists in the rat , which would allow the calculation of a dermal AOEL. In this study, a NOAEL of 1000 mg/kg bw/d was reported.

AOEL dermal = 10 mg/kg bw/d

2.3.5 Establishment of the (theoretical) drinking water limit.

On the basis that exposure through drinking water should not account for more than 10% of the ADI, assuming an average consumption of 2 l of water per day and an average body weight of 70 kg, a limit of 0.07 mg/l is proposed.

$$\mathbf{MAC = \frac{ADI \times bw \times P}{C} = \frac{0.02 \times 70 \times 0.1}{2} = 0.07\ mg/l}$$

MAC = maximum allowable concentration
This concentration of 70 ppb is quite above the European maximal concentration in drinking water for any pesticide, e.g.,0.1 ppb.

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

Health risk for humans:
There are no epidemiological studies available at this time and no major accidents or exposure of the general population to metalaxyl or metalaxyl-M have been reported to date. Symptoms of acute intoxication in rats were rather unspecific and transient. Metalaxyl-M is irritating to eyes.There was no evidence of bioaccumulation.
Metalaxyl can undergo enzymatic hydrolysis to 2,6-dimethylaniline metabolite, that is usually excreted in urine as an N-glucuronide. Hemoglobin adducts of 2,6-dimethylaniline were detected in rats and humans exposed to 2 ,6 dimethylaniline. Methaemoglobinemia has been reported following i.v .adminsitration of 2,6 dimethylaniline. Similar findings have not been reported with metalaxyl-M or metalaxyl.

Health risk for animals :
Metalaxyl-M is harmful by ingestion, and is also a severe eye irritant. Metalaxyl-M is not a skin irritant or sensitizer. Symptoms occurring after acute oral or inhalation exposure suggest that metalaxyl-M depresses the central nervous system and induces pulmonary-cardiac insufficiency. According to the open literature, the cardiopulmonary effect induced by metalaxyl appears to be due to activation of α_1-adrenoreceptors. The acetylcholinesterase activity in the brain and heart of rats was not modified.
Short-term, repeated dose, oral administration of metalaxyl-M/metalaxyl produces adaptative changes in the liver, characterized by an increase in liver weight and enzyme induction. These effects were reversible and not associated with histopathological data. Metalaxyl was not demonstrated to be carcinogenic in rats and mice. Metalaxyl-M/metalaxyl was not genotoxic.
Metalaxyl did not produce adverse effects on reproductive performance or pup viability. There were no indications of embryotoxic or teratogenic effects in either rats or rabbits.

Exposure resulting from the application of formulations containing metalaxyl-M :

Ridomil Gold MZ 68 WP is used as a foliar spray to control airborne disease; the exposure evaluation was performed on field crops (orchard, vineyard, tomatoes and potatoes) which cover the application rates for all other crops.

Ridomil Gold 480 EC is sprayed on the soil surface or the seedling bed using hand-held or mechanized equipment. It may also be used as a dip for seedlings or painted on stems.

For both formulations , exposure were calculated using as dermal penetration factor of 10% based on the *in vivo* dermal absorption study .

- Operator exposure :
An estimation of the operator exposure involved with the operation of foliar spray was performed according to the UK and German model. Foliar application of Ridomil Gold 68 WP lead to an exposure which can be considered as acceptable for all the crop scenarios when protective equipment is worn.

For operator exposure to Ridomil Gold 480 EC, exposure can be considered as ' acceptable ' for the 2 scenarios

(foliage, ornamentals , crops or trees) according to the german model. Exposure is higher than the AOEL with or without PPE according to the UK model. It must be taken into account that the models do not perfectly cover the application profile of Ridomil Gold 480 EC, and it is therefore justified to conclude that adherence to the recommended operator protection measures is sufficient to guarantee for a safe use.

- Bystander exposure:
Ridomil Gold 68 WP is applied by hand held or tractor mounted equipment. Also since the vapour pressure of the a.s. is low, an inhalative exposure of bystanders can be excluded.
Ridomil Gold 68 WP, dermal exposure during application represents 0.51, 0.38 or 0.24 mg/kg bw/day which is lower than the AOEL. Therefore, bystander exposure is acceptable for Ridomil Gold 68 WP.

Ridomil Gold 480 EC is applied by downward spraying of the soil, dipping of seedlings or direct painting on the stem of affected plants. Hardly any exposure of bystanders can therefore be anticipated from the normal use of the product.
Bystander exposure can be deduced from operator exposure, using the POEM model.

- Worker exposure:
Since Ridomil Gold MZ 68 WP is applied in crops which may require cultivation work shortly after application, the applicant proposes to calculate the worker exposure by using a model calculation taken from a currently German re-entry model approach.
Based on this approach , assuming that the foliar dislogeable residues are not decreasing, the systemic exposure to metalaxyl-M would be 0.476 mg/kg bw /day for the non-protected person and 0.024 mg/kg bw/day for the protected person. This correspond to 634% and 32% of the systemic AOEL. Therefore, exposure of workers is acceptable if protective equipment is worn.
Ridomil Gold 480 EC is applied onto or into the soil and the vapor pressure of its active ingredient is low. It is therefore not necessary to define a particular re-entry period for workers.

Human exposure resulting from ingestion of residues:
Residue data covering the intended uses for the major crops and in conformity with the proposed residue definition in plants were submitted. These data allow an estimation of the intake of residues by the consumer of treated crops to be carried out. TMDI and IEDI calculations were made using FAO guidelines and resulted in an acceptable exposure level for average consumers. Some underestimation can be expected since the contribution of animal products was not considered.

2.4 Residues

2.4.1 Definition of the residues relevant to MRLs

Plant products.
Metabolism studies have been submitted on various crops (grapevines, lettuce, potatoes and tobacco) and reflecting the main modes of application of metalaxyl. In all cases the parent compound was if not the major constituant of the residue, at least a valid indicator of the level of contamination of the commodity.

The residue definition for monitoring is proposed as the parent compound alone. This definition would allow the use of multiresidue methods in routine laboratories.

Livestock products
Metabolism studies have been submitted in lactating goats and laying hens.
The metabolism study in goat indicated an extensive degradation of the parent compound. The predominant component of the total residue was found to be the hydroxy acid CGA-107955 in all tissues except in milk for which the major metabolite was a fatty acid conjugate of CGA-67869.
All the identified metabolites were considered as out of any toxicological concern as they were also produced in the rat.
An extensive metabolization of the parent compound was also observed in laying hens.

The residue definition for monitoring is proposed as the total metalaxyl including all the metabolites forming

the 2,6-dimethylaniline moiety upon hydrolysis and expressed as metalaxyl equivalents.
A residue definition taking into account a series of relevant metabolites would increase the work of laboratories.

2.4.2 Residues relevant to consumer safety

The total dietary intake of metalaxyl-M which takes into account the major crops uses represents up to 0.29% of the ADI. Some underestimation can be expected since the contribution of animal products was not considered.

2.4.3 Residues relevant to worker safety

See point 2.3.6

2.4.4 Proposed EU MRLs and compliance with existing MRLs

Metalaxyl-M is a new compound. There is currently no specific Community MRL for metalaxyl-M.

However, there are Community MRLs for the racemate metalaxyl. The revision of these MRLs is ongoing in the framework of the Directive 94/30/EC. The evaluation of the residue data for metalaxyl and metalaxyl-M which were submitted by Novartis in support of its dossier 'Metalaxyl-M' were communicated to the Metalaxyl Rapporteur.

Several MRLs for metalaxyl-M, based specifically on the supervised trials which were performed with metalaxyl-M, were proposed here below. These MRLs cover the main uses of metalaxyl-M : foliar spray on grape, potato, tomato and other vegetables.

At this stage, no analytical method for residue in plant commodities allows to specifically distinguish between metalaxyl and its isomer metalaxyl-M.

Proposed MRLs for metalaxyl-M - commodities of plant origin

Expression of the residue	Products	MRL (mg/kg)	STMR (mg/kg)
Metalaxyl-M	Table and wine grapes	1	0.1
Metalaxyl-M	Onion	0.02*	0.02*
Metalaxyl-M	Tomato	0.1	0.02*
Metalaxyl-M	Cucumber	0.5	0.15
Metalaxyl-M	Melon	0.05	0.02*
Metalaxyl-M	Broccoli	0.02*	0.02*
Metalaxyl-M	Lettuce	0.05	0.02
Metalaxyl-M	Spinach	0.05	0.02*
Metalaxyl-M	Artichoke	0.02*	0.02*
Metalaxyl-M	Potato	0.02*	0.02*

At this stage, as the residue level in the potential feed of livestock could not be assessed, the MRLs for commodities of animal origin cannot be proposed. However, the expression of the residue could be

established as total metalaxyl (+ its metabolites with the 2,6-dimethylaniline moiety)

2.4.5 Proposed EU import tolerances and compliance with existing import tolerances

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2.5 Fate and behaviour in the environment

2.5.1 Definition of the residues relevant to the environment

Definition of the residue in soil
Relevant residue in soil is metalaxyl-M and CGA 62826.

Definition of the residue in water
Relevant residue in water is metalaxyl-M and CGA 62826.

2.5.2 Fate and behaviour in soil

Route of degradation
Under aerobic conditions, the main degradation proceeds via ester cleavage yielding the free acid metabolite CGA 62826. The metabolite was found in all the soil metabolism studies at high levels (maximum 22, 26.23, 40.36 % RR in Ellgehausen, 1996).

The degradation of CGA 62826 further proceeds with the formation of metabolite CGA 67868 and polar residues. The metabolite CGA 67868 was found in several studies at low levels (max 2.28-2.75, 3.72-6.15 % RR in Ellgehausen, 1996 and Schanné, 1991). It was also the main degradate recovered in the metabolism studies performed with CGA 62826 (Suter, 1982).

Several minor metabolites were also detected.
- Beside the a.s. and the major metabolites also found in the other soil studies, several minor metabolites were detected in the rotational crop study (CGA 108905, CGA 108906, CGA 107955, CGA 37734, CGA 79353, CGA 78532). The objective of the study (Mac Farland, 1992, described under point B.6) was to investigate the uptake and metabolism of metalaxyl in several rotational crops grown in the greenhouse following a target crop of tobacco. The tobacco was grown in soil treated with 3.36 kg a.s./ha preemergent application.
- The metabolite CGA 42447 was found at very low level (0.5% RR) in a soil metabolism study (Elgehaussen, 1978).
- Some polar compounds were found in different studies at very low amounts, and therefore not further characterized.

The final degradation occurred via mineralization and formation of bound residues. Mineralization reached 22-33% RR after 84 days. At that time 63-73% RR was recovered as unextractable (Ellgehausen, 1996)

A study evaluating the degradation of metalaxyl under anaerobic and sterile conditions was provided. This study, although of poor quality, showed that degradation is low under anaerobic conditions. Under sterile conditions no degradation occurred indicating that the a.s. degradation is mainly biotic.

A study of good quality evaluating the photolysis of metalaxyl-M and metalaxyl in parallel showed that both compounds are photolytically stable (DT_{50} = 248 and 303 days respectively for metalaxyl-M and metalaxyl).

Some additional information was provided on the possible adaptation of the soil microflora leading to an accelerated degradation on soils repeatadly treated with the a.s. This phenomenon of adaptation is not observed in all the soil conditions.

Laboratory degradation
Several studies were realized under different conditions with metalaxyl and metalaxyl-M.

- The comparison of the 4 studies where the degradation of metalaxyl-M and metalaxyl were followed in parallel reveal that the degradation of both compounds are similar :

		median
DT_{50} metalaxyl-M	3.9, 8.13, 73.5, 167.9	40.8 d
DT_{50} metalaxyl	10.8, 13.97, 58.4, 123.4	36.2 d

The notifier argues that metalaxyl-M degraded more rapidly than the racemate metalaxyl particularly under environmental conditions enhancing the biological processes. The notifier proposes therefore to apply a correction factor of 1.4 for the extrapolation from metalaxyl to metalaxyl-M. Under conditions of low biological activity, abiotic chemical processes would be involved, leading to slower, not enantiospecific processes. (Ellgehausen, 1998)

The RMS did not follow this statement and considers that degradation rates of metalaxyl should be extrapolated to metalaxyl-M without conversion factor because the examinationof studies realized in parallel with both a.s. did not lead to the unequivocal conclusion of a more rapid degradation of metalaxyl-M.

The metalaxyl values were used to extrapolate to metalaxyl-M since numerous data at several temperatures are available for the racemate.
The values of the California sandy loam study (DT_{50} = 167.9, 123.4) were not taken into account in the determination of the typical DT_{50} because the goal of this study was the identification of the metabolic pathway with less emphasis on the degradation rate.

		median
DT_{50} metalaxyl, 20-25°C	7, 10.8, 13.97, 14, 20, 40, 40, 50, 58.4	**20 d**
DT_{50} metalaxyl, 15°C	33, 42	38 d
DT_{50} metalaxyl, 10°C	43	43 d
DT_{90} metalaxyl, 20-25°C	35.7, 36, 45, 46.4, 140	45 d
DT_{50} CGA 62826 , 20°C	4.2, 5.3, 14.9, 25.3, 102, nd	14.9 d
DT_{50} CGA 62826 , 10°C	62.1	62 d

Field dissipation

The notifier recalculates dissipation rates for the a.s. and the metabolite CGA 62826 on the basis of the field dissipation studies containing information on the metabolite CGA 62826. The results of this recalculation are presented in the table B.7.3-2 (results between brackets). The original results from the studies are also presented in the same table (without brackets). The median of the original a.s. data and the recalculated data are similar : DT_{50} = 36, DT_{90} = 157.
The examination of individual results shown below reveal that the median is a good approximation of the realistic worst case for the DT_{50} and DT_{90} field for metalaxyl as well as for metalaxyl-M.

		median
DT_{50} metalaxyl, field	39.4, 20.4, 19.5, 86.9, 38.8, 38.5	**38.7 d**
DT_{90} metalaxyl, field	132, 67.8, 64.7, 288.7, 128.8, 127.8	128.3 d
DT_{50} CGA 62826, field	nd, nd, 10.4, 36.4, 27.9, 36.4	31.2 d

Residue testing studies were performed with metalaxyl at an application rate (200-250 g/ha) and a number of applications (3-13) slightly higher than the major intended uses (110-150 g/ha; 2-5 applications). These studies show that the maximum concentrations are found in the top soil just after application. The a.s. degraded rapidly between the applications. Soil concentrations did not increase with the number of applications. The maximum concentrations observed just after the applications were in the range 0.13- 0.20 - 0.44 mg a.s./kg soil.

Adsorption/desorption

Several adsorption/desorption studies were performed.

Metalaxyl-M is classified in the low to very high mobility classes :	Koc = 20-1299
Metalaxyl is classified in the medium medium to very high mobility classes :	Koc = 29-283.8
The major metabolite CGA 62826 is classified in the high to very high mobility classes :	Koc = 3-72

The wide Koc ranges could indicate different adsorption behaviours in function of the soil types (clay or sand).

Column leaching

The columns leaching studies confirm the adsorption/desorption results. They indicate the high mobility of both metalaxyl-M and metalaxyl. The mobility of the metabolite CGA 62826 is even higher.

Lysimeter studies

2 lysimeter studies were performed with metalaxyl. Metalaxyl was applied at the rate of 330-365 g a.s./ha/season on 4 sandy soil monoliths. Crops were potatoes and vines. Metalaxyl was recovered in the combined leachate of one year at concentrations of <0.01 to 0.05 µg/l. The metabolite CGA 62826 was recovered at the concentration of 0.25-4.12 µg/l. The metabolite CGA 108906 was recovered at the concentration of 0.16-1.11 µg/l.

Field leaching data

3 field leaching studies were submitted. The quality of the studies is questionable and no real conclusion can be taken from these data. Leachate concentrations of <1 to 2000 µg a.s./l were recovered.

Drain water concentrations were measured in two studies of dissipation. Drain systems were at 0.8 and 1.2 m depth. Water concentrations were generally measured after heavy rainfall. The maximum concentrations were 17-87 µg a.s./l. Levels of CGA 62826 in the range <10-32 µg/l were measured in one of the studies

Groundwater monitoring

Data on groundwater monitoring in several European countries, Canada and the United States are also available. Detailed evaluation of these data on metalaxyl should be performed at Member State level in order to assess whether the proposed uses of metalaxyl-M would lead to unacceptable water contamination in the future.

“In the studies performed in Europe that did include metalaxyl, no or only few detections of this compound were made. Where quantitatively reported, the concentrations found were <0.1 µg/l. On the whole, the conclusion can be drawn that the uses of metalaxyl over the past 20 years have not led to more than occasional detections of metalaxyl in groundwater. Hardly ever did residues exceed 0.1 µg/l.”

Data from USA and Canada show that metalaxyl is detected in a limited number of wells at levels >0.1 µg/l. These data reveal that applications at high rates are susceptible to contaminate groundwater.

Predicted Environmental Concentrations in soil (Foliar uses)

The estimations of the PECs were calculated assuming that :

- Metalaxyl-M has a DT_{50} (soil) = 38.5 days (= median field DT_{50} of metalaxyl ≈ maximum DT_{50})
- Equal distribution in the top 5 cm of the soil with a bulk density of 1.5 g/cm^3
- Major uses of metalaxyl-M are

Crop	Application rate	Number of applications/season
grapes (foliar use)	120 g a.s./ha	2-4
potatoes (foliar use)	110 g a.s./ha	2-5

PEC soil - Foliar spray to control airborne diseases (formulation RIDOMIL GOLD MZ 68 WP)

Time after applications (days)	Grapes 120 g a.s./ha 4 applications with 7 d interval 70% of applied dose reaching the soil	Potatoes 110 g a.s./ha 5 applications with 7 d interval 50% of applied dose reaching the soil
	Actual concentration (mg a.s./kg soil)	Actual concentration (mg a.s./kg soil)
0	0.112	0.073
1	0.110	0.072
2	0.108	0.071
4	0.104	0.068
7	0.099	0.065
7	(2nd appl) 0.210	(2nd appl.) 0.138
14	(3rd appl) 0.298	(3rd appl.) 0.195
21	(4th appl) 0.374	(4th appl.) 0.245
28	0.330	(5th appl.) 0.290
50	0.222	0.195
100	0.090	0.079

PEC for the major metabolite CGA 62826 **could be considered as equivalent to the PEC of the a.s. (field DT_{50} of the a.s. and its metabolite are quite similar.). Soil accumulation studies were provided which give measured concentrations for metalaxyl and its metabolite. These data are in good accordance with the PEC which were calculated. Moreover the (eco)toxicity data showed that the metabolite is less toxic than the parent.**

Predicted Environmental Concentrations in soil (Soil uses)

The estimations of the PECs were calculated assuming that :

- Metalaxyl-M has a DT_{50} (soil) = 38.5 days (= median field DT_{50} of metalaxyl ≈ maximum DT_{50})
- Equal distribution in the top 5 cm of the soil with a bulk density of 1.5 g/cm^3
- The following scenarios were followed :

Crop	Application rate	Number of applications/season
orchard and ornamental crops annual field crops	1000 g a.s./ha (typical high dose rate)	1
orchard crops and ornamentals	1 g a.s./ m^2 in root zone	1-2

PECsoil - Soil treatment against soilborne diseases (formulation RIDOMIL GOLD 480EC)

Time after applications (days)	orchard and ornamental crops annual field crops 1000 g a.s./ha 1 application 100 % of applied dose reaching the soil		Root zones in plantation 1 g/m^2 1 application 100 % of applied dose reaching the soil	
	Actual concentration (mg/kg soil)	Time weighed average (mg/kg soil)	Actual concentration (mg/kg soil)	Time weighed average (mg/kg soil)
0	1.33	1.33	13.33	13.33
1	1.31	1.32	13.10	13.21
2	1.29	1.31	12.86	13.10
4	1.24	1.29	12.40	12.86
7	1.18	1.25	11.75	12.53
14	1.04	1.18	10.36	11.79
21	0.91	1.11	9.14	11.10
28	0.81	1.05	8.05	10.47
50	0.54	0.88	5.42	8.79
100	0.22	0.62	2.20	6.18

2.5.3 Fate and behaviour in water

Physico-chemical properties
Metalaxyl-M is not photodegradable in water. The a.s. is not hydrolyzed at any pH. The a.s. is not readily biodegradable

Water/sediment studies
In water/sediment study under aerobic conditions, metalaxyl is distributed to both sediment and water phases. Metalaxyl is degraded to metabolite CGA 62826 (DT_{50} whole system are 47.5 and 22.4 days for the river and pond system respectively). The metabolite CGA 62826 is a major metabolite slightly decreasing from day 112-181 to day 240 (Maximum 61.0-68.8% applied radioactivity in water after 112-181 days). DT_{50} (CGA 62826) > 1 year. Other metabolites (CGA 67868 and 5 unknown peaks) are found at low levels (<10% radioactivity)
Mineralization is low (7.6% and 4.1% of the radioactivity are recovered as CO_2 after 240 days)
Amounts of bound residue are increasing slowly during the whole incubation period and are reaching 10.4 and 13.8% of the applied radioactivity after 240 days.

In water/sediment study under anaerobic conditions, metalaxyl is distributed to both sediment and water phases. Metalaxyl is degraded anaerobically to metabolite CGA 62826 (DT_{50} whole system = 29.9 days). Two major metabolites were observed (CGA 62826 at 77 % applied radioactivity after 100 days, CGA 119857 at 16% radioactivity after 198 days)
Amount of bound residue is low during the whole incubation period (generally 1.0 -3.1 % applied radioactivity).
Metabolites CGA 325631 and hydroxy-metalaxyl were found only at two sampling times at very low concentrations.

Rice paddy field studies
Results of two rice paddy field studies performed with metalaxyl were submitted. They reveal that the a.s. has a DT_{50} of 5-20 days in water while the DT_{50} in the top soil is 11-24 d

Degradation in the saturated zone
Due to the very low degradation of metalaxyl-M under abiotic conditions, it should be concluded that no degradation of metalaxyl-M and its metabolite occur in the saturated zone.

Predicted Environmental Concentrations in surface water (Foliar uses)

To estimate the PECsw several routes have to be considered : direct overspray, spray drift, run off, discharge via drainage.

1- Direct overspray would not correspond to good agricultural practice and is not further considered

2 - Run off. The estimation of the PEC surface water resulting from runoff is based on the following assumptions

- **0.5% a.s. applied runoff from a 1 ha field into a 0.2 ha pond of 1 m depth**
- **120 g a.s./ha applied.**

The concentration in water is estimated to 0.3 μg/l.

3 - Drain discharge. Drain water concentrations were measured in two studies of dissipation. Drain systems were at 0.8 and 1.2 m depth. Water concentrations were generally measured after heavy rainfall. The maximum concentrations were 17-87 μg a.s./l. Levels of CGA 62826 in the range <10-32 μg/l were measured in one of the studies

4 - Spray drift

The estimations of the PEC surface water were calculated assuming that :
- Metalaxyl-M has a DT_{50} (whole system) = 47.5 days
- Distribution to a 30 cm deep waterbody

- Major foliar uses of metalaxyl-M are

Crop	Application rate	Number of applications/season
grapes (foliar use)	120 g a.s./ha	2-4
potatoes (foliar use)	110 g a.s./ha	2-5

PEC surface water - Foliar spray to control airborne diseases (formulation RIDOMIL GOLD MZ 68 WP)

Time after applications (days)	Grapes 120 g a.s./ha 4 applications with 7 d interval 5 m drift , 5 % of applied dose reaching the water body	Potatoes 110 g a.s./ha 5 applications with 7 d interval 1 m drift, 5% of applied dose reaching the water body
	actual concentration (mg a.s./l)	actual concentration (mg a.s./l)
0	0.0020	0.0018
1	0.0019	0.0018
2	0.0019	0.0018
4	0.0019	0.0017
7	0.0018	0.0017
7	(2nd appl.) 0.0038	(2nd appl.) 0.0035
14	(3rd appl.) 0.0054	(3rd appl.) 0.0050
21	(4th appl.) 0.0069	(4th appl.) 0.0063
28	0.0062	(5th appl.) 0.0076
42	0.0051	0.0061
100	0.0022	0.0026

Predicted Environmental Concentrations in surface water (Soil uses)

The estimations of the PECsurface water were calculated assuming that :

- Metalaxyl-M has a DT_{50} (whole system) = 47.5 days
- Distribution to a 30 cm deep waterbody
- The following scenario was followed :

Crop	Application rate	Number of applications/season
orchard and ornamental crops annual field crops	1000 g a.s./ha (typical high dose rate)	1

PECsurface water - Soil treatment against soilborne diseases (formulation RIDOMIL GOLD 480EC)

Time after applications (days)	perennial crops and ornamentals, annual crops, application on the soil 1000 g a.s./ha 1 application 1 m drift , 5% of applied dose reaching the water body	
	Actual concentration (mg/l water)	Time weighed average (mg/l water)
0	0.017	0.017
1	0.016	0.016
2	0.016	0.016
4	0.016	0.016
7	0.015	0.016
14	0.014	0.015
21	0.012	0.014
28	0.011	0.014
50	0.008	0.012
100	0.004	0.009

PEC surface water for the metabolite CGA 62826
The DT_{50} of CGA62826 in water is more than 1 year. It seems therefore more appropriate to take the initial actual concentration calculated for the a.s. as a good approximation of the PEC of CGA 62826

PEC ground water

Input parameters

Crop	Application rate	Number of applications/season
grapes (foliar use)	**120 g a.s./ha**	**2-4**
potatoes (foliar use)	**110 g a.s./ha**	**2-5**

Median DT_{50} of metalaxyl under laboratory conditions at 20°C is 20 days.
The notifier considers that the DT_{50} of metalaxyl-M is 1.4-2 times shorter than the DT_{50} of metalaxyl. This difference should be more marked in biologically active soils.
The rapporteur MS considers that metalaxyl-M and metalaxyl have similar DT_{50}. Studies performed with mixtures of biologically active soil and inactive soil are not considered as representative and could simply reveal the normal distribution of degradation rates in different soils.

DT_{50} of CGA62826 of 5 to 100 days were reported in several laboratory studies performed at 20°C

Koc values of metalaxyl-M of 20 to 570 (1299) were reported in the adsorption study
Koc values of CGA 62826 of 3 to 72 were reported in the adsorption study

Computer simulations were conducted to assess the leaching potential of the fungicide metalaxyl-M and its acid metabolite CGA 62826 under Italian Belgian and Norwegian conditions. The calculations are based on three scenarios which are to represent the soil and climate conditions typically encountered in the Northern, the Central and the Southern par of the EU.
All calculations were performed with the LEACHP model (Hutson & Wagenet 1992).The simulations were to comply with the Dutch registration requirements for pesticides and therefore were based on the PESTLA model and the Dutch standard weather and soil scenarios. As for farming conditions, spring and autumn applications were considered.

- The notifer presents a wide range of DT_{50}/Koc/pedo-climatic scenarios for the a.s. and its metabolite CGA62826.

- The assumptions taken into account in these two modelling studies reflect partially the actual properties of the a.s. and its metabolite. (DT_{50} are too short, Koc too high for the a.s. and the metabolite). It is therefore necessary to consider these models calculations in some ways as 'best cases' situations.

- In some scenarios, however not unrealistic, groundwater contamination by the active substance is observed.

- The water contamination by the metabolite CGA 62826 is possible in a large number of scenarios

2.5.4 Fate and behaviour in air

The volatility of metalaxyl from soil and from leaves surface were determined. It is difficult to determine the relevance of these results in the evaluation of the general behaviour of metalaxyl in the air.

It is not expected that metalaxyl-M would be present in air for extended time periods or be transported over long distances or even into the stratosphere because :

- Metalaxyl-M is slightly volatile ($3.3\ 10^{-3}$ Pa at 25°C)
- The estimated half-life of metalaxyl-M in the atmosphere (by hydroxyl radical oxidation) is between 4 and 6 hours.

2.6 Effects on non-target species

2.6.1 Effects on terrestrial vertebrates

Birds

Acute and dietary toxicity of metalaxyl-M to *Colinus virginianus* were determined : LD_{50} = 981-1419 mg a.s./kg bw; LC_{50} > 5620 mg a.s./kg feed. The comparison of these results with results of metalaxyl studies revealed that both substances have similar toxicity.
The lowest NOEC (reproduction,18weeks, metalaxyl, *Anas platyrhynchos*) is 300 mg a.s./kg feed.

TER birds

The risk assessment for birds is based on the following assumptions :
- small birds (< 100 g) with a food consumption of 30% bw
- the contamination of the food is estimated according to Hoerger and Kenaga (1972)
- the uses of metalaxyl-M susceptible to contaminate the food of birds are :

1 - The foliar spray to control airborne diseases (formulation RIDOMIL GOLD MZ 68 WP). Grapes and potatoes are the main crops treated with this type of formulation.

2 - The soil treatment against soilborne diseases (formulation RIDOMIL GOLD 480EC). The formulation is applied on the soil at sowing or (pre)-planting or at the base of the trees. The application rate of 1000 g/ha was taken into account in the evaluation of the risk to birds.

- The application of the a.s. in the root zone of orchard trees (1 g/m^2) was not considered as a route leading to a high contamination of the bird food.

The risk to leaf-eating and insectivorous birds resulting from the exposure to the a.s. in crops treated with foliar spray formulation is negligible (TER acute = 1272-15930; TER short term = 264-3303; TER long term = 81-1010)

The risk to leaf-eating, insectivorous birds resulting from the exposure to the a.s. in crops treated with soil treatment formulation is negligible (TER acute = 153-3638; TER short term = 32-363; TER long term = 10-111)

TER small mammals

The risk assessment for small mammals is based on the following assumptions :
- LD_{50} (oral, _ rat) = 375 mg a.s./kg bw
- NOEC (oral, rat, 90 days) = 250 mg a.s./kg food
- small mammals (< 100 g) with a food consumption of 30% bw
- the contamination of the food is estimated according to Hoerger and Kenaga (1972)
- the uses of metalaxyl-M susceptible to contaminate the food of small mammals are :

1 - The foliar spray to control airborne diseases (formulation RIDOMIL GOLD MZ 68 WP). Grapes and potatoes are the main crops treated with this type of formulation.

2 - The soil treatment against soilborne diseases (formulation RIDOMIL GOLD 480EC). The formulation is applied on the soil at sowing or (pre)-planting or at the base of the trees. The application rate of 1000 g/ha was taken into account in the evaluation of the risk to small mammals.

- The application of the a.s. in the root zone of orchard trees (1 g/m^2) was not considered as a route leading to a high contamination of the mammals food.

The risk to leaf-eating and insectivorous mammals resulting from the exposure to the a.s. in crops treated with foliar spray formulation is negligible (TER acute = 336-4209 ; TER short term = 67-842)
The evaluation of the risk resulting from mancozeb should be evaluated at Member State level.

The risk to leaf-eating, insectivorous mammals resulting from the exposure to the a.s. in crops treated with soil treatment formulation is negligible (TER acute = 40-463; TER short term = 8-93) The TER short term is slightly

below the trigger value of 10. We can nevertheless accept that the risk is low because the NOEC is derived from a 90-day study and because the food concentration is expressed as an initial residue.

2.6.2 Effects on aquatic species

Acute toxicity to aquatic organisms
Metalaxyl-M and the 3 tested metabolites are non-toxic to fish and daphnia.
Metalaxyl-M and metabolite CGA 108906 are harmful to algae. Metabolites CGA 62826 and CGA 67868 are non-toxic to algae

The acute toxicity studies performed with metalaxyl-M and and with racemic metalaxyl reveal that both substances have a similar pattern of toxicity to aquatic organisms. Therefore the results of the chronic toxicity studies (fish and daphnia) performed with metalaxyl were extrapolated to metalaxyl-M.

Chronic toxicity to aquatic organisms
Chronic toxicity of metalaxyl was evaluated in two studies performed with fish and daphnia. The NOEC were 9.1 ml and 1.2 mg/l respectively for fish and daphnia.

Bioaccumulation
The maximum BCF determined in non-edible part at day 14 is 15.
Significant elimination of ^{14}C residues was observed during the first 3 days of depuration . The depuration half-lifes were between 1 and 3 days.
The bioaccumulation potential of metalaxyl is low. This conclusion is confirming the results of the log Pow study (log Pow of metalaxyl-M = 1.71).

TER aquatic organisms
The main uses of metalaxyl-M susceptible to lead to a contamination of surface waters are :

- The foliar spray treatment to control airborne diseases (formulation RIDOMIL GOLD MZ 68 WP) : grapes and potatoes
- The soil treatment against soilborne diseases (formulation RIDOMIL GOLD 480EC) : orchard, ornamental and annual field crops

The details of the PEC calculations are presented on point B.7.6. The calculations presented in this monograph are only related to the active substance metalaxyl-M. The toxicity endpoints were compared to the maximum concentrations found just after the last application of the active substance.

- The TER was also evaluated taking into account the figures from a drain discharge study where 2 kg a.s./ha was applied on bare soil. The maximum concentration found in the drain water was 87 µg/l.

The toxicity of the 3 metabolites is similar/lower than the toxicity of metalaxyl-M. Therefore, the TER calculations for the a.s. cover the risk resulting from the presence of the metabolites.

For both types of formulation the acute and long term risk to aquatic organisms are negligible.

2.6.3 Effects on bees and other arthropods

Bees
Several laboratory studies were performed with metalaxyl-M, metalaxyl and with both representative metalaxyl-M formulations. These studies revealed that metalaxyl-M is not toxic to bees.

LD_{50} (48h, metalaxyl-M, contact) > 25 µg a.s./bee

LD_{50} (48 h, metalaxyl, oral) > 200 µg a.s./bee
LD_{50} (48 h, metalaxyl, contact) > 200 µg a.s./bee

The applications of RIDOMIL GOLD MZ 68 WP in grape and potatoes were chosen as representative scenarios for the foliar spray.

Application of RIDOMIL GOLD 480 EC is made essentially at sowing and pre-planting, or at the base of the trees. The exposure of bees resulting from this use pattern is negligible. Nevertheless we calculated the hazard quotient taking into account an application rate of 1000 g a.s./ha (typical high dose rate in a wide variety of orchard, ornamental and field crops)

The hazard ratios calculated for both use types (10-17) indicate that risk of metalaxyl-M to bees is negligible.

Other non-target arthropods
Laboratory studies were performed with both representative formulations RIDOMIL GOLD MZ 68 WP and RIDOMIL GOLD 480EC. These studies revealed that metalaxyl-M was harmless to *Poecilus cupreus* and *Orius insidiosus*, moderately harmful to *Typhlodromus* ***pyri*** **and harmful to *Aphidius colemani* at the application rate of 1 kg a.s./ha.**

Extended lab test performed with *Aphidius rhopalosiphi* and field test performed with *Typhlodromus pyri* revealed that the substance present low risk to non-target arthropods under more realistic use conditions.

2.6.4 Effects on earthworms and other soil macro-organisms

Earthworms
The LC_{50} (*Eisenia foetida*, 14 d, metalaxyl-M) = 830 mg a.s./kg soil

TER earthworms
The main uses of metalaxyl-M susceptible to lead to a contamination of soil are :

- The foliar spray to control airborne diseases (formulation RIDOMIL GOLD MZ 68 WP)
- The soil treatment against soilborne diseases (formulation RIDOMIL GOLD 480EC)

The calculations presented in this monograph are only related to the active substance metalaxyl-M. The toxicity endpoints were compared to the maximum concentrations found just after the last applications of the active substance.

The acute risk to earthworms is negligible.

The calculation of the TER acute show very favourable results even in the case of orchard soil disinfection with very high application rate (1 g a.s./m^2) (TER acute = 62 to 2862). Therefore, specific studies to determine the long term risk seem not appropriate.

2.6.5 Effects on soil micro-organisms

The effects on soil respiration and nitrification were evaluated with the Speyer 2.1 (sand) and Speyer F3 (sandy silty loam) soils. The study was realized with metalaxyl at the concentrations of 0.66 and 6.6 mg a.s./kg soil equivalent to 500 and 5000 g a.s./ha , related to a soil depth of 5 cm and a soil density of 1.5 kg/dm^3 and no crop interception . No process modification > 25% at the termination of the test was observed at both concentration levels.

The application rates of metalaxyl-M are covered by the study realized with metalaxyl at the maximum rate of 5000 g/ha (typical uses as foliar spray 100-150 g/ha; typical use as soil treatment up to 1000 g a.s./ha; application rate as root zone treatment : 10000 g/ha).

Other studies such as the aerobic soil degradation studies, the activated sludge respiration studies reveal that metalaxyl and metalaxyl-M have similar effects on the microflora. It is therefore possible to extrapolate from the racemic metalaxyl to metalaxyl-M.

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

No specific information was submitted.

2.6.7 Effects on biological methods of sewage treatment

The inhibitory effect of the metalaxyl on the oxygen consumption of activated sludge suspension (1.68 g sludge/l water) was determined. The 3-hour EC_{20}, EC_{50} and EC_{80} were all calculated to be >100 mg/l (nominal)

LEVEL 2

Metalaxyl-M

Appendix 1 : Standard Terms and Abbreviations

Part 1 Technical Terms

A	ampere
ACH	acetylcholine
AChE	acetylcholinesterase
ADI	acceptable daily intake
ADP	adenosine diphosphate
AFID	alkali flame-ionization detector or detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD_{50}	approximate median lethal dose, 50%
AOEL	acceptable operator exposure level
AMD	automatic multiple development
approx.	approximate
as	active substance
at. wt.	atomic weight
ATP	adenosine triphosphate
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
b.p.	boiling point
BSP	bromosulfophthalein
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10^{-2})
°C	degree celsius (centigrade)
CAD	computer aided design
cd	candela
CDA	controlled drop(let) application
CEC	cation exchange capacity
cf	confer, compare to
ChE	cholinesterase
cm	centimetre
CNS	central nervous system
CoC	code of conduct
COD	chemical oxygen demand
cu	cubic

cv	coefficient of variation
Cv	ceiling value
cyt	cytogenetic analysis
d	day
DL	racemic (optical configuration, a mixture of dextro- and laevo-; preceding a
dlt	dominant lethal test
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic Acid
dnd	DNA-damage
dni	DNA-inhibition
dnr	DNA-repair
dns	unscheduled DNA-synthesis
DO	dissolved oxygen
DOC	dissolved organic carbon
DT	disappearance time
DTH	delayed-type hypersensitivity
EC	effective concentration
ECD	electron capture detector
ELISA	enzyme linked immunosorbent assay
EMDI	estimated maximum daily intake
EP	end-use product
ERL	extraneous residue limit
F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second
FID	flame ionization detector
f.p.	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
g	gram
GAP	good agricultural practice
GC-EC	gas chromatography with electron capture detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice

GFP	good field practice
G.I.	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GPC	gel-permeation chromatography
GPPP	good plant protection practice
h	hour(s)
ha	hectare
Hb	haemoglobin
HCG	human chorionic gonadotropin
hl	hectolitre
hma	host-mediated assay
HPLC	high pressure liquid chromatography or high performance liquid
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gas chromatography
Ht	haematocrit
I_{50}	inhibitory dose, 50%
IC_{50}	median immobilization concentration
i.d.	internal diameter
ID	ionization detector
i.m.	intramuscular
inh	inhalation
i.p.	intraperitoneal
IPM	integrated pest management
IR	infrared
i.v.	intravenous
k	kilo
K	Kelvin
kg	kilogram
l	litre
LBC	loosely bound capacity
LC	lethal concentration

LC	liquid chromatography
LC_{50}	lethal concentration, median
LCA	life cycle analysis
LC_{Lo}	lethal concentration low
LD_{50}	lethal dose, median; dosis letalis media
LD_{Lo}	lethal dose low
LOAEL	lowest observable adverse effect level
LOD	limit of determination
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LT	lethal threshold
m	metre
M	molar
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
µg	microgram
mg	milligram
min	minute(s)
ml	millilitre
MLD	minimum lethal dose
mm	millimetre
mma	microsomal mutagenicity test
mmo	mutation in microorganisms
mnt	micronucleus test
mo	month(s)
mol	Mol
m.p.	melting point
MP	manufacturing-use product
mrc	gene conversion and mitotic recombination
MRE	maximum residue expected
MRL	maximum residue level
msc	mutation in mammalian somatic cells
MSDS	material safety data sheet
MTD	maximum tolerated dose

n	normal (defining isomeric configuration)
NAEL	no adverse effect level
n.d.r.	not dose-related
NEDI	no effect daily intake (mg/kg body wt/day)
NEL	no effect level
NERL	no effect residue level
NMR	nuclear magnetic resonance
no.	number
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
nse	non standard exposure
o	ortho (indicating position in a chemical name)
ODP	ozone-depleting potential
OP	organophosphorous pesticide
otr	oncogenic transformation
p	para (indicating position in a chemical name)
Pa	pascal
2-PAM	2-pralidoxime
PC	paper chromatography
PCV	haematocrit (packed corpuscular volume)
PD	position document
PEC	predicted environmental concentration
PED	plasma-emissions-detector
pH	pH-value
PHI	pre-harvest interval
pic	phage inhibition capacity
PNEC	predicted no effect concentration
p.o.	by mouth
P_{ow}	partition coefficient between n-octanol and water
ppb	parts per billion
ppm	parts per million
ppq	parts per quadrillion
ppt	parts per trillion

PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	prothrombin time
PTT	partial thromboplastin time
RAC	raw agriculture commodity
RBC	red blood cell
Rf	ratio of fronts
RL_{50}	residual lifetime
RNA	ribonucleic acid
rns	rinsed
RPM	reversed phase material
RRT	relative retention time
s.c.	subcutaneous
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SBLC	shallow bed liquid chromatography
sce	sister chromatid exchange
SD	standard deviation
SE	standard error
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
sin	sex chromosome loss and nondisjunction
slt	specific locus test
sp/spp.	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
sp gr	specific gravity
spm	sperm morphology
sq	square
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
SVAT	soil-vegetation-atmosphere transfer

t	tonne (metric ton)
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TC_{Lo}	toxic concentration, low
TD	thermionic detector, alkali flame detector
TD_{Lo}	toxic dose low
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGAI	technical grade of the active ingredient
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
trn	heritable translocation test
TWA	time weighted average
UDS	unscheduled DNA synthesis
ULV	ultra low volume
UV	ultraviolet
v/v	volume ratio (volume per volume)
WBC	white blood cell
wk	week
wt	weight
wt/vol	weight per volume
w/w	weight per weight
yr	year
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

Part 2 Organisations and Publications

BA	Biological Abstracts (Philadelphia)
CA	Chemical Abstracts
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCPR	Codex Committee on Pesticide Residues
CIPAC	Collaborative International Pesticides Analytical Council Ltd
COREPER	Comite des Representants Permanents
EC	European Commission
ECCA	European Crop Care Association
ECPA	European Crop Protection Association
EHCD	Environmental Health Criteria Document
EINECS	European Inventory of Existing Commercial Chemical Substances
EPPO	European and Mediterranean Plant Protection Organization
EU	European Union
FAO	Food and Agriculture Organization of the UN
FJCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
GATT	General Agreement on Tariffs and Trade
GIFAP	Groupement International des Associations Nationales de Fabricants de Produits Agrochimiques
IARC	International Agency for Research on Cancer
IBT	Industrial Bio-Test Laboratories
IMO	International Maritime Organisation
IOBC	International Organization for Biological Control of Noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IR-4	Interregional Research Project No 4
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JECFA	FAO/WHO Joint Expert Committee on Food Additives
JMPR	Joint Meeting of 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
NCI	National Cancer Institute (USA)
NCTR	National Center for Toxicological Research (USA)
NGO	non-governmental organization
OECD	Organization for Economic Cooperation and Development
PAN	Pesticide Action Network
RNN	Re-registration Notification Network
SCPH	Standing Committee on Plant Health
SI	Systeme International d'Unites
SITC	Standard International Trade Classification
UN	United Nations
UNEP	United Nations Environment Programme
WHO	World Health Organization
WTO	World Trade Organization
WWF	World Wildlife Fund

LEVEL 2

Metalaxyl-M

Appendix 2 : Preparation (Formulation) Types and Codes

Preparation (Formulation) Types and Codes*

Code	Description	Definition
AB	Grain bait	Special forms of bait.
AE	Aerosol dispenser	A container-held preparation which is dispersed generally by a propellant as fine droplets/particles upon actuation of a valve.
AL	Other liquids to be applied undiluted	Self defining.
BB	Block baits	Special forms of bait.
BR	Briquette	Solid block designed for controlled release of active substance into water.
CB	Bait concentrate	A solid or liquid intended for dilution before use as a bait.
CG	Encapsulated granule	A granule with a protective or release controlling coating.
CS	Capsule suspension	A stable suspension of capsules in a fluid normally intended for dilution with water before use.
DC	Dispersible concentrate	A liquid homogeneous preparation to be applied as a solid dispersion after dilution in water.
DP	Dustable powder	A free-flowing powder suitable for dusting.
DS	Powder for dry seed treatment	A powder for application in the dry state directly to seed.
EC	Emulsifiable concentrate	A liquid, homogeneous preparation to be applied as an emulsion after dilution in water.
ED	Electrochargeable liquid	Special liquid preparation for electrostatic (electrodynamic) spraying.
EO	Emulsion, water in oil	A fluid, heterogeneous preparation consisting of a dispersion of fine globules of pesticide in water in a continuous organic liquid phase.
ES	Emulsion for seed treatment	A stable emulsion for application to the seed either directly or after dilution.
EW	Emulsion, oil in water	A fluid, heterogeneous preparation consisting of a dispersion of fine globules of pesticide in an organic liquid in a continuous water phase.
FD	Smoke tin	Special form of smoke generator.
FG	Fine granule	A granule in the particle size range from 300 to 2500 µ.
FK	Smoke candle	A smoke generator in the form of a candle.
FP	Smoke cartridge	Special form of smoke generator.
FR	Smoke rodlet	Special form of smoke generator.
FS	Flowable concentrate for seed treatment	A stable suspension for application to the seed either directly or after dilution.
FT	Smoke tablet	Special form of smoke generator.
FU	Smoke generator	A combustible preparation generally solid, which upon ignition releases the active substances in the form of a smoke.
FW	Smoke pellet	Special form of smoke generator.

Code	Description	Definition
GA	Gas	A gas packed in pressure bottle or pressure tank.
GB	Granular bait	Special forms of bait.
GE	Gas generating product	A preparation which generates a gas by chemical reaction.
GG	Macrogranule	A granule in the particle size range from 2000 to 6000 µ.
GP	Flo-dust	Very fine dustable powder for pneumatic application in glass-houses.
GR	Granule	A free-flowing solid preparation of a defined granule size range ready for use.
GS	Grease	Very viscous preparation based on oil or fat.
HN	Hot fogging concentrate	A preparation suitable for application by fogging equipment either directly or after dilution.
KN	Cold fogging concentrate	A preparation suitable for application by cold fogging equipment, either directly or after dilution.
LA	Lacquer	A solvent based film-forming preparation.
LS	Solution for seed treatment	A solution for application to the seed either directly or after dilution.
MG	Microgranule	A granule in the particle size range from 100 to 600 µ.
OF	Oil miscible flowable (=oil active substances in a miscible suspension)	A stable suspension of concentrate fluid intended for dilution in an organic liquid before use.
OL	Oil miscible liquid	A liquid, homogenous preparation to be applied as a homogenous liquid after dilution in an organic liquid.
OP	Oil dispersible powder	A powder preparation to be applied as a suspension after dispersion in an organic liquid.
PA	Paste	A water based film forming preparation.
PB	Plate bait	Special forms of bait.
PC	Gel or paste concentrate	A solid preparation to be applied as a gel or a paste after dilution with water.
PR	Plant rodlet	A small rodlet, usually a few centimetres in length and a few millimetres in diameter containing active substance.
PS	Seed coated with a pesticide	Self defining.
RB	Bait (ready for use)	A preparation designed to attract and be eaten by the target species.
SB	Scrap bait	Special forms of bait.
SC	Suspension concentrate	A stable suspension of active substance(s) in a fluid (= flowable concentrate) intended for dilution with water before use.
SE	Suspo-emulsion	A fluid, heterogeneous preparation consisting of a stable dispersion of active substance(s) in the form of solid particles and of fine globules in a continuous water phase.
SG	Water soluble granules	A preparation consisting of granules to be applied as a true solution of active substance after dissolution in water but may contain insoluble inert

Code	Description	Definition
		ingredients.
SL	Soluble concentrate	A liquid homogenous preparation to be applied as a true solution of the active substance after dilution with water.
SO	Spreading oil	A preparation designed to form a surface layer on application to water.
SP	Water soluble powder	A powder preparation to be applied as a true solution of the active substance after solution in water but which may contain insoluble inert ingredients.
SS	Water soluble powder for seed treatment	A powder to be dissolved in water before application to the seed.
SU	Ultra low volume (ULV) suspension	A suspension ready for use through ULV equipment.
TB	Tablet	Solid preparation in the form of small, flat plates for dissolution in water.
TP	Tracking powder	A rodenticidal contact preparation in powder form.
UL	Ultra low volume (ULV) liquid	A homogenous liquid ready for use through ULV equipment.
VP	Vapour releasing product	A preparation containing one or more volatile ingredients, the vapours of which are released into the air. Evaporation rate normally is controlled by using suitable preparations and/or dispensers.
WG	Water dispersible granule	A preparation granule consisting of granules to be applied after disintegration and dispersion in water.
WP	Wettable powder	A powder preparation to be applied as a suspension after dispersion in water.
WS	Water dispersible powder for slurry seed treatment	A powder to be dispersed at high concentration in water before application as a slurry to the seed.
XX	Others	

*based upon the catalogue of Pesticide Formulation types and International Coding Systems, developed by GIFAP in co-operation with the German working group on documentation questions. (Arbeitsgruppe EDV Pflanzenschutz Versuchswesen). GIFAP Technical Monograph No 2. 1989.

LEVEL 2

Metalaxyl-M

Appendix 3 : Listing of endpoints

LEVEL 3

Metalaxyl-M

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

3.1 Background to the proposed decision

Background to the proposed decision of restriction of use

Laboratory studies (adsorption/desorption, column leaching) on metalaxyl-M and its metabolite CGA62826 showed that these compounds are susceptible to leach to ground water.

Lysimeter studies were conducted with metalaxyl at an application rate of 330-365 g a.s./ha/season on 4 sandy soil monoliths. Metalaxyl was recovered in the combined leachate of one year at concentrations of <0.01 to 0.05 µg/l. The metabolite CGA 62826 was recovered at the concentration of 0.25-4.12 µg/l. The metabolite CGA 108906 was recovered at the concentration of 0.16-1.11 µg/l.

PEC calculations were performed by the notifier for a wide range of DT_{50}/Koc/pedo-climatic scenarios for the a.s. and its metabolite CGA62826 under the conditions of several European countries
The assumptions taken into account in thesemodelling studies reflect partially the actual properties of the a.s. and its metabolite. (DT_{50} are too short, Koc too high for the a.s. and the metabolite). It is therefore necessary to consider these models calculations in some ways as 'best cases' situations.

- In some scenarios, however not unrealistic, groundwater contamination by the active substance is observed.
- The water contamination by the metabolite CGA 62826 is possible in a large number of scenarios

Data on groundwater monitoring in several European countries, Canada and the United States are also available. The monitoring studies from Europe, that did include metalaxyl indicate that a few detections of metalaxyl have been made at level >0.1 µg/l.
Data from USA and Canada showed that metalaxyl is detected in a number of wells at levels >0.1 µg/l. These data also reveal that applications at high rates are susceptible to contaminate groundwater.

The whole data package indicates that metalaxyl-M used at low application rate per season (350 g a.s./ha/season) would generally not be detected in ground water. However, under some specific pedo-climatic scenarios or at high application rate per season (>350 g a./ha) ground water contamination can not be excluded. The contamination of ground water by the major metabolite CGA 62826 can be expected in a large number of pedo-climatic scenarios at levels of 1-5 µg/l (lysimeter data, modelling, monitoring).

3.2 Proposed decision concerning inclusion in Annex I

The RMS proposes to include the active substance metalaxyl-M in the Annex I of the Directive 91/414/EEC.

It is however necessary to restrict the uses to application rate of 350 g a.s./ha/season or less, and to specifically evaluate the ground water contamination by the a.s. and its metabolite under specific pedo-climatic situations.

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

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LEVEL 4

Metalaxyl-M

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

4.1 Identity of the active substance

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4.2 Physical and chemical properties

4.2.1 Physical and chemical properties of the active substance

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4.2.2 Physical and chemical properties of the plant protection products

Point addressed	Information or study required	Deadline
IIIA 2.2.2	Study on oxidizing properties of RIDOMIL GOLD 480 EC using suitable method (alternative to EEC A17) or, at least, statement addressing oxidizing properties, based on thermodynamic information	

4.3 Data on application and further information

Point addressed	Information or study required	Deadline
IIIA 4.1.2	Reports describing the results of the ADR-tests performed on the packaging material for RIDOMIL GOLD 480 EC and RIDOMIL GOLD MZ 68 WP	
IIIA 4.2	Recommendations regarding the cleaning of protective clothing	

4.4 Classification, packaging and labelling

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4.5 Methods of analysis

Point addressed	Information or study required	Deadline
IIIA 5.1.1	Methods that allow to determine the enantiomer ratio of the a.s. in formulations (EC, WP)	
IIIA 5.1.2	Validated analytical methods for the determination of 2,6-dimethylaniline in formulations (EC, WP)	
IIA 4.2.1 IIIA 5.2.1	Analytical method for specific determination of metalaxyl/metalaxyl-M (and metabolites .....) in food matrices of animal origin The methods proposed until now do not allow to distinguish between (metalaxyl/ metalaxyl-M/ metabolites with DMA moiety) and other substances with the DMA moiety	
IIA 4.2.2 IIIA 5.2.2	- Methods REM 16/76 and REM 7/77 : confirmation of proposed LOQ of 0.05 mg/kg by additional validation data - Method REM 7/77 : precision data for acid metabolite CGA 62826	

Point addressed	Information or study required	Deadline
IIA 4.2.3 **IIIA 5.2.3**	**Validation data demonstrating the applicability of methods REM 2/86 and REM 12/87 to surface water**	
IIA 4.2.4 **IIIA 5.2.4**	**Method REM 143.02 : confirmation of proposed LOQ of 10 μg/m³ by additional validation data**	

4.6 Toxicology and metabolism

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4.7 Residue data

Point addressed	Information or study required	Deadline
IIA 6.3 **IIA 6.5** **IIA 6.4**	**Supervised trials of crops used as feedingstuffs : kale/cabbage, fruit pomace, pulses, sugar beet, soybean, rape, sunflower** **Effects of the industrial processing on the residue in these crops** **Amended intake calculations for livestock** **Livestock feeding studies in lactating cow and poultry at relevant dosage** **MRL proposals for commodities of animal origin** **(See above : specific analytical method for commodities of animal origin)**	
IIA 6.6	**Residue trials in succeeding crops (in order to establish MRLs)** **Proposals in order to avoid the presence of residue in succeeding crops (waiting period between last application and sowing or planting date, list of crops allowed/not allowed as succeeding crops ...)**	
IIA 6.8	**Establishement of waiting period between the last application and sowing or planting succeeding crops, witholding period for animal feedingstuffs, re-entry period for livestock**	
IIA 6.9	**Amended intake calculations for human**	

4.8 Environmental fate and behaviour

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4.9 Ecotoxicology

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