ANNEX B

Metalaxyl-M

B.6 Residue data

Introduction.

Metalaxyl-M is a mixture of the R-enantiomer (CGA 329351) (min. 97%) and the S-enantiomer (CGA351920) (max.3%) of the racemic compound metalaxyl (CGA 48988). Metalaxyl is the active ingredient of the fungicide RIDOMIL ^{R} which is used for the control of Late Blight of potatoes and Downey Mildew on various crops as well as seedling diseases caused by Oomycetes.

Informations about the residue behaviour of metalaxyl-M mainly relies on studies carried out with the racemic compound metalaxyl (consisting of approx. 50% of each R- and S-enantiomers). This is considered as acceptable for the following reasons:

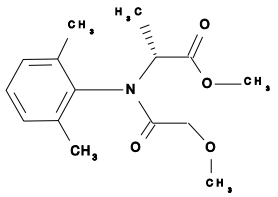
- As an intrinsic part of the racemate, the plant and livestock metabolism, the potential to leave residues in/on crops and animal tissues and the behaviour during processing of commodities of metalaxyl-M has been subject to extensive investigations through experimentations carried out with metalaxyl.
- It is highly unlikely that the enhanced activity of metalaxyl-M compared to metalaxyl as a disease control agent is linked to a different plant metabolism (for instance a decreased rate of degradation). Available data from the literature demonstrate that the enhanced level of activity seen with metalaxyl-M is inherent from the properties of the molecule and is based on the efficiency in which metalaxyl-M reaches or binds to the active site of the inhibition of RNA synthesis in target fungi.

Also data from side by side field residue studies completed in the USA using a total analytical method that detects metabolites demonstrates that residues in the foliage and fruit match the application rate reduction of metalaxyl-M.
Finally, comparison of the metabolite pattern from lettuce treated with radiolabeled metalaxyl-M and metalaxyl used to validate the total plant residue method reveals a similar pattern of metabolites for the R-enantiomer and the racemate (Larry W.,1996).
In conclusion it is reasonable to use metalaxyl data to assess the residue behaviour of metalaxyl-M.

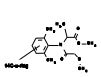
The chemical structures of the metabolites mentioned under their code numbers in this section and the different metabolic pathways are given in the appendix to this section.

Metabolism studies were carried out with Metalaxyl labelled with ^{14}C uniformly on the phenyl ring. : ^{14}C-u-ring

Structural formula of metalaxyl-M
(CGA 329351)



Structural formula of metalaxyl
(CGA 48988)



B.6.1 Metabolism, distribution and expression of residues in plants (Annex IIA 6.1)

B.6.1.1 Metabolism, distribution and expression of residues of metalaxyl in grapevine

Metabolism of metalaxyl (CGA 48 988) in grapevine (Gross D., 1978).
Identification of metabolites of metalaxyl (CGA 48 988) (RIDOMIL^{R}) in grapevine (Gross D., 1979b).
Guidelines :
not specified
GLP :
No - not required at the time the study was conducted.
Material and Methods :
The study was carried out in Switzerland.
Test substance : ^{14}C(phenyl)-metalaxyl.
Experimental design :
Field grown grapevines received 7 applications to run-off of test substance at a concentration of 50 g a.s./100 l water. 52 Days after the final application ripe grapes and leaves were collected. Grapes were processed into juice and presscake.
Extraction procedure :
The radioactivity in the different fractions was determined by liquid scintillation counting. The residues in juice were extracted with hexane, methylene chloride (CH_2Cl_2)and ethyl acetate while residues in whole grapes, presscake and leaves were extracted with methanol/water and subsequently partitioned with hexane, CH_2Cl_2 and ethyl acetate. The water soluble residues were treated with cellulase.
Thin layer chromatography was used to characterize the radioactivity present in the organic phases and fractionation was carried out by HPLC analysis.
The isolated fractions were analyzed by GLC/MS with reference compounds.
Findings :
Table B.6.1-1 : Investigation of the nature and the amounts of residues of metalaxyl (CGA 48988) in/on grapevines following a run-off treatment at a field rate of 50 g a.s./100 L water (residues expressed as mg metalaxyl equiv./kg).

Sample	Leaves	Whole grapes	Juice	Presscake
Total radioactive residues (mg metalaxyl equiv./kg)				
	30.13	3.06	1.04	7.31
Extractability of total radioactive residues (% TRR in leaves and in whole grapes)				
Methanol extraction phase	95.8	90.6	na	90.6
Organosoluble hexane phase	22.4	64.1	7.8	56.3
Organosoluble CH_2Cl_2/ethyl acetate phase	34.2	16.8	7.0	9.8
Water soluble phase	39.1	9.7	2.7	7.0
Elucidation of radioactive residues (% TRR)				
Metalaxyl (CGA 48988)	22.4	64.1	7.8	56.3
CGA 94 689 (free + conjugated)	55.4	20.4 (11.8+8.6)	7.0 (4.6+2.4)	13.4 (7.2+6.2)
CGA 100 255 (free + conjugated)	13.0	4.3 (3.5+0.8)	1.7 (1.5+0.2)	2.6 (2.0+0.6)
CGA 62 826 + CGA 107955 (free + conjugated)	5.0	1.8 (1.5+0.3)	1.0 (0.9+0.1)	0.8 (0.6+0.2)
Unextracted radioactive residues (%TRR)				
	4.2	9.4	-	9.4
Total recovery (extracted phase + URR) (%TRR in leaves and in whole grapes)	100	100	17.5	82.5
- : Not applicable.				

At harvest the total amount of radioactive residues in/on grapes was about 3 mg/kg metalaxyl equivalents. Metalaxyl accounted for 64% (1.96 mg/kg) of these residues.
Less than 20% of the total residues were transfered into juice at processing. The concentration of metalaxyl in juice was 0.46 mg/kg, thus 25% of the initial content in raw grapes. Metalaxyl represented the most important compound of the residue in juice and presscake.
Several metabolites existing in free and conjugated forms were characterized by TLC. A chemical structure could be assigned to each of them by GLC/MS.
The nature of residues present on the leaves was the same as on the fruits. Only the ratio between the parent compound and the metabolites was different with higher level of metabolites in the case of the leaves.
Conclusions :
Metalaxyl is the major constituant of the residue in/on grapes 52 days after application.
The degradation of metalaxyl in grapevine proceeds primarily via three independent pathways:
- oxidation of one of the ring methyl groups,
- ring hydroxylation,
- hydrolysis of the methyl ester and ether bonds.
The metabolites formed are then conjugated with sugars.
The metabolism seems faster on leaves of grapevines than on grapes.

B.6.1.2 Metabolism, distribution and expression of residues of metalaxyl in lettuce

Fate of metalaxyl (CGA 48 988) in lettuce (Gross D., 1979a).
Identification of degradation products of metalaxyl (CGA 48 988) (RIDOMIL^{R}) in lettuce (Gross D., 1980).
Guidelines :
not specified
GLP :
No - not required at the time the study was conducted.
Material and Methods :
Test substance : ^{14}C(phenyl)-metalaxyl.
Experimental design :
The study was carried out in Switzerland.
Glasshouse grown lettuce were treated twice with ^{14}C-phenyl-metalaxyl at a rate of 0.25 kg a.s./ha for each application.
The plants were harvested 14 days after the second application.
Extraction procedure :
The radioactivity in green plant parts was determined by radiocombustion analysis. Extraction was carried out with methanol/water and followed by partition with hexane and methylene chloride.The water soluble residues were treated with cellulase. The level of radioactivity in the different fractions was determined by liquid scintillation counting.
The radioactivity present in the different organic phases was characterized by TLC and fractionated by HPLC. The nature of degradation products was determined by GC/MS with reference compounds.

Findings :

Table B.6.1-2 : Investigation of the nature and the amounts of residues of metalaxyl (CGA 48988) in lettuce following a treatment at a field rate of 0.25 kg a.s./ha (residues expressed as mg metalaxyl equiv./kg).

Sample	Lettuce leaves		
Total radioactive residues (mg metalaxyl equiv./kg)	5.5		
Extractability of residues with methanol/water (%TRR)	74.4		
Organosoluble hexane partition phase	18.6		
Organosoluble CH_2Cl_2 partition phase	21.6		
Water soluble phase	34.2		
Elucidation of the radioactive residues (% of TRR)			
Compounds	Free	Conjugated	Total
Metalaxyl (CGA 48988)	18.6	-	18.6
CGA 37 734	1.2	1.7	2.9
CGA 67 869	4.5	4.4	8.9
CGA 94 689	5.1	20.0	25.1
CGA 100 255	2.7	3.5	6.2
CGA 62 826	4.6	1.4	6.0
CGA 107 955	3.9	6.2	10.1
CGA 108 905	1.2	-	1.2
Unknowns			0.4
Unextracted radioactive residues (% TRR)			
	-	-	23.6
Total recovery (extracted +unextracetd residues)			98

Metalaxyl undergoes an important degradation in lettuce. 14 days after the application the parent compound represents only 20% of the total residues. Several metabolites are formed, existing in both free and conjugated forms. A chemical structure could be assigned to each of them by GLC/MS.

Conclusions :

The major constituants of the residue in/on lettuce were metalaxyl and its metabolite CGA 94689 (in free and conjugated forms) 14 days after application. The degradation of CGA 48 988 in lettuce proceeds via:

- hydroxylation of the phenyl ring;
- oxidation of a ring methyl group;
- cleavage of the methylester and methylether bonds;
- N-dealkylation.

The metabolites formed are conjugated with sugars.

B.6.1.3 Metabolism, distribution and expression of residues metalaxyl in potato plants

Metabolism of metalaxyl (CGA 48 988) in field grown potato plants (Gross D., 1977).
Identification of metabolites of metalaxyl (CGA 48 988) (RIDOMIL^{R}) in field grown potato plants (Gross D., 1979c).
Guidelines :
not specified
GLP :
No - not required at the time the study was conducted.
Material and Methods :
Test substance : (^{14}Cphenyl)-metalaxyl.
Experimental design :
The study was carried out in Switzerland.
Plants of potatoes received 4 foliar sprays of ^{14}C-(phenyl)-metalaxyl at a rate corresponding to 0.0625 kg a.s./ha.
47 days after the final application leaves, stalks, roots and tubers were sampled.
Extraction procedure :
The total radioactivity in the various plant parts was determined by liquid scintillation counting.
Leaves and tubers were extracted with methanol/water. After evaporation of methanol the aqueous residue was partitioned with methylene chloride at pH 6 and 3 as well as with ethyl acetate. The remaining water soluble residues were treated with cellulase.
Ion-exchange chromatography and HPLC were used to fractionate the residues. TLC and GLC/MS with reference compounds allowed the identification of the degradation products.
Findings:
Table B.6.1-3 : Investigation of the nature and the amounts of residues of metalaxyl (CGA 48988) in potatoes plants following a foliar treatment at a field rate of 0.0625 kg a.s./ha (residues expressed as mg metalaxyl equiv./kg).

Samples	Leaves	Stalks	Roots	Tubers
TRR: Total radioactive residues (mg metalaxyl equiv./kg)	2.35	0.05	0.06	0.02
Extractability of residues with methanol/water (% of TRR in sample)				
	83.0	Extraction not performed		80
Organosoluble CH2Cl2/EtoAc partition phase - pH3	67.6			
Organic soluble CH2Cl2/EtoAc partition phase - pH6	9.7			
Water soluble phase	5.8			
Elucidation of radioactive residues (% of TRR in whole plant)				
Metalaxyl (CGA 48988)	3.0	Identification not performed		
CGA 62 826	15.0			
CGA 94 689	6.3			
CGA 108 905	47.6			
CGA 108 906	5.0			
Not identified organosoluble metabolites	0.3			
Sugar conjugates (nature not elucidated)	5.8			
Unextracted radioactive residues				
	17.0	Extraction not performed		20

Total recovery (total extracted +URR)	100		

Metalaxyl is extensively metabolized in potatoes. 47 days after the final application the parent compound represented only3 % of the total radioactive residues. The radioactivity in tubers was very low but accounted for 7% of the residues in/on the whole plant, indicating a limited basipetal transport.
The nature of the residues present on leaves has been elucidated by TLC and GLC/MS. The major compound present was CGA 108 905, resulting from the oxydation of one of the ring methyl groups. The metabolites formed were present in both free and conjugated forms.
The residues in tubers consisted in polar compounds (80% of the radioactivity in tubers was extractable with methanol/water. However this extractable radioactivity was not partitionable into methylene chloride).
In stalks, roots and tubers the level of radioactivity was very low in comparison with the leaves so that no identification of the nature of the residue was performed on those matrices.

Conclusion:
The major compound present on potato leaves 47 days after foliar treatment with metalaxyl was CGA 108905. Two degradation pathways of metalaxyl are observed in potatoes:
- ring methyl oxidation and further oxidations of the benzylalcohol group to give acidic metabolites,
- hydrolysis of the methylester bond.
The metabolites formed are predominantly present as free metabolites.

B.6.1.4 Metabolism, distribution and expression of residues of metalaxyl in potato plants

Uptake, balance and metabolism of φ-^{14}C-CGA-48988 in field grown potatoes (Honeycutt R., 1981).
Guidelines :
not specified
GLP :
No - not required at the time the study was conducted.
Material and Methods :
Test substance : (^{14}Cphenyl)-metalaxyl.
Experimental design :
The study was carried out in the United States.
2 plots of potato plants were treated 6 times by foliar spray with ^{14}C-phenyl-metalaxyl at respective total rates of 0.426 (1x rate) and 1.28 (3x rate) kg a.s./ha. The first application occured 6 weeks after planting and the last one was carried out one week before the harvest.
Mature tubers and foliage were sampled. Tubers were brushed free of soil in the field and washed in the laboratory.
Extraction procedure :
The total radioactivity in the tubers and foliage was determined by liquid scintillation counting after extraction.
Biphasic extractions of foliage samples were made to give organic, aqueous and non extractable fractions. Tubers were extracted with methanol/water. After evaporation of methanol the aqueous residue was partitioned with methylene chloride at pH 6 and 3. Extracts were analyzed by two-dimensional TLC. Reference compounds were co-chromatographed on the plates.

Findings:

Table B.6.1-4 : Investigation of the nature and the amounts of residues of metalaxyl (CGA 48988) in potatoes plants following 6 foliar treatment at field rates of 0.426 kg a.s./ha (1x rate) and 1.28 kg a.s./ha (3 x rate) (residues expressed as mg metalaxyl equiv./kg).

	Foliage		Tubers	
	(1x rate)	(3x rate)	(1x rate)	(3x rate)
TRR: Total radioactive residues (mg metalaxyl equiv./kg)	5.7	31.9	0.14	0.5
Extractability of residues (%TRR)	not performed			
Organosoluble phase		43.5	44.2	50.0
Aqueous soluble phase		63.8	34.3	33.0
Elucidation of radioactive residues (% of TRR in sample)				
Metalaxyl (CGA 48988)	Identification not performed	2.2	Identification not performed	57
CGA 100 255		2.7 (0+2.7)*		4.4 (4.0+0.4)*
CGA 62 826		-		2.8
CGA 94 689 (2 atropisomers)		50.6 (20.2+30.4)*		4.1 (1.6+2.5)*
CGA 108 905		<0.2		0.6
CGA 108 906		-		0.6
CGA 107 955		1.9 (1.0+0.9)*		2.0
Different aqueous soluble		20.3		6.6
unresolved		1.8		4.3
Non-extractable		5.3	14.7	10.0
Total recovery (organic/aqueous phases+non-extractable residues)		112.6	93.2	93

()*: free + glucose conjugates
- : Not radiodetected

As in the study carried out in Switzerland metalaxyl was extensively degraded in foliage. CGA 94 689 was the major radioactive compound present on leaves indicating that oxydation of the ring methyl group is a major way of degradation. A lot of other metabolites were present at lower levels.

In tubers residues resulting from translocation from the soil and/or the foliage were present. The parent compound accounted for 50% of these residues. Metabolites were similar to those observed in foliage.

Conclusion:

The major compound present on potato leaves 7 days after foliar treatment with metalaxyl was CGA94689 (in free and conjugated forms). In tubers, the metabolism of metalaxyl was less extensive than in foliage; the parent compound itself was the major constituant of the residue.

The degradation of metalaxyl in this study followed 3 pathways:

- hydroxylation of the phenyl ring;
- oxidation of a ring methyl group;
- cleavage of the methylester and methylether bonds.

Metabolites formed are then conjugated with glucose.

The ratio between the different degradation products is not the same as in the Swiss study. This can be due to the varieties of potatoes used, the local growth conditions and the different experimental conditions (PHI...).

B.6.1.5 Metabolism, distribution and expression of residues of metalaxyl in potato plants

Balance and metabolism of ^{14}C-(Phenyl)-metalaxyl in potatoes (Fischer W.C. and Cassidy J.E., 1978c)
This study was not considered in this monograph as the identification of the metabolites was not conducted in details.

B.6.1.6 Metabolism, distribution and expression of residues of metalaxyl in tobacco plants

-Uptake, balance and metabolism of φ-^{14}C-CGA-48988 and its metabolites in greenhouse grown bright and burley tobacco (Seim V. And Honeycutt R., 1978).
-Characterisation of polar metabolites φ-^{14}C-CGA-48988 in greenhouse grown bright tobacco (Honeycutt R., 1978c).
-Identification of the major aglycones of φ-^{14}C-CGA-48988 conjugated metabolites in cured greenhouse grown bright tobacco (Honeycutt R., 1979b).
Guidelines :
not specified
GLP :
No - not required at the time the study was conducted.
Material and Methods :
Test substance : ^{14}C(phenyl)-metalaxyl.
Experimental design :
The study was carried out in the United States.
The behaviour of metalaxyl in plants after soil treatment was studied in glasshouse bright and burley tobacco.
The substance was applied as soil treatment at transplanting (on bright tobacco, rates of application corresponding to 0.28 and 0.56 kg a.s./ha) and as preplanting soil incorporation treatment (on burley tobacco, rate of application corresponding to 3.53 kg a.s./ha).
Leaves were sampled at regular intervals from 3 to 20 weeks after the transplanting. The last three samplings were primings of the bottom, middle and top leaves respectively.
Bright leaves were oven cured and burley leaves were air dried.
Extraction procedure :
The samples were extracted with methanol/water followed by solvent partitioning to give organic, aqueous and non extractable phases. The radioactivity in the extracts was determined by liquid scintillation counting.
The radioactivity present in the extracts was characterized by two-dimensional thin layer chromatography. The effect of enzymatic treatment by cellulase and β-D-glucosidase as well as of acid hydrolysis on the chromatographic behaviour of the aqueous fractions was investigated. The major aglycones formed after cellulase hydrolysis were identified by GLC-Mass Spectroscopy.

Findings:

Table B.6.1.6-1 : Balance and characterization of ^{14}C-(phenyl) metalaxyl in greenhouse bright tobacco -Transplant water treatment

Rate of application (kg a.s./ha)	0.28 kg a.s./ha								0.56 kg a.s./ha							
Samples	Leaves		Lower leaves		Mid. leaves		Upper leaves		Leaves		Lower leaves		Mid. leaves		Upper leaves	
			uncured	cured	uncured	cured	uncured	cured	uncured	cured	uncured	cured	uncured	cured	uncured	cured
Pre Harvest Interval (weeks)	3	6	12	12	18	18	20	20	3	6	12	12	16	16	19	19
Total radioactive residues (mg/kg metalaxyl equiv.)																
	35.3	15.2	7.8	69.3	-	69.6	-	36.6	73.9	32.6	14.1	147.7	-	74.0	-	93.7
Extractability of residues (%TRR in plant sample)																
Organosoluble phase	67.1	65.8	53.4	47.8	-	18.9	-	25.6	73.4	73.5	56.2	31.3	-	24.2	-	34.0
Aqueous soluble phase	27.2	20.7	40.5	44.8	-	76.4	-	73.4	25.1	29.6	46.8	49.6	-	60.7	-	64.6
Elucidation of radioactive residues (%TRR in plant sample)																
Metalaxyl (CGA 48988)	-	-	38.4	34.5	-	-	-	-	64.7	58.2	34.7	26.9	-	10.9	-	-
Organosoluble metabolites (at least 7 compounds)	-	-	-	12.5	-	-	-	-	-	-	-	-	-	9.9	-	-
Polar metabolites (at least 25 compounds)	-	-	39.1	38.2	-	-	-	-	22.2	24.3	43.7	45.2	-	-	-	-
Major compounds:																
IV			5.4	4.6					1.7	2.7	4.7	6.5				
V			3.3	3.5					1.0	0.8	2.5	3.2				
VI			11.0	6.1					5.7	7.7	13.5	6.9				
VII			2.6	1.9					1.8	2.2	3.3	2.8				
VIII			2.9	2.4					0.8	3.2	3.2	3.0				
XIII			1.8	3.3					-	-	2.9	3.2				
Unextracted radioactive residues (%TRR)																
	1.7	1.6	2.7	5.9	-	9.6	-	5.2	1.3	2.0	2.4	9.9	-	12.2	-	6.5
Total recovery (extracted +unextracted residues)	96	88.1	96.6	98.5	-	104.9	-	104.2	99.8	105.1	105.4	90.8	-	97.1	-	105.1
-: result not available																

Tables B.6.1.6-2 : Balance and characterization of ^{14}Cphenyl metalaxyl in greenhouse burley tobacco - preplanting soil

incorporation treatment.

Rate of application (kg a.s./ha)	3.53 kg a.s./ha							
Sample	Leaves		Lower leaves		Middle leaves		Upper leaves	
			uncured	cured	uncured	cured	uncured	cured
Pre Harvest Interval (weeks)	3	6	12	12	13	13	16	16
Total radioactive residues (mg/kg metalaxyl equiv.)								
	23.4	31.3	15.0	161.8	-	110.7	-	80.2
Extractability of radioactive residues (%TRR)								
Organosoluble phase Aqueous soluble phase	73.5 19.0	53.9 37.1	49.4 44.6	43.6 44.7	- -	- -	- -	41.3 47.9
Elucidation of radioactive residues (%TRR)								
Metalaxyl (CGA 48988)	61.2	38.9	32.9	28.1	-	-	-	-
Organosoluble metabolites	-	-	-	-	-	-	-	-
Polar metabolites (at least 25 compounds) Major compounds: IV V VI VII	13.9 0.7 - 4.6 2.0	30.8 3.6 1.2 10.3 3.0	41.8 5.4 2.2 12.0 4.7	36.3 5.4 3.0 7.5 3.1	-	-	-	-
Unextractable radioactive residues (%TRR)								
	1.6	2.1	2.1	7.8	-	-	-	9.4
Total recovery (extracted + unextracted residues)	94.1	93.1	96.1	96.1	-	-	-	98.6
-: result not available								

Table B.6.1.6-3 : Quantification and identification of the major constituants of the radioactive residues in cured leaves from greenhouse bright tobacco (19 weeks after transplant water treatment - application rate : 0.56 kg a.s./ha) and after cellulase hydrolysis of the aqueous extract.

Radioactive fraction	Nature of the radioactive aglycones	% of total radioactivity in leaves
hexane extract	parent	15
I'a	unknown	1.0
I'	unknown	8.8
II'	CGA 100255	14.7
II'a	unknown	1.5
III'	CGA 94 689 (atropisomer A)	4.7
III'a	unknown	1.5
IV'	CGA 94 689 (atropisomer B)	10.6
V'	unknown	4.2
V'a	unknown	2.2
V'b	unknown	4.1
VI'	CGA 107 955	16.0
VII	unknown	0.8
VIII'	unknown	1.1
IX'	unknown	0.4
Total		86.6

Residues were present in all samples of leaves in a rather high level; what is in accordance with the systemic nature of metalaxyl. The highest levels of radioactivity were observed in the first formed leaves.
Metabolism of metalaxyl in tobacco resulted in the formation of many organosoluble and polar metabolites. At least 7 organosoluble and 25 polar metabolites were observed although the parent compound remained a major constituant of the residue all over the study. The relative amount of polar compounds increased with time.
Cellulase hydrolysis of the polar conjugates of uncured tobacco 12 weeks after treatment released 9 aglycones, 6 of which corresponding to 6 unconjugated metabolites. The amount of sugar conjugated compounds was 14% of the total leaf radioactivity 3 weeks after treatment and 31% at 12 weeks (mature stage). The absence of effect of other types of enzymes indicated the absence of glucuronides, proteins and sulfate conjugates.
GLC-MS carried out after cellulase digestion allowed the identification of 4 key aglycones II', III', IV' and VI' (table B.6.1.6-3).
Curing increased the residue level by a factor of about 10, due to a loss of water during the process. The effect on the nature of the residues was however minor.
Bright and burley tobaccoes had the same qualitative and quantitative pattern of polar metabolites, indicating that the species of tobacco or the type of soil treatment has no influence on the metabolic pattern.
Conclusion:
Metalaxyl can be considered as a major constituant of the residue of tobacco after soil treatment.
The degradation of metalaxyl in tobacco after soil treatment follows basically the same pathways as already observed on other plants after foliar treatment. Competitive hydrolysis, oxidation and hydroxylation of metalaxyl lead to a multiplicity of metabolites which are acids, alcohols and phenols and which are converted to multiple sugar

conjugates.

- Uptake and balance of φ-^{14}C-CGA-48988 and its metabolites in field grown bright tobacco (Honeycutt R., 1979a).
Guidelines :
not specified
GLP :
No - not required at the time the study was conducted.
Material and Methods :
Test substance : ^{14}C(phenyl)-metalaxyl.
The study was carried out in the United States.
Plants of tobacco were transplanted on a soil that had been previously treated with the test substance at a rate corresponding to 3.36 kg a.s./ha. Leaves were collected 5, 9 (bottom leaves), 13 (middle leaves) and 16 (top leaves) weeks after transplanting and were oven cured.
Leaves were extracted to give organic, aqueous and non extractable phases. The organosoluble extracts were analyzed by 2 dimensional TLC (CGA48988 and other selected standards were used for co-chromatography).
Findings:
Table B.6.1.5-4 :Balance and characterization of φ-^{14}C-CGA-48988 in field grown bright tobacco - Soil incorporation before transplantation

Rate of application (kg a.s./ha)	3.36 kg a.s./ha						
Sample	Leaves (uncured)	Lower leaves		Middle leaves		Upper leaves	
		uncured	cured	uncured	cured	uncured	cured
Pre Harvest Interval (weeks)	5	9	9	13	13	16	16
Total radioactive residues (mg metalaxyl equiv./kg)	12.5	6.7	21.5	4.0	10.3	1.7	7.3
Extractability of residues	(%TRR in plant sample)						
Organosoluble phase Aqueous soluble phase	49.1 43.0	38.4 49.1	14.9 50.3	42.0 47.0	13.3 80.0	31.0 67.5	13.1 71.2
TLC characterization	(%TRR in plant sample)						
Metalaxyl (CGA48988)	-	-	7.5	-	4.3	10.0	3.3
organosoluble metabolites	-	-	-	-	-	-	-
polar metabolites (at least 25 compounds) Major compounds: IV V VI VII	- - - - -	- - - - -	42 13.7 1.1 9.2 4.1	- - - - -	- - - - -	- - - - -	- - - - -
Non extractable (%TRR)	5.0	3.9	20.3	2.5	11.5	4.5	10.4
Total recovery (extracted + unextracted phases)	97.1	91.4	85.5	91.5	104.8	103	94.7
-: result not available							

Radioactive residues in the leaves decreased with time due to dilution during growth. The levels of radioactivity in the bottom leaves were higher than in the top leaves.
The metabolism of metalaxyl resulted in the formation of many polar metabolites. The contribution of the parent compound to the total radioactive residues was lower than in the previous study carried out under glasshouse

conditions, probably indicating a faster metabolism in field conditions.
TLC profiles of the extracts were qualitatively very similar to those observed with glasshouse grown bright tobacco. Curing the leaves increased the radioactivity by about three times. The level of non extractable radioactivity increased significantly during this process; this increase is probably due to occlusion of φ-^{14}C-CGA-48988 and its metabolites during the process.
Conclusion:
The metabolism of metalaxyl in tobacco under field conditions can be considered qualitatively similar to the metabolism under glasshouse conditions.

The metabolic pathway of metalaxyl in grapevine, lettuce, potato and tobacco is presented in fig. 6.1. in appendix D to this section.

B.6.2 Metabolism, distribution and expression of residues in livestock (Annex IIA 6.2)

B.6.2.1 Metabolism, distribution and expression of residues in lactating cows or goats

Metabolism of [φ-^{14}C]-metalaxyl in goats (Emrani J., 1990).
Supplemental report on the metabolism of [φ-^{14}C]-metalaxyl in goats - Identification of the major metabolite "A" (Emrani J., 1991).
Guidelines :
US EPA Pesticide assessment Guidelines, Subdivision O, Residue Chemistry, Series 171-4(a), Nature of residue, Animals: 40 CFR 158.125
GLP :
The work performed after October 1989 was conducted in accordance with EPA Good Laboratory Practices Standards - 40 CFR 160.
The work conducted before October 1989 was performed in accordance with good and acceptable scientific practices.
Material and Methods :
Test substance : ^{14}C(phenyl)-metalaxyl.
Experimental design :
2 lactating goats received a daily dose corresponding to 3.9 mg/kg body weight (approximately 76.9 mg/kg in the feed) of test substance for 4 consecutive days. These doses were administered in gelatine capsules by balling gun. Urine and faeces were collected daily. Milk samples were collected in the morning and afternoon. The animals were sacrificed 6 hours after the last dose and samples of blood, leg muscle, tenderloin, gall blader, liver, kidney, omental and perirenal fat, heart and rumen were taken.
Extraction procedure :
Radioactivity in urine, milk and extracts of tissues was measured directly by liquid scintillation counting. Radioactivity in tissues was determined by combustion and liquid scintillation counting.
Different solvents were used to extract and partition the radioactivity present in samples.
All extracts were digested by glucuronidase before being partitioned with ethyl acetate, dichloromethane and analyzed by TLC. Protease was also used on the protein precipitate of milk and on the post extraction solids of liver as they still contained high amounts of radioactivity. The ethyl acetate soluble residues released by this way were also analyzed by TLC.
Metabolites were characterized by 2 dimensional TLC and one dimensional reverse phase TLC by co-chromatography with reference compounds.
Column chromatography, HPLC and GC/MS were used to confirm the structure of metabolites.

Findings:

Table B.6.2.1-1 : Recovery of radioactivity from goats after oral administration of ^{14}C(phenyl)-metalaxyl (% of total administered radioactivity).

	Goat 1	Goat 2	Average
Urine	64.8	68.3	66.6
Faeces	10.2	8.3	9.3
Milk	0.07	0.13	0.10
Total excretion	*75.1*	*76.7*	*75.9*
Tissue residues	1.1	0.6	0.8
Blood	0.2	0.1	0.2
Rumen/intestin. contents	3.8	3.8	3.8
Total recovery	80.2	81.2	80.7

Table B.6.2.1-2 : Level and extractability of residual radioactivity in tissues of goats after oral administration of ^{14}C (phenyl)-metalaxyl.

Tissue	Milk		Liver		Kidney		Muscle		Fat	
Goat number reference	1	2	1	2	1	2	1	2	1	2
Total radioactive residues (mg metalaxyl equiv./kg)	0.12	0.42	1.92	1.37	2.30	1.06	0.14	0.07	0.40	0.10
Extractability of radioactive residues (%TRR)										
Methanol/H_2O (80/20) phase		-	45.4	25.4	98.3	93.2	92.8	88.5	96.8	
Acetonitrile phase		74.4	-	-	-	-	-		-	
Partition of extracted residues after glucuronidase digestion (%TRR)										
Ethyl acetate partition phase*		10.3	12.8	2.8		24.3		41.8	30.6	
Dichloromethane partition phase*		37.8	15.3	16.8		54.6		26.3	51.5	
Aqueous soluble phase		26.4	17.2	5.8		14.3		20.4	14.7	
Post extraction residue		25.6	54.6	74.6	1.7	6.8	7.2	11.5	3.2	
Protease digestion (%TRR)										
Ethyl acetate soluble residues released*		17.7	10.5	14.4	Protease digestion not performed on kidney, muscle and fat samples					
Aqueous soluble residues released		1.8	36.4	54.1						
Final solid residue (%TRR)		2.5	7.8	6.1						
*Fractions used for TLC characterization and metabolite identification										

Table B.6.2.1-3 : Summary of metabolite characterization in tissue, milk and urine of lactating goats orally dosed with ^{14}C-metalaxyl at 3.9 mg/kg body weight.

Samples	Total radioactive Residues (mg/kg)	Metabolite fractions (%TRR)										Total %
		CGA 67869	CGA 94689 Isomer A	CGA 94689 Isomer B	CGA 100255	CGA 37734	CGA 62826	CGA 107955	Unknown organo-solubles	Unknown aqueous solubles	non extracted	
Muscle	0.07	8.7	3.9	8.2	5.4	8.3	10.9	18.4	3.8	20.4	11.5	99.5
Liver goat 1	1.92	2.8	nd	nd	14.5*		nd	15.8	6.0	53.6	7.8	100.5
Liver goat 2	1.37	1.8	3.5	4.5	5.1*		1.6	13.5	3.9	59.9	6.1	99.9
Kidney	1.06	3.4	11.7	22.5	2.7	0.7	0.7	31.5	6.1	14.3	6.8	100.4
Fat	0.4	13.3	6.2	8.2	3.4	6.8	3.1	29.6	11.6	14.7	3.2	100.1
Milk	0.42	70	2.3	3.8	8.7*		0.4	4.6	2.3	Not available		92.1
Urine	-	3.9	8.7	19.3	1.7*		1.6	42.8	9.6	12.8	-	100.4

nd = not detected
* : include both CGA 100255 and CGA 37734

6 Hours after the last dose 80% of the total administered radioactivity was recovered in excreta, milk and tissues (table B.6.2.1-1). There is no explanation for lacking 20%. The amount of radioactivity recovered in milk and tissues was 1% of the dose.
The residue levels in tissues were the highest in liver and kidney (respectively 1.64 and 1.68 mg metalaxyl equivalent/kg). The amount of residues in milk increased to reach 0.12 and 0.42 mg metalaxyl equivalent/kg for goats 1 and 2 respectively.
Combined extraction with polar solvents and digestion with protease allowed the solubilization of most of the radioactivity (table B.6.2.1-2). The extracted material from all tissues was digested by glucuronidase before being partitioned with other solvents. For that reason the level of conjugation of the metabolites with glucuronic acid in tissues is not known.
In urine TLC analysis before and after glucuronidase treatment revealed that most of the metabolites were present as glucuronic acid conjugates. Sulfuric acid conjugates were not detected. The major metabolites in urine were identified as CGA 107 955 (42.8%) and the 2 isomers of CGA 94 689 (8.7 and 19.3%). 4 Other metabolites were also present in lesser quantities (table B.6.2.1-3).
In milk and edible tissues the parent compound was never found. The same metabolites as those observed in urine were present. Globally, the major metabolite was CGA 107 955 in liver, kidney, fat and muscle. In milk the major metabolite was a C8 and C10 fatty acid conjugate of CGA 67 869, representing 67.5% of the milk residues. The part of the radioactivity allocated to identified compounds varies from 30% (liver) to 90% (milk). The not identified part of the radioactivity consists mainly in polar and non extractable compounds.

Conclusion. :
Metalaxyl was efficiently degraded in the goat. A large number of metabolites were formed reflecting the existence of several degradation pathway. The parent compound is hydrolysed to the ester alcohol and the acid alcohol which may be N-dealkylated. Alternatively, oxidation of the phenyl ring can lead to benzylic alcohol and hydroxylation of the phenyl ring to phenolic derivatives.

Many metabolites are present as conjugated compounds (to glucuronic acid in urine, lipophilic conjugates in milk, amino acid conjugates in milk and liver).
Enzymatic treatment of urine led to the identification of 7 metabolites (CGA 107955-67869-62826-100255-37734 and both isomers of CGA-94689).
All these metabolites were identified in rat urine.
The metabolic pathway of metalaxyl in the lactating goat can be considered as similar to that identified in the rat.

B.6.2.2 Metabolism, distribution and expression of residues of metalaxyl in hens

Metabolism of [φ-^{14}C]-metalaxyl in hens - Report ABR-90077(Kennedy E., 1990).
Supplemental report on the metabolism of [φ-^{14}C]-metalaxyl in hens - Report ABR-91077 (Kennedy E., 1991).

Guidelines :
US EPA Pesticide assessment Guidelines, Subdivision O, Residue Chemistry, Series 171-4(a), Nature of residue, Animals: 40 CFR 158.125
GLP :
The work performed after October 1989 was conducted in accordance with EPA Good Laboratory Practices Standards - 40 CFR 160.
The work conducted before October 1989 was performed in accordance with good and acceptable scientific practices.
Material and Methods :
Test substance : ^{14}C(phenyl)-metalaxyl.
Experimental design :
5 Hens received daily oral doses of test substance contained in gelatine capsules for 4 consecutive days. The doses were 6 mg/kg body weight or approximately 100 ppm in feed.
Excreta and eggs were collected daily. Eggs were separated into white and yolks. The animals were sacrificed approximately six hours after the last dose and samples of blood, skin and attached fat, thigh and breast muscle, peritoneal fat, heart, liver, kidney and gizzard were taken.
Total radioactive residues in the various samples were determined by radioactive combustion and liquid scintillation counting.

Extraction procedure :
Various solvents were used to extract and partition the radioactivity present in samples. Enzymes (protease for eggs and kidney, glucuronidase for gizzard and liver, collagenase for liver) and base hydrolysis (lipophilic conjugates in fat and egg yolk) were also used to investigate the conjugated radioactivity.
Identification of the metabolites was carried out on the excreta samples as these contained the highest residue levels. The identification of the organosoluble metabolites was accomplished by co-chromatography with unlabeled standards in both normal phase and reverse phase TLC systems. The TLC patterns of the various tissue extracts were compared by co-chromatography with the corresponding extracts from the hen excreta. Some metabolites, which did not co-chromatograph with standards were isolated and analyzed by GC/MS.

Additional work was carried out in order to elucidate the nature of the major polar metabolites present in excreta eggs and muscle. Extracts from excreta, tissues and eggs were therefore concentrated, defatted and/or desalted by solid phase extraction. This procedure allowed the collection of the majority of the radioactive residue in a single organic phase that was profiled by TLC. The fractions obtained were characterized/identified by NMR, GC-MS, IR and enzymatic hydrolysis (action of glucuronidase, protease, collagenase, lipase and esterase).
Mild base hydrolysis was also performed on conjugated metabolites.
Derivatisation of metabolites by silylation was performed followed by direct analysis on GC/MS.
Findings:

Table B.6.2.2 -1 : Recovery of radioactivity from hens after oral administration of ^{14}C(phenyl)-metalaxyl (% of total administered radioactivity).

Hen	1	2	3	4	5	Mean
Total excreta	87.8	90.1	99.2	89.5	88.3	91.0
Eggs	0.1	0.1	<0.1	0.1	0.1	0.1
Tissue residues	0.9	0.9	0.9	0.9	0.8	0.9
Total recovery	88.8	91.1	100.1	90.5	89.2	92.0

Table B.6.2.2 -2 : Level and extractability of residual radioactivity in tissues of hens after oral administration of ^{14}C-(phenyl)-metalaxyl.

Tissue	Egg yolk	Egg white	Liver	Kidney	Heart	Gizzard	Muscle (thigh+ breast)	Fat	Excreta
Total radioactive residues (mg metalaxyl equivalent/kg)	0.21	0.18	1.39	1.47	0.57	1.41	0.55-0.67	0.25-0.32	-
Extractability of radioactive residues (%TRR)									
Organosoluble phase	68.5 (a)	42.2 (a)	38.2 (b) (c)	39.9 (a)/(c)	27.1	62.3 (a)/ (c)	56.5-61.1	82.0 (d)-67.7	39.8
Water soluble phase	17.2 (a)	45.7 (a)	42.1 (b) (c)	44.4 (a)/(c)	52.9	28.3 (a)/ (c)	34.2-36.9	14.4 (d)-19.6	57.2 (a)/(c)
Unextracted radioactive residues	14.3	12.1	19.7 (b)	15.7	20.0	9.4	4.5-6.5	3.6-12.6	3.1

(a): after protease hydrolysis
(b): after collagenase digestion
(c): after glucuronidase digestion
(d): after base hydrolysis on fat
- : Result not available

Table B.6.2.2 - 3 : Identification and characterization of metabolites of ^{14}C-(phenyl)-Metalaxyl in hens - Initial study

	Metabolite fraction	Excreta	Egg white	Egg yolk	Liver	Gizzard	Kidney	Heart	Breast muscle	Thigh muscle	Fat
	TRR (mg/kg)	N.A.	0.18	0.21	1.39	1.41	1.47	0.57	0.55	0.67	0.25-0.32
	Elucidation of the radioactive residues (% TRR)										
A	Parent	3.5	4.9	7.9	1.3	18.6	-	-	0.4	-	-
B	CGA94689 (A)	0.8	1.4	-	1.0 (sum B+D)	-	-	-	0.4	-	-
C	Unknown	1.7	-	-	0.7	-	0.8	-	-	-	-
D	CGA94689 (B)	2.8	3.0	22.2		0.4	0.7	1.2	1.6	0.6	-
E	Unknown	1.0	-	1.8	-	0.2	0.8	0.9	1.1	0.6	-
F	CGA67869	5.8	-	-	0.7	2.1	1.3	-	-	-	-
G	Unknown	5.3	-	-	-	4.5	2.7	-	30.9	-	-
H	Unknown		-	-	-			4.9		14.8	-
I	Unknown		-	-	-					3.3	-
J	CGA108905	2.3	-	-	-	1.0	0.7	-	-	-	-
K	CGA107955	8.0	-	-	17.1	11.0	5.1	2.1	-	-	60.7
L	CGA108906	7.4	24.8	-	12	7.8	10.0	10.9	17.8	21.6	8.7
M	Unknown			-			3.0				
N *	CGA78532 CGA68124 CGA79353	1.3		-	3.5	21.7	11.5	4.8	3.5	43.8	7.6
Aqueous soluble metabolites		57.2	53.8	12.4	43.5	18.2	45.1	53.9	38.5	8.2	6.6
Unextracted radioactive residues		3.1	12.1	14.3	19.7	9.4	15.7	20.0	4.5	6.5	12.6
Total recovery (Organic + aqueous residues +URR)		100.2	100.0	58.6	99.5	94.9	97.4	98.7	98.7	99.4	96.2

*: The metabolite N consisted of CGA-78532, CGA-68124, CGA-79353.
Fat : TLC patterns showed that the majority of the radioactive material was present in the form of lipophilic conjugates (60.7% of TRR). Mild base hydrolysis yielded primarily to a single metabolite which was identified as CGA-107955 (49.8% of TRR). The other metabolites were not identified.
Egg white : The water fraction, following protease treatment, contained multiple components which were insufficiently resolved by TLC.
Liver : After collagenase and glucuronidase treatments, metabolites in the aqueous layer were unresolved by TLC.
- : result not available
CGA 94689 A/B : atropisomers

Metalaxyl was rapidly eliminated in hens. Within 6 hours after the last dose, 92% of the total administered radioactivity was recovered (table B.6.2.2 -1). The majority of the radioactivity (up to 91%) was recovered in the excreta with 0.9% in the edible tissues and 0.1% in the eggs.
The highest residue levels were found in liver, kidney and gizzards (about 1.4 mg metalaxyl equiv./kg in these tissues) (Table B.6.2.2 -2). In eggs, residues were lower (0.21 mg/kg) but it is possible that a plateau had not been reached since residues were continuously increasing along the 4 days of the dosing.

At least 80% of the radioactivity was extractable by solvents from all the matrices. The amount of residues that were organosoluble and water soluble is given in table B.6.2.2 -2.
Characterization and identification of the radioactive residues in the different tissues revealed the presence of numerous compounds.
Parent compound was present in all matrices except in kidney, heart, thigh muscle and fat where it was not radiodetected. Unchanged metalaxyl accounted for 18.6% of TRR in the gizzard but ranged between 0.4 to 8 % of the total radioactivity in the other tissues.
The hydroxyacid CGA-107955 was found to be the major metabolite in excreta, liver, gizzard and in fat although This metabolite was absent from eggs and muscle.
Metabolites as CGA-94689, CGA-67869, CGA-108905 were also identified.

Additional work reported in the supplemental report on the metabolism of Metalaxyl in hens detailed the chromatographic resolution and isolation of the unknown polar metabolites which made up the majority of the radioactive residues found in the excreta, eggs and tissues.
The objectives of this study was :
1) to identify and quantify the major unknowns in the thigh muscle, eggs and peritoneal fat,
2) to subject the lipophilic conjugates in the yolk and peritoneal fat to lipase and/or esterase hydrolysis and to identify the exocons released by this treatment,
3) to subject the liver to additional enzymatic treatment so as to optimize the extractable residues.

Table B.6.2.2-4 : Identification and characterization of metabolites of ^{14}C-(phenyl)-metalaxyl in hens - Supplemental report.

	Metabolite fraction	Excreta	Egg white	Egg yolk	Liver(a)	Gizzard	Kidney(b)	Heart	Breast muscle	Thigh muscle	Fat
	TRR (mg metalaxyl equiv./kg)	-	0.179	0.360	1.39	1.41	1.47	0.57	0.57	0.674	0.254-0.32
	Elucidation of the radioactive residues (% of TRR)										
A	Parent (CGA48988)	3.5	7.0	2.7	1.3	18.6	-	-	0.4	<0.01	<0.01
B	CGA-94689 (A)	0.8	3.8	0.7	1.0 (Sum B+D)	-	-	-	0.4	<0.01	<0.01
D	CGA-94689 (B)	2.8	5.4	4.02		0.4	0.7	1.2	1.6	<0.01	<0.01
F	CGA-67869	5.8	<0.01	(*)	0.7	2.1	1.3	-	-	<0.01	(*)
J	CGA-108905	2.3	<0.01	2.01	-	1.0	0.7	-	-	<0.01	<0.01
K	CGA-107955	8.0	<0.01	14.5 (**)	17.1	11.0	5.1	2.1	-	<0.01	40.3 (**)
P0	Free acid of CGA-94689	p	6.2	1.34	/	/	/	/	/	<0.01	<0.01
P1***	Isomer A	p	17.82	10.6	/	/	/	/	/	37.3	5.31
P2***	Isomer B	p	13.2	9.6	/	/	/	/	/	9.1	1.8
FAT-U3	Mixture of unresolved P1&P2	p	<0.01	3.62 (**)	/	/	/	/	/	<0.01	26.9(**)
P3a	Glucuronic acid conjugate of CGA-67869	p	<0.01	1.7	/	/	/	/	/	<0.01	0.9
P4	Sulfate of CGA- 94689	p	7.75	4.1	/	/	/	/	/	29.9	8.23
L	CGA-108906	<7.4	<24.8	-	<12	<7.8	10.0	<10.9	<17.8	<21.6	<8.7
Unextracted radioactivity		3.1	12.1	19.7	31.0	9.4	15.7	20.0	4.5	11.4	4.1

- : result not available
p : Present but not quantified.
/ : Metabolites not searched in these tissues.
(*) : Exocons of fat conjugates which may be CGA-67869 or CGA-107955. Pig liver esterase converts CGA-67869 to CGA-107955.
(**) : include metabolites released from fat and egg yolk conjugates. Esterase hydrolysis released the exocons (CGA 107955, P1 and P2).
(***) : P1 and P2, the 2 isomers of N-(2-(hydroxymethyl)-6-methylphenyl)-N-(hydroxyacetyl)alanine.
(a) : after collagenase and glucuronidase treatments
(b) : including protease treatment

Findings :
The parent compound was recovered in all tissues except in kidney and in heart.
Identified metabolites included CGA 94689,CGA 67869, CGA 107955, CGA 108905 and CGA 108906.
The major metabolites P1 and P2 were identified. P4 was identified as the sulphuric acid conjugate of CGA 94689 while the minor metabolite P3a was determined as the glucuronic acid conjugate of CGA 67869.
In fat, the major part of radioactivity was present as lipophilic conjugates. Enzyme treatment released the metabolite CGA 107955 and a mixture of P1 and P2.

It must be noted that the metabolites CGA-78532, CGA-68124 and CGA-79353 which were present in egg white and in muscle at a high level (Report ABR-90077) were not mentioned anymore in the supplemental study (Report ABR-91077).

Conclusion :

The major metabolic pathway in the hen is substantially the same as in the goat but with probably a faster metabolic rate in hen.

It initially involves the processes of oxidation and demethylation of the parent compound.. Sequential demethylation of the ether and the ester groups gives first the alcohol CGA-67869 and then the hydroxyacid CGA-107955. The ester alcohol CGA-67869 undergoes conjugation with both fatty acids and glucuronic acid, the latter labeled as metabolite P3a.

Oxidation of the benzylic carbon of metalaxyl produces the benzylic alcohol CGA-94689 which undergoes sequential demethylation to give metabolites as P0, P1 and P2.

The benzylic alcohol of CGA-94689 also forms the sulfuric acid conjugate, P4 and to a minor extent the acidic CGA-108905 and CGA 108906.

All the metabolites except CGA 108906 were identified in rat urine and in faeces and were therefore out of toxicological concern..

B.6.2.3 Metabolism, distribution and expression of residues of metalaxyl in pigs

No particular degradation pathway has been observed in goat and in laying hens in comparison to rats. Consequently, a pig metabolism study is not required.

The metabolic pathway of metalaxyl in lactating goat and in laying hen is presented in fig. 6.2. in appendix D to this section.

B.6.3 Definition of the residue

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 metabolic pathway of metalaxyl in plants could be considered as sufficiently investigated (figures B.6.1/2/3/4). None of the metabolite formed was of particular toxicological concern as they were generally also produced by the rat. Only one metabolite (CGA 108906) was observed in plants and not in rats. However, this metabolite was not indicative of any particular degradation pathway in plants but resulted from a combination of reactions occuring also in the rat. The toxicological relevance of this metabolite has been adressed by an acute short-term oral toxicity study in the rat. The result showed an LD50 in rats (both sexes) as >2000 mg/kg body weight.

Methods of analysis for residues in plant commodities were available allowing to determine the parent compound. A total method also exist to determine all metabolites containing the 2,6-dimethylaniline moiety.

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

Conversion factors for assessment of consumer safety (calculation based on the ratio extractable residues/residue to be monitored) :

-grapes : 2
-lettuce : 4
-potato tuber : 1

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 by the rat.
An extensive metabolization of the parent compound was also observed in laying hens.
One metabolite, the CGA-108906, not present in rat metabolism, was also observed but as in plant products, this metabolite was not indicative of any particular degradation pathway in animals.

A method of analysis for the determination of total residues of metalaxyl as 2,6-dimethylaniline is available.
This method is suitable for total metalaxyl residues analysis in eggs, muscle tissue, fat/skin but is not sufficiently validated in the case of liver and milk.

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.
Taking into account the relevant metabolites in the residue definition would increase the work of laboratories.

Conversion factor for commodities of animal origin : 1

Regarding the liposolubility of metalaxyl, no fat soluble metalaxyl-M residue could be drawn with the value of the partition coefficient n-octanol/water which is <3 (log K*ow* = 1.71 at pH 7.6).

B.6.4 Use pattern

The tables B.6.4-1, B.6.4-2, B.6.4-3 present all the intended uses of metalaxyl-M. However at this time the data package which was submitted by the notifier does not allow a full evaluation of all these uses.

Table B.6.4.1 Intended uses of metalaxyl-M in the EU - Foliar Application

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
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	0.7 g a.s. per tree	2		15

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
		treated)				
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, Portugal	0.094 - 0.12	0.28 - 0.36	3		3 - 21
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,	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

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
	Spain, Sweden, UK					
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, Italy, Portugal, Spain	0.04 - 0.15 kg a.s./ha	0.6 kg a.s./ha	3 - 4	from start of first disease	3 - 28
Watermelon (foliar spray)	France, Italy	0.094 - 0.12	0.28 - 0.36	3		3 - 21

Table B.6.4.2 : Intended uses of metalaxyl-M in the EU - Soil Application

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

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
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
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	12 g a.s. /m^3 soil in potting mix,	1		

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
		to 7.5 kg a.s. / ha (containers greenhouses only)[1]	0.1 g / m^2 and up to 7.5 g a.s. / ha (containers greenhouses only)			
Ornamentals - Flowers (soil application)	Italy	0.05 - 1 g a. I. / m^2	3 g a.s. / m^2	1 - 3	at sowing	
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,	0.18 - 1 kg a.s./ha	1 kg a.s./ha	1 - 2	pre and post planting	15 - 60

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
	Spain					
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 application)	Italy	0-05 - 0.1 g a.s. / m^2	0.2 g a.s. / m^2	2	at sowing or pre planting	3

Table B.6.4.3 : 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	-

B.6.5 Identification of the critical GAPs

The critical GAPs mentioned hereafter concerned the crops for which metalaxyl-M residue trials were submitted.

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
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
Peach (= Stone Fruit in Spain) (soil application)	Italy, Spain	1 g a.s. / m^2	2 g a.s. / m^2	2	root growth flushes	15
Grapes (foliar spray)	Austria, France, Germany, Greece, Italy, Portugal, Spain	0.12 kg a.s./ha	0.42 kg a.s./ha	4	pre and post flowering	15
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
Carrot (soil application)	France, Ireland, UK	0.6 kg / ha	0.6 kg / ha	2	4 - 6 weeks after drilling	30
Onion (foliar spray)	Austria, France, Germany, Italy, Spain, UK	0.15 kg a.s./ha	0.45 kg a.s./ha	3	first sign of disease	14
Tomato (foliar spray)	France, Greece, Italy, Portugal, Spain	0.15 kg a.s./ha	0. 6 kg a.s./ha	3 - 4	from start of first disease	3
Peppers (soil application)	Italy, Spain (mainly greenhouses	0.1 g a.s. /m^2 0.480 kg	0.3 g a.s. /m^2 1.44 kg	3	pre and post transplanting	15

Crop	Country	Maximum rate per application	Maximum rate per season	Maximum N° of applications per season	Time of application	PHI in days (range)
	in Spain)	a.s./ha	a.s./ha			
Cucumber (foliar spray)	Austria, France, Greece, Italy Portugal, Spain	0.15 kg a.s./ha	0.6 kg a.s./ha	4		3
Melon (foliar spray)	France, Italy, Portugal	0.12 kg a.s./ha.	0.36 kg a.s./ha.	3		3
Broccoli (foliar spray)	Italy	0.1 kg a.s./ha	0.3 kg a.s./ha	3		20
Cauliflower (& calabrese in UK) (foliar spray)	Italy, UK, Ireland	0.1 kg a.s./ha	0.3 kg a.s./ha	3		14
Lettuce (foliar spray)	Belgium, Luxemburg, Germany, Italy, Netherlands	0.125 kg a.s./ha.	0.32 kg a.s./ha.	3		14
Spinach (foliar spray)	Italy	0.1 kg a.s./ha	0.2 kg a.s./ha	2		20
Beans, field (foliar spray)	Ireland	0.1 kg a.s./ha	0.3 kg a.s./ha	3	preventative program	14
Artichoke (foliar spray)	Italy	0.1 kg a.s./ha	0.3 kg a.s./ha	3		20
Leek (foliar spray)	(Belgium), UK	(0.085) kg a.s./ha	(0.255) kg a.s./ha	3	at first sign of disease	14
Potato (foliar spray)	Austria, Belgium, Finland, France, Germany, Ireland, Italy, Luxembourg ,Netherland, Portugal, Spain, Sweden, UK	0.113 kg a.s./ha	0.4 kg a.s. / /ha	5	from start of disease development until before desiccation	7
Tobacco (foliar spray)	Austria, France, Greece, Italy, Portugal	0.15 kg a.s./ha	0.9 kg a.s./ha	6	active growth stage	7

B.6.6 Residues resulting from supervised trials (Annex IIA 6.3; Annex IIIA 8.1)

The presentation of the supervised trials data follows the layout of the report on open positions and MRL proposals for metalaxyl.
In this monograph, the proposals of MRLs for metalaxyl-M are based only on the metalaxyl-M package. The metalaxyl data were mentionned. However, they could not be taken into account in the final assessement (quality of the data, GAPs, trial location)

Analytical methods :
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.
The submitted methods REM 181.01, REM 181.02, REM 181.03 were the only methods that were validated through fortification of untreated samples with metalaxyl-M.
Basically, the methodology consisted of extraction of crop material, clean-up steps of the extract involving partitioning and adsorption chromatography (column or cartridge), and/or preparative Liquid Chromatography, followed by final determination by GC using a N-specific detector.
The evaluation of another method (DFGS19) which was also used in the determination of the parent compound in residue trials was not conducted in point B.4 of this monograph.

Summary tables :
The residue data are summarized according to the standard summary sheets in appendix F to this section.
The figures selected for statistical analysis and MRL proposals are indicated in bold and underlined in the summary sheets.

B.6.6.1 Grapefruit

Metalaxyl-M data
No residue trials were submitted.
No MRL can be proposed.

Metalaxyl data
4 residue trials were performed in Israel and North America. They were not taken into account

B.6.6.2 Lemons

Metalaxyl-M data
No residue trials were submitted.
No MRL can be proposed.

Metalaxyl data
3 residue trials were performed in Chile and North America. They were not taken into account as no residue trials were conducted in Europe.

B.6.6.3 Mandarins (including clementines)

Metalaxyl-M data
Determination of residues of CGA 329351 + Copper (ASF 45), WP 42.5, A-9402 A, Mandarines, Spain-Final report No. 2021/97 (Kühne, R.O., 1998ad).
Determination of residues of CGA 329351 + Copper (ASF 45), WP 42.5, A-9402 A, Mandarines, Spain-Final report No. 2022/97 (Kühne, R.O., 1998ae).
Determination of residues of CGA 329351 + Copper (ASF 45), WP 42.5, A-9402 A, Mandarines, Spain-Final report No. 2023/97 (Kühne, R.O., 1998af).
Determination of residues of CGA 329351 + Copper (ASF 45), WP 42.5, A-9402 A, Mandarines, Italy-Final report

No. 2063/97 (Kühne, R.O., 1998ag).
Determination of residues of CGA 329351 + Copper (ASF 45), WP 42.5, A-9402 A, Mandarines, Italy-Final report No. 2064/97 (Kühne, R.O., 1998ah).
Determination of residues of CGA 329351 + Copper, WP 42.5, GR 2.5, A-9402 A ,A-9600 A, Citrus (oranges, mandarins), Spain-Final report No. 126/97 (Kühne, R.O., 1998bq).

GLP: All submitted studies were carried out in compliance with GLP conditions.

6 residue trials were conducted in Spain and in Italy.
Levels of parent compound were determined according to the method of analysis REM 181.01.
Decay curves are given with last sampling 30 days after last application.

5 trials supported the critical GAP of 0.00035 kg a.s./tree, 2 applications and a PHI of 15 days (foliar - skirt spray application).

Results : 0.07-0.12-0.14-0.15-0.20 mg/kg for the whole fruit.
Mean = 0.136 mg/kg
3 x mean = 0.408 mg/kg
R(max) = 0.335 mg/kg
R(ber) = 0.35 mg/kg

No MRL can be proposed (Insufficient data base).

Metalaxyl data
One residue trial was conducted in Italy but couldn't be used in support of the metalaxyl-M uses (soil application).

B.6.6.4 Oranges

Metalaxyl-M data
Determination of residues of CGA 329351, EC 480, A-9408 B, Oranges, Israel-Final report No. 2325/97 (Kühne, R.O., 1998at)
Determination of residues of CGA 329351, EC 480, A-9408 B, Oranges, Israel-Final report No. 2326/97 (Kühne, R.O., 1998au)
Determination of residues of CGA 329351, EC 480, A-9408 B, Oranges, Israel-Final report No. 2327/97 (Kühne, R.O., 1998av)
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A, Oranges, Spain-Final report No. 2033/96 (Kühne, R.O., 1997i)
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A, Oranges, Spain-Final report No. 2034/96 (Kühne, R.O., 1997j)
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A, Oranges, Spain-Final report No. 2035/96 (Kühne, R.O., 1997k)
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A, Oranges, Spain-Final report No. 2036/96 (Kühne, R.O., 1997l)
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A, Oranges, Italy-Final report No. 2071/96 (Kühne, R.O., 1997m)
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A, Oranges, Italy-Final report No. 2072/96 (Kühne, R.O., 1997n)
Determination of residues of CGA 329351 + Copper, WP 42.5, GR 2.5, A-9402 A ,A-9600 A, Citrus (oranges, mandarins), Spain-Final report No. 126/97 (Kühne, R.O., 1998bq).
GLP : All submitted studies were carried out under GLP conditions.

7 residue trials were available from Spain and Italy.
Levels of parent compound were determined according to the method of analysis REM 181.01.
Decay curves are given with last sampling 21 days after last application.

Foliar application / Stem paint :
2 trials supported the critical GAP of 0.0035 kg a.s./tree, 2 applications and a PHI of 30 days.
Results : <0.03-<0.03 mg/kg for the whole fruit.

Foliar application / Skirt spray :
2 trials supported the critical GAP of 0.00035 kg a.s./tree, 2 applications and a PHI of 15 days.
Results : 0.07-0.11 mg/kg for the whole fruit.

3 residue trials concerning a post-harvest application of Metalaxyl-M in "packing house"were performed in Israel. These trials were not taken into account.

No MRL can be proposed (Insufficient data base for both types of application).

Metalaxyl data
25 residue trials were performed in Brazil, Italy, South Africa, North America, Israel, Chile and Spain. They were not taken into account.

B.6.6.5 Apple

Metalaxyl-M data
No residue trials were provided
No MRL can be proposed.

Metalaxyl data

North :
17 residue trials were provided but couldn't be taken into consideration as no metalaxyl-M GAPs for the North of Europe were given.

South :
6 residue trials were performed in Italy and 2 trials could be used in support of the metalaxyl-M GAP of 1 g a.s./tree, 2 applic. and a PHI of 18 days for soil application.

B.6.6.6 Pear

Metalaxyl-M data
No residue trials were provided
No MRL can be proposed.

Metalaxyl data
One residue trial was performed in UK but no metalaxyl-M GAPs were provided for Northern Europe.

B.6.6.7 Apricot

Metalaxyl-M data
No residue trials were provided
No MRL can be proposed.

Metalaxyl data
One residue trial was submitted for North America.

B.6.6.8 Cherries

Metalaxyl-M data
No residue trials were provided.
No MRL can be proposed.

Metalaxyl data
No residue trial was conducted in Europe.

B.6.6.9 Peaches (including nectarines)

Metalaxyl-M data
Determination of residues of CGA 329351, GR 2.5, A-9600 A, Peaches, Spain-Final report No. 2017/97 (Kühne, R.O., 1998aw)
Determination of residues of CGA 329351, GR 2.5, A-9600 A, Peaches, Spain-Final report No. 2018/97 (Kühne, R.O., 1998ax)

GLP : All submitted studies were carried out under GLP conditions.

Levels of parent compound were determined according to the method of analysis REM 181.01.

2 residue trials were conducted on peach in Spain but didn't support the critical GAP of 0.001 kg a.s./m^2, 2 applications and a PHI of 15 days (soil application).

No MRL can be proposed.

Metalaxyl data
6 residue trials were conducted in Italy and in Spain on peach and nectarine. No trial could be used in support of metalaxyl-M uses.

B.6.6.10 Table and wine grapes

Metalaxyl-M data
Determination of residues of CGA 329351 + Copper, WP 42.5 in Grapes (berries) in Italy - Project Report 2124/94 (Kühne, R.O, 1995g).
Determination of residues of CGA 329351 + Copper, WP 42.5 in Grapes (berries) in Italy - Project Report 2125/94 (Kühne, R.O, 1995h).
Determination of residues of CGA 329351 + Copper, WP 42.5 in Grapes (berries, must and wine) in Spain - Project Report 2091/94 (Kühne, R.O, 1995i).
Determination of residues of CGA 329351 + Copper, WP 42.5 in Grapes (berries, must and wine) in Spain - Project Report 2091/94 (Kühne, R.O, 1995i).
Determination of residues of CGA 329351 + Copper, WP 42.5 in Grapes (berries, must and wine) in Spain - Project Report 2092/94 (Kühne, R.O, 1995j).
Determination of residues of CGA 329351 + Copper, WP 42.5 in Grapes (berries, must and wine) in Greece - Project Report 2073/94 (Kühne, R.O, 1995k).
Determination of residues of CGA 329351 + Folpet, WP 45 in Grapes (berries) in Italy - Project Report 2122/94 (Kühne, R.O, 1995l).
Determination of residues of CGA 329351 + Folpet, WP 45 in Grapes (berries) in Italy - Project Report 2123/94 (Kühne, R.O, 1995m).
Determination of residues of CGA 329351 + Folpet, WP 45 in Grapes (berries, must and wine) in Spain - Project Report 2093/94 (Kühne, R.O, 1995n).
Determination of residues of CGA 329351 + Folpet, WP 45 in Grapes (berries, must and wine) in Spain - Project Report 2094/94 (Kühne, R.O, 1995o).
Determination of residues of CGA 329351 + Folpet, WP 45 in Grapes (berries, must and wine) in Germany - Project Report gr 5194 (RR 2180/94)(Leiblein, M, 1995a).
Determination of residues of CGA 329351 + Folpet, WP 45 in Grapes (berries, must and wine) in Germany - Project Report gr 5194 (RR 2181/94)(Leiblein, M, 1995b).
Determination of residues of CGA 329351 + Copper, WP 42.5 (A-9402A) in grapes (berries, must and wine)- Project Report OF94133 (RR 2221/94) (Maffezzoni, M, 1995a).
Determination of residues of CGA 329351 + Copper, WP 42.5 (A-9402A) in grapes (berries, must and wine)- Project Report OF94133 (RR 2222/94) (Maffezzoni, M, 1995b).
Determination of residues of CGA 329351 + Folpet, WP 45 (A-9402A) in grapes (berries, must and wine)- Project Report OF94133 (RR 2219/94) (Maffezzoni, M, 1995c).
Determination of residues of CGA 329351 + Folpet, WP 45 (A-9402A) in grapes (berries, must and wine)- Project Report OF94133 (RR 2220/94) (Maffezzoni, M, 1995d).
Determination of residues of CGA 329351 + Mancozeb, WP 68, A-9407 A in Grapes (berries, must, new wine and wine)in Switzerland - Final report No. 2032/95 (Kühne, R.O., 1997a).
Determination of residues of CGA 329351 + Mancozeb, WP 68, A-9407 A in Grapes (berries, must, new wine and wine) in Switzerland - Final report No. 2033/95 (Kühne, R.O., 1997b).
Determination of residues of CGA 329351 + Mancozeb, WP 68, A-9407 A in Grapes (berries, must and wine) in Switzerland - Final report No. 2017/95 (Kühne, R.O., 1997c).
Determination of residues of CGA 329351 + Mancozeb, WP 68, A-9407 A in Grapes (berries, must and wine) in Spain - Final report No. 2018/95 (Kühne, R.O., 1997d).
Determination of residues of CGA 329351 + Chlorothalonil (ASF 41), WG 56.7 (F 70567) in Grapes in France (North) - Final report No. 2375/97 (Kühne, R.O., 1998j).
Determination of residues of CGA 329351 + Chlorothalonil (ASF 41), WG 56.7 (F 70567) in Grapes in France (North) - Final report No. 2376/97 (Kühne, R.O., 1998k).
Determination of residues of CGA 329351 + Chlorothalonil (ASF 41), WG 56.7 (F 70567) in Grapes in France (North) - Final report No. 2377/97 (Kühne, R.O., 1998l).
Determination of residues of CGA 329351 + Chlorothalonil (ASF 41), WG 56.7 (F 70567) in Grapes in France (North) - Final report No. 2378/97 (Kühne, R.O., 1998m).
Determination of residues of CGA 329351 + Chlorothalonil (ASF 41), WG 56.7 (F 70567) in Grapes in France (South) - Final report No. 2379/97 (Kühne, R.O., 1998n).
Determination of residues of CGA 329351 + Chlorothalonil (ASF 41), WG 56.7 (F 70567) in Grapes in France (South) - Final report No. 2380/97 (Kühne, R.O., 1998o).
Determination of residues of CGA 329351 + Chlorothalonil (ASF 41), WG 56.7 (F 70567) in Grapes in France (South) - Final report No. 2381/97 (Kühne, R.O., 1998p).
Determination of residues of CGA 329351 + Chlorothalonil (ASF 41), WG 56.7 (F 70567) in Grapes in France

(South) - Final report No. 2382/97 (Kühne, R.O., 1998q).
Determination of residues of CGA 329351 + Mancozeb, WP 68, A-9407 A in Grapes (berries, must, new wine and wine) in Italy - Final report No. 2113/95 (Kühne, R.O., 1997e).
Determination of residues of CGA 329351 + Mancozeb, WP 68, A-9407 A in Grapes (berries, must, new wine and wine) in Italy - Final report No. 2114/95 (Kühne, R.O., 1997f).

GLP : All submitted studies were carried out under GLP conditions.

12 and 18 outdoor residue trials were conducted respectively in Northern Europe (France, Germany, Switzerland) and in Southern Europe (Spain, Greece and Italy).
In both regions, trials were made following 4 foliar spray applications at the rate of 0.10 kg a.s./ha. Commodities which were analysed were the berries, must and wine.
Levels of parent compound were determined according to the methods 181.01 for berries and 181.02 for must and wine.

North :
6 residue trials supported the critical GAP of 0.12 kg a.s./ha, 4 applic. and a PHI of 14 to 30 days (foliar application)

The residue values are : <0.02-0.04-0.07-0.19-0.30-0.33 mg/kg for berries.
-14 d PHI : 0.19-0.33,
-28 d PHI : <0.02,
-30 d PHI : 0.04-0.07,
-31 d PHI : 0.30 mg/kg.

Mean = 0.156 mg/kg
3 x mean = 0.469 mg/kg
R(max) = 0.156+3.711 x 0.1382 = 0.669 mg/kg
R(ber) = 0.615 mg/kg

South :
10 trials supported the critical GAP of 0.12 kg a.s./ha, 4 applic. and a PHI of 14 to 39 days (foliar application).

The residue values are : 0.03-0.04-0.05-0.05-0.06-0.09-0.13-0.15-0.21-0.55 mg/kg for berries.
-14 d PHI : 0.04-0.15-0.21-0.55,
-27 d PHI : 0.05,
-29 d PHI : 0.05-0.06,
-30 d PHI : 0.09,
-38 d PHI : 0.13,
-39 d PHI : 0.03 mg/kg.

Mean = 0.136 mg/kg
3 x mean = 0.408 mg/kg
R(max) = 0.15 + 2.815 x 0.1555 = 0.587 mg/kg
R(ber) = 0.42 mg/kg

MRL proposal for grape : 1 mg/kg

Metalaxyl data
87 residue studies were submitted for the North and the South of Europe and also for Israel, South Africa, Morocco.

B.6.6.11 Strawberries

Metalaxyl-M data
Determination of residues of CGA 329351, EC 480, A-9408 B, Strawberries, France (South)-Final report No. OF97102/AC89 (Maffezzoni, M., 1998a)
Determination of residues of CGA 329351, EC 480, A-9408 B, Strawberries, France (South)-Final report No. OF97102/LD10 (Maffezzoni, M., 1998b)

GLP : All submitted studies were carried out under GLP conditions

2 residue trials were conducted in the South of France under plastic tunnel. These trials were made following 2 plant applications at the rate of 0.480 kg a.s./ha.
Levels of parent compound were determined according to the method 181.01 modified.

No study supported the critical GAP of 0.35 kg a.s./ha, 2 applic. and a PHI of 14 days (foliar application).

No MRL can be proposed.

Metalaxyl data
29 outdoor and indoor residue trials were submitted for the North of Europe (Germany, UK, Switzerland, Netherlands) and 8 outdoor trials covered the South of Europe (Spain, Italy and France).

North :
No metalaxyl-M GAPs were provided.

South :
6 outdoor residue trials which were made following 3 foliar spray applications at a rate of 0.350 kg a.s./ha could be used in support of the critical GAP of metalaxyl-M for foliar application (0.35 kg a.s./ha, 2 applic., PHI : 14 days).
Results : 0.06-0.15-0.15-0.18-0.18-0.27 mg/kg for berries.

Mean = 0.165 mg/kg,
3 x mean = 0.495 mg/kg,
R(max) = 0.165+3.711x0.0678 = 0.416 mg/kg,
R(ber) = 0.405 mg/kg.

B.6.6.12 Avocados

Metalaxyl-M data
No residue trials were provided
No MRL can be proposed.

Metalaxyl data
5 residue trials were conducted in North America and in South Africa.

B.6.6.13 Kiwi fruit

Metalaxyl-M data
No residue trials were provided.
No MRL can be proposed.

Metalaxyl data
10 residue trials were conducted in Italy and Greece of which 7 could be used in support of the metalaxyl-M uses (0.001 kg a.s./m^2, 2 applic., PHI of 180 days -soil application).
Results : 7 x <0.02 mg/kg for the whole fruit (trials at 2.55 g a.s./plant, 1-2 applic., PHI : 84-154-160-184-189 days).

B.6.6.14 Sugarbeet

Metalaxyl-M data
No residue trials were submitted.
No MRL can be proposed.

Metalaxyl data

Seed treatment :
6 residue trials were submitted for Northern Europe (France, Germany, UK) and 1 trial was performed in Canada.
4 trials could be used in support of the metalaxyl-M GAP (105 g a.s/100 kg seeds, 1 applic.)
Results : <0.04-<0.04-<0.04-<0.02 mg/kg for tuber.

B.6.6.15 Carrots

Metalaxyl-M data
Determination of residues of CGA 329351 and CGA 48988, FUBOL 58 WP, A-9408 B, A-9407 A, FL-950334, Carrots, United Kingdom - Final report No. FR0695AR (Adams, S.P., 1998c)
Determination of residues of CGA 329351, EC 480, A-9408 B, Carrots, France (South)-Final report No. OF96131/AC19(Pointurier, R., 1998a)

Determination of residues of CGA 329351, EC 480, A-9408 B, Carrots, France (North)-Final report No. OF96131/KJ78 (Pointurier, R., 1998b)
Determination of residues of CGA 329351, EC 480, A-9408 B, Carrots, France (South)-Final report No. OF96131/LD78 (Pointurier, R., 1998c)
Determination of residues of CGA 329351, EC 480, A-9408 B, Carrots, France (North)-Final report No. OF96131/SJ22 (Pointurier, R., 1998d)

GLP : All submitted studies were carried out under laboratories GLP conditions.

5 outdoor residue trials were conducted in the North of France and in UK and 3 outdoor trials were submitted for the South of France.
Levels of the parent compound were determined according to the methods REM 181.01 and REM 181.01 modified.

North :
3 residue trials supported the critical GAP of 0.6 kg a.s./ha, 2 applic. and a PHI of 30 days (soil application).

Results :
- at a rate of 0.336 kg a.s./ha, 2 applic., 30 d PHI : <0.02,
- at a rate of 0.620 kg a.s./ha, 1 applic., 73 d PHI : <0.02,
- at a rate of 0.594 kg a.s./ha, 1 applic., 73 d PHI : <0.02 mg/kg for root.

South :
No GAPs were provided for soil/foliar application.

No MRL can be proposed.

Metalaxyl data
17 outdoor residue trials were conducted in Northern Europe (France and UK) and 2 outdoor trials were conducted in Italy.

North :
Seed treatment :
5 trials could be used in support of the metalaxyl-M GAP of 35 g a.s./100 kg seed.

Results : 5 x <0.02 mg/kg for root.

Soil/foliar application :
6 trials carried out at 1.2 kg a.s./ha, 2 applic. could be used in support of the metalaxyl-M critical GAP.
Results : <0.01-<0.01-0.01-0.02-0.05-0.05 mg/kg for root.

South :
Trials for soil application.

B.6.6.16 Bulb vegetables (garlic-onions-shallots-others)

Metalaxyl-M data
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A, Onions, Switzerland-Final report No. 2338/97(Kühne, R.O., 1998ak).
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A, Onions, Switzerland-Final report No. 2340/97(Kühne, R.O., 1998al).
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A, Onions, Spain-Final report No. 2013/97(Kühne, R.O., 1998am).
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A, Onions, Spain-Final report No. 2014/97(Kühne, R.O., 1998an).
Determination of residues of CGA 329351 + ASF 41 (Chlorothalonil / CGA 329351 + ASF 21 (Mancozeb), SC 537.5/WP68, A-9652 B/A-9407 A, Onions, Spain-Final report No. 116/97 (Kühne, R.O., 1998ao).
Determination of residues of CGA 329351 + ASF 41 (Chlorothalonil), SC 537.5, A-9652 B, Onions, Italy-Final report No. 2033/97(Kühne, R.O., 1998ap).
Determination of residues of CGA 329351 + ASF 41 (Chlorothalonil), SC 537.5, A-9652 B, Onions, Switzerland-Final report No. 2339/97(Kühne, R.O., 1998aq).
Determination of residues of CGA 329351 + ASF 41 (Chlorothalonil), SC 537.5, A-9652 B, Onions, Switzerland-Final report No. 2341/97(Kühne, R.O., 1998ar).
Determination of residues of CGA 329321 + Copper, WP 42.5, A-9402 A, Onions, Italy-Final report No. 2032/97 (Kühne, R.O., 1998as).
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Onions, France (South)-Final report No. OF96129/BY05 (Pointurier, R., 1998k)
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Onions, France (North)-Final report No. OF96129/KJ79 (Pointurier, R., 1998l)
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Onions, France (North)-Final report No. OF96129/LD79 (Pointurier, R., 1998m)
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Onions, France (North)-Final report No. OF96129/SJ21 (Pointurier, R., 1998n)

GLP : All submitted studies were carried out under laboratories GLP conditions.

9 and 7 outdoor residue trials were provided respectively for Northern (Switzerland, UK, France) and Southern Europe (Spain, Italy, France).
Levels of the parent compound were determined according to the methods 181.01 and DFG S19.
The trial designs are the same for both regions : 3 applications at rates of 0.1 and 0.15 kg a.s./ha with 7 to 12 days between applications. Decay curves are given with last sampling 21 days after last application.

North :
9 trials supported the critical GAP of 0.15 kg a.s./ha, 3 applic., PHI 14 days (foliar application).
Results : 9 x <0.02 mg/kg for bulb.

South :
7 trials were in accordance with the critical GAP of 0.15 kg a.s./ha, 3 applic. and a PHI 14 days (foliar application).
Results : 7 x <0.02 mg/kg for bulb.

MRL proposal for bulb vegetables (garlic, onions, shalots, others): 0.02* mg/kg.

B.6.6.17 Tomatoes

Metalaxyl-M data
Determination of residues of CGA 329351 + Chlorothalonil, SC 550 (A-9406A) in tomato in Spain - Project Report RR 2087/94 (Kühne, R.O, 1995a)
Determination of residues of CGA 329351 + Chlorothalonil, SC 550 (A-9406A) in tomato in Italy - Project Report RR 2128/94 (Kühne, R.O, 1995b)
Determination of residues of CGA 329351 + Chlorothalonil, SC 550 (A-9406A) in tomato in Switzerland - Project Report RR 2066/94 (Kühne, R.O, 1995c)
Determination of residues of CGA 329351 + Chlorothalonil, SC 550 (A-9406A) in tomato in Switzerland - Project Report RR 2067/94 (Kühne, R.O, 1995d)
Determination of residues of CGA 329351 + Chlorothalonil, SC 550 (A-9406A) in tomato in Spain - Project Report RR 2088/94 (Kühne, R.O, 1995e)
Determination of residues of CGA 329351 + Chlorothalonil, SC 550 (A-9406A) in tomato in Italy - Project Report RR 2127/94 (Kühne, R.O, 1995f)
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A, Tomatoes, Switzerland-Final report No. 2335/97 (Kühne, R.O, 1998bc)
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A, Tomatoes, Switzerland-Final report No. 2337/97 (Kühne, R.O, 1998bf)
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A, Tomatoes, Italy-Final report No. 2073/96 (Kühne, R.O, 1997p)
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A, Tomatoes, Italy-Final report No. 2074/96 (Kühne, R.O, 1997q)
Determination of residues of CGA 329351 + ASF 41 (Chlorothalonil), SC 537.5, A-9652 B, Tomatoes, France-Final report No. 2345/97 (Kühne, R.O, 1998bg)
Determination of residues of CGA 329351 + ASF 41 (Chlorothalonil), SC 537.5, A-9652 B, Tomatoes, France-Final report No. 2346/97 (Kühne, R.O, 1998bh)
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A, Tomatoes, Switzerland-Final report No. 2334/97 (Kühne, R.O, 1998bi)
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A, Tomatoes, Switzerland-Final report No. 2336/97 (Kühne, R.O, 1998bj)
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A, Tomatoes, France-Final report No. 2347/97 (Kühne, R.O, 1998bk)
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A, Tomatoes, France-Final report No. 2348/97 (Kühne, R.O, 1998bl)
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A, Tomatoes, France-Final report No. 2349/97 (Kühne, R.O, 1998bm)
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A, Tomatoes, France-Final report No. 2350/97 (Kühne, R.O, 1998bn)
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A, Tomatoes,Spain-Final report No. 2011/97 (Kühne, R.O, 1998bo)
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A, Tomatoes,Spain-Final report No. 2012/97 (Kühne, R.O, 1998bp)
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Tomatoes, France (South)-Final report No. OF96127/AC18 (Pointurier, R., 1998o)
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Tomatoes, France (South)-Final report No. OF96127/BY04 (Pointurier, R., 1998p)
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Tomatoes, France (South)-Final report No. OF96127/FP05 (Pointurier, R., 1998q)
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Tomatoes, France (South)-Final report No. OF96127/TP98 (Pointurier, R., 1998r)

GLP : All submitted studies were carried out under laboratories GLP conditions.

16 outdoor residue trials were submitted covering Northern (Switzerland, France) and Southern Europe (Italy, France, Spain).
9 indoor residue trials were also provided.

Levels of the parent compound were determined according to the methods 181.01 and DFG S19.
The trial designs are the same for both regions : 4 applications at rates of 0.1 and 0.15 kg a.s./ha with 6 to 11 days between applications. Decay curves are given with last sampling 28 days after last application.

Outdoor conditions :
North :
6 trials supported the critical GAP of 0.15 kg a.s./ha, 4 applic. (foliar application).
Results :
PHI : 3 days : <0.02-<0.02-0.02 mg/kg for fruit.
PHI : 7 days : <0.02-<0.02-<0.02 mg/kg.

South :
10 residue trials supported the critical GAP of 0.15 kg a.s./ha, 4 applic. (foliar application).
Results :
PHI : 3 days : <0.02-<0.02-<0.02-<0.02-<0.02-0.02 mg/kg for fruit.
PHI : 4 days :<0.02 mg/kg
PHI : 7 days :<0.02-<0.02 mg/kg
PHI : 10 days :<0.02 mg/kg

Indoor conditions :
9 trials were in accordance with the same critical GAP.
Results :
PHI : 3 days : <0.02-<0.02-<0.02-0.02-0.04-0.08 mg/kg for fruit.
PHI : 7 days : <0.02-<0.02-<0.02 mg/kg.

MRL proposal for tomatoes with a critical PHI of 3 days : 0.1 mg/kg.

Metalaxyl data
South :
9 outdoor trials were performed in Spain, Argentina, Brazil, France and one indoor trial was performed in Morocco.
4 outdoor trials and the indoor trial could be used in support of the Metalaxyl-M uses (foliar application).
Results : <0.01-<0.04-0.02-(0.18) mg/kg for fruit.

Remark : The residue value of 0.18 mg/kg could be considered as an “outlier” according to the Dixon Q-test and was not included in the data base.

Indoor conditions :
Result : 0.02 mg/kg for fruit.

B.6.6.18 Sweet peppers
Metalaxyl-M data
Determination of residues of CGA 329351, GR 2.5, A-9600 A, Sweet peppers, Italy-Final report No. 121/97 (Kühne, R.O., 1998az).
Determination of residues of CGA 329351, GR 2.5, A-9600 A, Sweet peppers, Spain-Final report No. 2007/97 (Kühne, R.O., 1998ba).

Determination of residues of CGA 329351, GR 2.5, A-9600 A, Sweet peppers, Spain-Final report No. 2008/97 (Kühne, R.O., 1998bb).
Determination of residues of CGA 329351, GR 2.5, A-9600 A, Sweet peppers, Italy-Final report No. 2044/97 (Kühne, R.O., 1998bc).
Determination of residues of CGA 329351, GR 2.5, A-9600 A, Sweet peppers, Italy-Final report No. 2045/97 (Kühne, R.O., 1998bd).

GLP : All submitted studies were carried out under laboratories GLP conditions.

4 outdoor and 4 indoor residue trials were conducted in Italy and Spain.
Levels of the parent compound were determined according to the method 181.01.
Trials were made following 2 to 3 applications on soil at a rate of 1 kg a.s./ha.
Decay curves were given with last sampling 20 days after last application.

7 outdoor and indoor residue trials were in accordance with the critical GAP of 0.1 g a.s./m^2, 3 applic. and a PHI of 15 days (soil application) and 1 indoor trial couldn't be taken into account as the residue value (0.35) was an "outlier" according to the Dixon Q-test.

Outdoor conditions :
Results : <0.02, <0.02, 0.02 mg/kg for the whole fruit.

Indoor conditions :
Results : <0.02, <0.02, 0.02 mg/kg for the whole fruit

No MRL can be proposed (Insufficient data base).

Metalaxyl data
8 residue trials were conducted in Bulgaria, Italy and North America but couldn't be used in support of the metalaxyl-M uses (soil application).

B.6.6.19 Cucumber

Metalaxyl-M data
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A in Cucumbers in Spain - Final report No. 2009/97 (Künhe, R.O., 1998g)
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A in Cucumbers in Spain - Final report No. 2010/97 (Künhe, R.O., 1998h)
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A in Cucumbers in North of France - Final report No. 117/97 (Künhe, R.O., 1998i)

GLP : All submitted studies were carried out under laboratories GLP conditions.

18 outdoor and indoor residue trials were conducted in Northern (France) and Southern Europe (Spain, Italy).
Levels of the parent compound were determined according to the method 181.01.
In both regions, trials were made following 4 foliar applications at a rate of 0.15 kg a.s./ha, with 3 and 10 days between applications.
Decay curves were given with last sampling 21 days after last application.

North - Indoor conditions :
6 trials supported the critical GAP of 0.15 kg a.s./ha, 4 applic. and a PHI of 7 days (foliar application).

Results : 0.12-0.13-0.15-0.18-0.19-0.32 mg/kg
Mean = 0.181 mg/kg
3 x mean = 0.544 mg/kg
R(max) = 0.451 mg/kg
R(ber) = 0.445 mg/kg.

South :
Outdoor conditions :
9 trials supported the critical GAP of 0.15 kg a.s./ha, 4 applic. and a PHI of 6 days (foliar application).
Results : 0.10-0.12-0.14-0.15-0.15-0.17-0.18-0.19-0.19 mg/kg
Mean = 0.154 mg/kg
3 x mean = 0.463 mg/kg
R(max) = 0.263 mg/kg
R(ber) = 0.370 mg/kg

Indoor conditions :
3 trials supported the critical GAP of 0.15 kg a.s./ha, 4 applic.and PHI values of 3 and 7 days (foliar application).
Results : 0.11-0.13-0.21 mg/kg.

MRL proposal for cucumbers : 0.5 mg/kg.

Metalaxyl data
7 residue trials were performed in Austria, UK, Switzerland and Sweden and 4 trials were conducted in the South of France (outdoor and indoor conditions are not specified).

North :
3 trials conducted in Switzerland could be used in support of the metalaxyl-M uses (foliar application).
Results :
0.06-0.06-0.09 mg/kg.

South :
No trial supported the metalaxyl-M critical GAP.

B.6.6.20 Melon

Metalaxyl-M data
Determination of residues of CGA 329351 + ASF 41 (Chlorothalonil), SC 537.5, A-9652 B, Melon, France-Final report No. 2351/97 (Kühne, R.O., 1998ai).
Determination of residues of CGA 329351 + ASF 41 (Chlorothalonil), SC 537.5, A-9652 B, Melon, France-Final report No. 2352/97 (Kühne, R.O., 1998aj).
Determination of residues of CGA 329351 + Copper (ASF 45), WP 42.5, A-9402 A, Melons, Italy-Final report No. 2060/97 (Kühne, R.O., 1998br).
Determination of residues of CGA 329351 + Copper (ASF 45), WP 42.5, A-9402 A, Melons, Italy-Final report No. 2061/97 (Kühne, R.O., 1998bs).
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Melons, France (South)-Final report No. OF96130/AC27 (Pointurier, R., 1998e).
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Melons, France (South)-Final report No. OF96130/AC28 (Pointurier, R., 1998f).
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Melons, France (South)-Final report No. OF96130/BY10 (Pointurier, R., 1998g).
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Melons, France (South)-Final report No. OF96130/BY11 (Pointurier, R., 1998h).
Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Melons, France (South)-Final report No. OF96130/LD67 (Pointurier, R., 1998i).

Determination of residues of CGA 329351 + Chlorothalonil, SC 537.5, A-9652 A, Melons, France (South)-Final report No. OF96130/TP97 (Pointurier, R., 1998j).

GLP : All submitted studies were carried out under GLP conditions.

10 residue trials were submitted for Southern Europe (France, Italy).
Levels of the parent compound were determined according to the method REM 181.01.
Trials were made following 3 foliar applications at rates of 0.112 and 0.125 kg a.s./ha, with 9 to 12 days between applications.
Decay curves were given with last sampling 21 days after last application.

Outdoor conditions :
7 trials were in accordance with the critical GAP of 0.12 kg a.s./ha, 3 applic. and a PHI of 3 days (foliar application).
Results : 5 x <0.02, 0.02, 0.03 mg/kg.

Indoor conditions :
2 trials supported the critical GAP of 0.12 kg a.s./ha, 3 applic. and a PHI of 3 days (foliar application).
Results : <0.02, 0.02 mg/kg

MRL proposal for melons : 0.05 mg/kg.

Metalaxyl data
5 outdoor trials and 3 trials under plastic tunnel were conducted in Italy, South of France and in Brazil.
3 outdoor trials could be used in support of the metalaxyl-M uses (foliar application).
Results : <0.02-<0.02-0.02 mg/kg.

B.6.6.21 Watermelon

Metalaxyl-M data
No residue trials were provided.
No MRL can be proposed.

Metalaxyl data
2 outdoor trials were conducted in Italy but couldn't be used in support of the metalaxyl-M uses.

B.6.6.22 Broccoli

Metalaxyl-M data
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A in Broccoli in Spain - Final report No. 119/97 (Künhe, R.O., 1998e)

GLP : All submitted studies were carried out under GLP conditions.

Levels of the parent compound were determined according to the method REM 181.01.
Trials were made following 3 foliar applications at a rate of 0.1 kg a.s./ha, with 10 days between applications.
Decay curves were given with last sampling 21 days after last application.

3 outdoor and 1 indoor residue trials were conducted in Spain and supported the critical GAP of 0.1 kg a.s./ha, 3 applic. and a PHI of 14 days (foliar application).

Outdoor conditions :
Results : <0.02, <0.02, 0.02 mg/kg for the flower head.

Indoor conditions :
Result : 0.02 mg/kg for the flower head.

MRL proposal for broccoli : 0.02* mg/kg, although the data base is insufficient.

Metalaxyl data
5 residue trials were performed in Canada.

B.6.6.23 Cauliflower

Metalaxyl-M data
Determination of residues of CGA 329351 + ASF 41 (Chlorothalonil), SC 537.5, A-9652 B in Cauliflower in France (North)-Final report No. 113/97 (Künhe, R.O., 1998f)

GLP : All submitted studies were carried out under GLP conditions.

Levels of the parent compound were determined according to the method REM 181.01.
Trials were made following 2 foliar applications at rates of 0.070 to 0.080 kg a.s./ha, with 11 to 13 days between applications.
Decay curves were given with last sampling 21 days after last application.

4 outdoor residue trials were submitted for North of France and supported the critical GAP of 0.1 kg a.s./ha, 3 applic. and a PHI of 14 days (foliar application).
Results : <0.02, <0.02, <0.02, 0.02 mg/kg for flower heads.

No MRL can be proposed (Insufficient data base)

Metalaxyl data
6 outdoor residue trials were conducted in Canada and in UK and one indoor trial was carried out in UK.

Outdoor conditions :
2 trials conducted in Canada could be used in support of the critical GAP of metalaxyl-M for Northern Europe.
Results : 0.074-0.077 mg/kg for the flower heads.

Indoor conditions :
Result : 0.03 mg/kg for the flower head.

B.6.6.24 Brussel sprouts

Metalaxyl-M data
No residue trials were submitted.
No MRL can be proposed.

Metalaxyl data
Seed treatment :
2 residue trials were submitted for UK and could be used in support of the metalaxyl-M critical GAP of 70 g a.s./100 kg seed, 1 applic.
Results : <0.02-<0.02 mg/kg for head buttons.

Foliar treatment :
11 residue trials were conducted in UK and 2 trials were performed in Canada.

7 residue trials from UK could be used in support of the metalaxyl-M critical use of 0.1 kg a.s./ha, 3 applic. and a PHI of 14 days.
Results : <0.02-<0.02-<0.02-<0.01-0.01-0.02-0.02 mg/kg for head buttons.

B.6.6.25 Head cabbage

Metalaxyl-M data
No residue trials were submitted.
No MRL can be proposed.

Metalaxyl data
Foliar treatment : 2 residue trials were performed in UK but were not taken into account as no metalaxyl-M uses were provided for Northern Europe.

B.6.6.26 Lettuce

Metalaxyl-M data
Determination of residues of CGA 329351 + Folpet, WP 45, A-9403A in Head Lettuce in Germany - Final report No. 2252/97 (Kühne, R.O., 1998s).
Determination of residues of CGA 329351 + Folpet, WP 45, A-9403A in Head Lettuce in Germany - Final report No. 2253/97 (Kühne, R.O., 1998t).
Determination of residues of CGA 329351 + Folpet, WP 45, A-9403A in Head Lettuce in Germany - Final report No. 2254/97 (Kühne, R.O., 1998u).
Determination of residues of CGA 329351 + Folpet, WP 45, A-9403A in Head Lettuce in Germany - Final report No. 2255/97 (Kühne, R.O., 1998v).
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A in Cos Lettuce in Spain-Final report No. 2005/97 (Kühne, R.O., 1998w).
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A in Cos Lettuce in Spain-Final report No. 2006/97 (Kühne, R.O., 1998x).
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A in Head Lettuce in France (North) - Final report No. 2260/97 (Kühne, R.O., 1998y).
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A in Head Lettuce in France (North) - Final report No. 2261/97 (Kühne, R.O., 1998z).
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A in Head Lettuce in France (South) - Final report No. 2262/97 (Kühne, R.O., 1998aa).
Determination of residues of CGA 329351 + Mancozeb (ASF 21), WP 68, A-9407 A in Head Lettuce in France (South) - Final report No. 2263/97 (Kühne, R.O., 1998ab).
Determination of residues of CGA 329351 + Copper (ASF 45), WP 42.5, A-9402 A in Lettuce in Italy-Final report No. 2062/97 (Kühne, R.O., 1998ac).
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A in Head Lettuce in Italy-Final report No. 2075/96 (Kühne, R.O., 1997g).
Determination of residues of CGA 329351 + Copper, WP 42.5, A-9402 A in Head Lettuce in Italy-Final report No. 2076/96 (Kühne, R.O., 1997h).

GLP : All submitted studies were carried out under GLP conditions.

10 outdoor and 2 indoor residue trials were conducted covering Northern (Germany, France) and Southern Europe (Italy, Spain, France).
Levels of the parent compound were determined according to the method REM 181.01.
Trials were made following 3 foliar applications at a rate of 0.1 kg a.s./ha, with 8 to 13 days between applications.
Decay curves were given with last sampling 21 days after last application.

North :
Outdoor conditions :
4 trials supported the critical GAP of 0.125 kg a.s./ha, 3 applic.and a PHI of 14 days (foliar application).
Results : 0.02-0.02-0.03-0.03 mg/kg for heads.
Mean = 0.025 mg/kg,
3 x mean = 0.075 mg/kg,
R(max) = 0.054 mg/kg,
R(ber) = 0.06 mg/kg

Indoor conditions :
The 2 trials were in accordance with the same critical GAP.
Results : 0.04-0.07 mg/kg for heads.

South :
Outdoor conditions :
6 trials supported the critical GAP of 0.125 kg a.s./ha, 3 applic.and a PHI of 14 days (foliar application).
1 trial couldn't be taken into account as the residue value (0.16) was considered as an "outlier" according to the Dixon Q-test.
Results : <0.02- <0.02- <0.02- <0.02 - 0.03 mg/kg for heads.

MRL proposal for lettuce : 0.05 mg/kg, although the data base is insufficient for the North and the South of Europe.

Metalaxyl data
32 residue trials covering Northern (France, Germany, Switzerland, UK) and Southern Europe (Spain, Italy) were submitted.
Other trialswere performed in Israel, North America and Canada.

North :
Outdoor conditions :
9 residue trials on head lettuce supported the Metalaxyl-M uses (foliar application) but 2 trials couldn't be taken into account as the residue values (0.21-0.46) were "outliers" according to the Dixon Q-test.
Results : <0.02-<0.02-<0.05-<0.05-0.02-0.09-0.09 mg/kg for heads.
Details :
- <0.02-0.02-0.02-0.09 mg/kg (trials at 0.25 kg a.s./ha, 3 applic., PHI : 14 days).
- <0.05-<0.05 mg/kg (trials at 0.2 and 0.3 kg a.s./ha, 3 applic., PHI : 14 days).
- 0.09 mg/kg (trial at 0.24 kg a.s./ha, 3 applic., PHI : 19 days).
- (0.21 mg/kg) (trial at 0.24 kg a.s./ha, 3 applic., PHI : 17 days).
- (0.46 mg/kg) (trial at 0.25 kg a.s./ha, 3 applic., PHI : 14 days).

Indoor conditions :
1 residue trial on head lettuce from Germany could be used in support of the Metalaxyl-M uses (foliar application).
Result : 0.32 mg/kg for heads (trial at 0.25 kg a.s./ha, 3 applic., PHI : 14 days).

South :
Outdoor conditions :
10 residue trials on cos lettuce could be used in support of the Metalaxyl-M uses (foliar application).
Results : <0.02-0.02-0.02-0.02-0.02-0.04-0.04-0.05-0.11-0.13 mg/kg for leaves.
Details :
- <0.02-0.02 mg/kg (trials at 0.16 kg a.s./ha, 3 applic., PHI : 14 days).
- 3 x 0.02 mg/kg (trials at 0.10 to 0.14 kg a.s./ha, 3 applic., PHI : 14 days).
- 2 x 0.04 mg/kg (trials at 0.2 to 0.3 kg a.s./ha, 3 applic., PHI : 14 days).
- 0.05 mg/kg (trial at 0.1 to 0.2 kg a.s./ha, 3 applic., PHI : 13 days).
- 0.11 mg/kg (trial at 0.24 kg a.s./ha, 3 applic., PHI : 12 days).
- 0.13 mg/kg (trial at 0.25 kg a.s./ha, 3 applic., PHI : 15 days).

Mean = 0.045 mg/kg
3 x mean = 0.135 mg/kg
R(max) = 0.045+2.911 x 0.0395 = 0.16 mg/kg
R(ber) = 0.125 mg/kg

B.6.6.27 Spinach

Metalaxyl-M data
Determination of residues of CGA 329351 + Copper, WP 42.5, ES 350, A-9402 A, A-9642 C, Spinach (foliar and seed treatment), France (South)-Final report No. 125/97 (Kühne, R.O., 1998ay)

Levels of the parent compound were determined according to the method DFG S19.
Decay curves were given with last sampling 21 days after the last application.

GLP : All submitted studies were carried out under GLP conditions.

South :
Seed treatment :
3 residue trials were submitted and supported the critical GAP of 70 g/100 kg seeds, 1 applic..
Results :<0.02, <0.02, <0.02 mg/kg on leaves

Foliar treatment :
6 outdoor residue trials were conducted in the South of France supporting the critical GAP of 0.1 kg a.s./ha, 2 applic. and a PHI of 20 days.
Results : <0.02, <0.02, <0.02, <0.02, 0.03, 0.03 mg/kg on leaves.

MRL proposal for spinach : 0.05 mg/kg.

Metalaxyl data
Seed treatment :
9 residue trials were conducted in Germany and in Sweden and could be used in support of the Metalaxyl-M uses.
Results : <0.01-4 x <0.02 - 0.02-0.02-0.025-0.03-0.04 mg/kg for the whole plant (trial at 0.035 kg a.s./100 kg seed, 1 applic.)

Foliar treatment :
4 residue trials were conducted in Northern Europe (Germany, Switzerland) but could not be considered as no GAPs for Metalaxyl-M were submitted for Northern Europe.

B.6.6.28 Beans (with pods)

Metalaxyl-M data
Determination of residues of CGA 329351 + ASF 41 (Chlorothalonil), SC 537.5, A-9652 B in Beans in United Kingdom - Final report No. 114/97 (Kühne, R.O., 1998d)

GLP : All submitted studies were carried out under GLP conditions.

4 outdoor residue trials were carried out in UK on common beans.
Levels of parent compound were determined according to the method DFG S19 mod.
The trials were carried out following 2 foliar applications at rates of 0.073 to 0.082 kg a.s./ha, with 13 to 14 days between applications.
Decay curves were given with last sampling 21 days after last application.

North :
4 trials could support the critical GAP of 0.1 kg a.s./ha, 3 applic., PHI 14 days (foliar application).
Results : <0.02-<0.02-<0.02-<0.02 mg/kg for pods with seeds.

Metalaxyl data

Seed treatment :
12 residue trials were conducted in UK and in Germany on Dwarf beans, Broad beans and Common beans.
10 trials could be used in support of the Metalaxyl-M seed treatment use for the 3 types of beans : 8.75-35 g/100 kg seed, 1 applic.
Results :
<0.02-<0.02-<0.02-<0.02 mg/kg for the whole pods.
<0.02-<0.02-<0.02-0.02-0.02-0.02 mg/kg for seeds.

Foliar treatment :
11 residue trials were conducted in Austria and in UK on broad beans.
6 trials could be used in support of the Metalaxyl-M critical GAP of 0.1 kg a.s./ha, 3 applic., PHI of 14 days.
Results : <0.02-<0.01-<0.01-<0.01-<0.01-0.02 mg/kg for seeds.

One residue trial was carried out in Italy on common beans. It couldn't be used in support of the Metalaxyl-M use of 0.12 kg a.s./ha, 2 applic. and a PHI of 14-28 days.

Soil treatment :
8 residue trials were carried out in North America on Green beans, Navy beans, Red Kidney beans and Common beans but were not taken into account as no residue trial was submitted for Europe.

B.6.6.29 Peas (with or without pods)

Metalaxyl-M data
No residue trials were performed.
No MRL can be proposed.

Metalaxyl data
Seed treatment :
12 residue trials were submitted for covering Northern Europe (France, UK, Germany) and 1 trial was performed by Canada and 3 by South Africa.
13 trials could be used in support of the Metalaxyl-M use (8.75-35 g a.s./100 kg seed, 1 applic.).
Results :
-<0.02-<0.02-<0.02-<0.02-<0.02-0.04 mg/kg for pea pods and peas.
-<0.02-<0.02-<0.02-<0.02-<0.02-0.02-0.03 mg/kg for seeds.

3 residue trials were performed in UK but couldn't be taken into account as no Metalaxyl-M GAPs were provided regarding a seed treatment followed by a foliar treatment.

B.6.6.30 Globe Artichoke

Metalaxyl-M data
Determination of residues of CGA 329351 + Copper (ASF 45), WP 42.5, A-9402 A in Artichokes in Italy - Final report No. 2065/97(Kühne, R.O., 1998a)
Determination of residues of CGA 329351 + Copper (ASF 45), WP 42.5, A-9402 A in Artichokes in Italy - Final

report No. 2066/97(Kühne, R.O., 1998b)
Determination of residues of CGA 329351 + Copper (ASF 45), WP 42.5, A-9402 A in Artichokes in Spain - Final report No. 120/97(Kühne, R.O., 1998c)

GLP : All submitted studies were carried out under GLP conditions.

Levels of parent compound were determined according to the method REM 181.01.
The trials were carried out following 3 foliar sprays at a rate of 0.1kg a.s./ha, with 8 to 12 days between applications.

South :
4 outdoor residue trials were conducted in Italy and Spain and supported the critical GAP of 0.1 kg a.s./ha, 3 applic. and a PHI of 20 days (foliar application).
Results : <0.02, <0.02, <0.02, <0.02 mg/kg for flower heads.

MRL proposal for globe artichoke: 0.02* mg/kg.

B.6.6.31 Leek

Metalaxyl-M data
Determination of residues of CGA 329351 + ASF 41 (Chlorothalonil), SC 537.5, A-9652 B in Leek in United Kingdom - Final report No. 115/97 (Kühne, R.O., 1998r).

GLP : All submitted studies were carried out under GLP conditions.

Levels of parent compound were determined according to the method REM 181.01.
The trials were carried out following 3 foliar applications at a rate of 0.073-0.078 kg a.s./ha, with 13 to 14 days between applications.
North :
4 outdoor residue trials were performed in UK supporting the critical GAP of 0.085 kg a.s./ha, 3 applic. and a PHI of 14 days (foliar application).
Results : <0.02, <0.02, <0.02, 0.02 mg/kg for the whole plant.

No MRL can be proposed (Insufficient data base)

Metalaxyl data
No residue trials were submitted.

B.6.6.32 Peas (pulses)

Metalaxyl-M data
No residue trials were performed.
No MRL can be proposed.

Metalaxyl data
One residue trial (seed treatment) was provided for the North of France. The study report was incomplete.

B.6.6.33 Sunflower seed

Metalaxyl-M data

No residue trials were submitted.
No MRL can be proposed.

Metalaxyl data
Seed treatment :
6 residue trials were conducted in Argentine and North America but couldn't be taken into account as no residue trials were submitted for Europe.

Foliar treatment :
1 residue trial was carried out in Austria but no Metalaxyl-M GAPs were provided for foliar treatment.

B.6.6.34 Rapeseed

Metalaxyl-M data
No residue trials were submitted.
No MRL can be proposed.

Metalaxyl data
Seed treatment :
One residue trial was submitted for the North of France and could be used in support of the Metalaxyl-M use (70 g a.s./100 kg seed, 1 applic.)
The residue value is : 0.020 mg/kg for seed.

Foliar treatment :
3 residue trials were performed in Austria but couldn't be taken into account as no Metalaxyl-M GAPs were provided for foliar application.

B.6.6.35 Soybean

Metalaxyl-M data
No residue trials were submitted.
No MRL can be proposed.

Metalaxyl data
Seed treatment :
2 residue trials were submitted for Canada and North America but no Metalaxyl-M GAPs were proposed..

Foliar treatment :
North :
1 trial was conducted in Austria but no Metalaxyl-M GAPs were submitted.

South :
3 residue trials were carried out in Italy and could be used in support of the Metalaxyl-M critical GAP of 0.1 kg a.s./ha, 3 applic. and a PHI of 35 days.
Results :
0.03-0.02 mg/kg for seeds,
0.07 mg/kg for pods with seeds.

Soil treatment :

5 residue trials were submitted for Canada. They were not taken into account.

B.6.6.36 Potato

Metalaxyl-M data
Determination of residues of CGA 329351 + Mancozeb, WP 68 (A-9407 A) in potato in Germany - Project Report FR 28/94/40 (Kühne, R.O, 1995p).
Determination of residues of CGA 329351 + Mancozeb, WP 68 (A-9407 A) in potato in Germany - Project Report FR 28/94/70 (Kühne, R.O, 1995q).
Determination of residues of CGA 329351 + Mancozeb, WP 68 (A-9407 A) in potato in Spain - Project Report FR 2089/94 (Kühne, R.O, 1995r).
Determination of residues of CGA 329351 + Mancozeb, WP 68 (A-9407 A) in potato in Spain - Project Report FR 2090/94 (Kühne, R.O, 1995s).
Determination of residues of CGA 329351 + Mancozeb, WP 68 (A-9407A)in potatoes in UK - Project Report RR 01/95 (Tack, T, 1995a).
Determination of residues of CGA 329351 + Mancozeb, WP 68 (A-9407A)in potatoes in UK - Project Report RR 02/95 (Tack, T, 1995b).
Determination of residues of CGA 329351 + Fluazinam, A-9575 A in Potatoes in United Kingdom- Final report No. FR0595AR (Adams, S., 1998a)
Determination of residues of CGA 329351 + Fluazinam, A-9575 A in Potatoes in United Kingdom- Final report No. FR0595BR (Adams, S., 1998b)
Determination of residues of CGA 279202 + CGA 329351, EC 200, A-9879 A in Potatoes in Switzerland - Final report No. 2329/97 (Kissling, M., 1998a)
Determination of residues of CGA 279202 + CGA 329351, EC 200, A-9879 A in Potatoes in Switzerland - Final report No. 2330/97 (Kissling, M., 1998b)
Determination of residues of CGA 329351 + Copper, 42.5 WP, A-9402 A, Potatoes, Italy-Final report No. 2077/96 (Kühne, R.O, 1997o).
Determination of residues of CGA 329351 + Copper, 42.5 WP, A-9402 A, Potatoes, Italy-Final report No. 2078/96 (Kühne, R.O, 1997p).
Determination of residues of CGA 329351 + Fluazinam, EC 600, A-9575 A, Potatoes, Germany-Final report No. GR 4895 (Smith, J.A., 1997a)
Determination of residues of CGA 329351 + Fluazinam, EC 600, A-9575 A, Potatoes, Germany-Final report No. GR 45396 (Smith, J.A., 1997b)
Determination of residues of CGA 329351 + Fluazinam, EC 600, A-9575 A, Potatoes, Germany-Final report No. GR 46696 (Smith, J.A., 1997c)

GLP : All submitted studies were carried out under GLP conditions.

11 residue trials were submitted for Northern Europe (Switzerland, Germany, UK) and 6 trials were carried out in Southern Europe (Italy, Spain, France).
In both regions, trials were made following 4 to 5 foliar spray applications at rates of 0.075 and 0.1 kg a.s./ha.
Levels of parent compound were determined according to the method REM 181.01 and REM 181.01 mod.

North :
11 trials were in accordance with the critical GAP of 0.113 kg a.s./ha, 5 applic. and a PHI of 7 days (foliar application).
Results :
7 d PHI : 8 x <0.02,
14 d PHI : <0.02-<0.02,
28 d PHI : <0.02 mg/kg for tuber

South :
5 trials supported the critical GAP of 0.113 kg a.s./ha, 5 applic. and a PHI of 7 days (foliar application).
Results :
17 d PHI : <0.02-<0.02,

20 d PHI : <0.02,
25 d PHI : <0.02,
35 d PHI : <0.02 mg/kg for tuber

For both Northern and Southern Europe, all the results were below the LOD.

MRL proposal for potato tuber : 0.02* mg/kg

Metalaxyl data
28 residue trials were submitted for Northern Europe (Germany, UK, Switzerland), 3 trials were performed in Spain, 5 trials by Canada and 2 by Brazil.

North :
11 trials could be used to support the Metalaxyl-M critical GAP of 0.113 kg a.s./ha, 5 applic. and a PHI of 7 days.
Results : 4 x <0.05 - 7 x <0.02 mg/kg for tuber.

The residue trials performed in Canada could also be taken into account to support the Metalaxyl-M use.
The residue values are : <0.02-<0.02-0.02-0.02-0.02 mg/kg.

South :
2 residue trials from Spain were used to support the Metalaxyl-M use for foliar application.
Results :
<0.02-<0.02 mg/kg for tuber.

B.6.6.37 Hop

Metalaxyl-M data
No residue trials were submitted.
No MRL can be proposed.

Metalaxyl data
Soil treatment :
13 residue trials were conducted in Germany but couldn't be used in support of the Metalaxyl-M critical GAP of 0.4 kg a.s./ha, 1 applic. and a PHI of 7 days.

Foliar treatment :
21 residue trials were carried out in Germany and in UK but couldn't be used in support of the Metalaxyl-M use of 0.15 kg a.s./ha, 6 applic. and a PHI of 7 days.

B.6.6.38 Maize

Metalaxyl-M data
No residue trials were submitted.
No MRL can be proposed.

Metalaxyl data
Seed treatment :
6 residue trials were conducted in Germany of which 3 could be used in support of the Metalaxyl-M GAP (52.5 g/100 kg seeds, 1 applic.).
Results : <0.02-<0.02-<0.02 mg/kg for maize corn.

B.6.6.39 Rice

Metalaxyl-M data
No residue trials were submitted.

Metalaxyl data
5 residue trials were conducted in North America (soil application).

B.6.6.40 Wheat

Metalaxyl-M data
No residue trials were submitted.

Metalaxyl data
One residue trial was submitted in North America (seed treatment).

B.6.6.41 Tobacco

Metalaxyl-M data
Determination of residues of CGA 329351 + Mancozeb, WP 68 (A-9407A) in Tobacco (green leaves) in Greece - Project Report RR 2074/94 - Interim Report (Kühne, R.O, 1995t).
Determination of residues of CGA 329351 + Mancozeb, WP 68 (A-9407A) in Tobacco (green and dried leaves) in Italy - Project Report RR 2126/94 (Kühne, R.O, 1995u).
Determination of residues of CGA 245704 (total) + CGA 329351, WG 44, A-9522 B, Tobacco (green, dried leaves), France-Final report No. OF96112/TP91(Maffezzoni, M., 1997)
Determination of residues of CGA 245704 (total) + CGA 329351, WG 44, A-9522 B, Tobacco (green, dried leaves), France-Final report No. OF96113/TP90(Maffezzoni, M., 1996)
Determination of residues of CGA 245704 + CGA 329351, WG 44, A-9522 B, Tobacco, France (South)-Final report No. 2357/97 (Walser, M., 1998a)
Determination of residues of CGA 245704 + CGA 329351, WG 44, A-9522 B, Tobacco, France (South)-Final report No. 2358/97 (Walser, M., 1998b)
Determination of residues of CGA 245704 + CGA 329351, WG 44, A-9522 B, Tobacco, France (South)-Final report No. 2369/97 (Walser, M., 1998c)
Determination of residues of CGA 245704 + CGA 329351, WG 44, Tobacco (green and dried leaves), Greece-Final report No. 2104/96 (Walser, M., 1996a)
Determination of residues of CGA 245704 + CGA 329351, WG 44, Tobacco (green and dried leaves), Greece-Final report No. 2105/96 (Walser, M., 1996b)
Determination of residues of CGA 245704 as CGA 210007 + CGA 329351, WG 44, Tobacco (green leaves and dried leaves), Italy-Final report No. 2044/96 (Walser, M., 1996c)
Determination of residues of CGA 245704 as CGA 210007 + CGA 329351, WG 44, Tobacco (green leaves and dried leaves), Italy-Final report No. 2045/96 (Walser, M., 1996d)
Determination of residues of CGA 245704 + CGA 329351, WG 44, A-9522 A, Tobacco, Greece-Final report No. 2025/95 (Walser, M., 1997a)
Determination of residues of CGA 245704 + CGA 329351, WG 44, A-9522 A, Tobacco, Greece-Final report No. 2026/95 (Walser, M., 1997b)

GLP : All submitted studies were carried out under GLP conditions.

15 residue trials were submitted for Southern Europe (France, Italy, Greece).
Trials were made following 4 to 8 foliar spray applications at rates of 0.12 to 0.16 kg a.s./ha.
Levels of parent compound were determined according to the method 181.03.
Decay curves are given with last sampling (green leaves) 28 to 75 days after last application.
Residues of Metalaxyl-M were determined in green and dried leaves.

South :
14 residue trials supported the critical GAP of 0.15 kg a.s./ha, 6 applic., PHI : 7 days (Foliar application).

Results :
-Green leaves : 0.1-0.11-0.26-0.28-0.46-0.52-0.53-0.63-0.70-0.72-0.73-0.73-0.87-1.1 mg/kg
Mean = 0.552 mg/kg,
3 x mean = 1.658 mg/kg,
R(max) = 0.552+2.614x0.2914 = 1.313 mg/kg,
R(ber) = 1.46 mg/kg.

-Dried leaves : 0.39-0.75-0.84-1.20-1.20-1.3-1.6-1.9-2.4-2.4-4.3-7.6-9.1 mg/kg.
Mean = 2.69 mg/kg,
3 x mean = 8.072 mg/kg,
R(max) =2.69 + 2.670 x 2.718 = 9.947 mg/kg,
R(ber) = 6.7 mg/kg.

Residue levels for tobacco :
-2 mg/kg for green leaves,
-10 mg/kg for dried leaves.

Metalaxyl data
19 residue trials were submitted for Italy, South Africa, Turkey and North America.

B.6.7 Effects of industrial processing and/or household preparation on the residue (Annex IIA 6.5; Annex IIIA 8.4)

B.6.7.1 Effects on the nature of the residues

Such studies are not required at this stage since the TMDI is below 10 % of the ADI (even if the intake calculations were slightly underestimated as the contribution of animals products was not taken into account).

B.6.7.2 Effects on the level of residues

4 processing studies were proposed and concerned the identification and characterization of metabolites of metalaxyl in cigarettes containing tobacco treated with metalaxyl.

Balance and characterization of pyrolysis products of ^{14}C-(phenyl)-metalaxyl and its metabolites in cigarettes containing bright and burley tobacco treated with ^{14}C-(phenyl)-metalaxyl (Honeycutt R.C. and Cassidy J.E., 1978a)
Balance and characterization of pyrolysis products of ^{14}C-(phenyl)-metalaxyl and its metabolites in cigarettes containing field bright tobacco treated with ^{14}C-(phenyl)-metalaxyl (Honeycutt R.C. and Cassidy J.E., 1978b)
Identification of the major radioactive smoke products from cigarettes made of tobacco treated with ^{14}C-(phenyl)-metalaxyl (Honeycutt R.C. and Cassidy J.E., 1980)
Natural product and ^{14}C profile of mainstream smoke from cigarettes made with tobacco treated with ^{14}C-(phenyl)-metalaxyl
(Fischer W.C. and Cassidy J.E., 1980)

These studies are out of interest.

A processing study on grapes (industrially or household produced wet pomace) still should be advisable in order to estimate correctly the transfer factor of residues and therefore to perform the feed intake calculations for the 4 indicator livestock species. (point B.6.8).

B.6.8 Livestock feeding studies (Annex IIA 6.4; Annex IIIA 8.3)

Intake calculations for livestock (according to Appendix G of the "Guidelines for the establishment of Community Maximum Residue levels (MRLs) of Plant Protection Products in Food and Feedingstuffs of Plant and Animal Origin"-Doc 1607/VI/97 rev.1) are presented herebelow.

The maximum feed intakes of the 4 indicator livestock species (beef cattle, dairy cattle, chicken and pig) species cannot be calculated as no MRL proposal is established for the following feedingstuffs : kale/cabbage, fruit pomace, pulses, sugar beet, soybean, rape seed and sunflower seed. These data are required.

B.6.8.1 Livestock feeding studies in lactating cows or goats

Residues of Metalaxyl and metabolites in tissues and milk of dairy cows receiving Metalaxyl in their diet (Burnett D.E., 1982).
Guidelines :
Not specified.
GLP :
No.
Material and Methods :
Test substance : Metalaxyl, unlabelled.
5 Holstein cows were fed once a day with oral doses of metalaxyl for 28 days at a level equivalent to 75 mg/kg in their diet corresponding approximately to a dosage rate of 1500 mg of metalaxyl/cow/day (equivalent to about 4.28 mg a.s./ kg body weight/day). The substance was incorporated in the ration.
Animals were sacrificed on test days 14, 21 and 28. The treated cow sacrificed on day 14 had a 4 hour post-treatment sacrifice interval and those animals sacrificed on days 21 and 28 had a post-treatment interval of 24 hours.
Milk and blood as well as edible tissues were sampled and analysed for total residues of metalaxyl as 2,6-

dimethylaniline according to the Analytical Method of AG-349.

Findings :
- Dairy cows after treatment with metalaxyl for up to 28 days didn't show any adverse effect.
- Milk residues reached a plateau immediately at a level of 0.02 mg/kg for total metalaxyl.
- The samples of omental fat and perirenal fat were below the limit of determination of the analytical method (0.05 mg/kg) for total residues of metalaxyl and its metabolites containing the 2,6-dimethylaniline moiety.
- The following table gives a summary of the results obtained from the analysis of tissues of cows sacrificed within 4-24 hours after the last dose. Figures in this table are the means of the 5 cows'results.

Table B.6.8-1 : Residues of total metalaxyl in cows tissues after feeding at a rate of 4.28 mg a.s./ kg b.w./day (residues expressed as metalaxyl equiv./kg).

Samples	Day 14	Day 21	Day 28
Blood	0.32	<0.05	<0.05
Muscle	0.17	0.08	0.10
Liver	1.1	0.14	<0.1
Kidney	5.5	0.11	0.11

<0.05 : below limit of determination of the analytical method.

Conclusions :
The results showed the highest residue levels of total metalaxyl at test day 14 with a 4 hour post-dosage sacrifice interval.
Residues were significantly lower at test days 21 and 28 (which are treatment duration much more realistic and in accordance with the guidance documents) suggesting the apparition of a plateau.

B.6.8.2 Livestock feeding studies in poultry

Metalaxyl-three level/28-day poultry study (Eudy L.W., 1991)
Guidelines :
US EPA Pesticide Assessment Guidelines, Subdivision O, Part 171-4.
GLP :
Yes (except the biological phase of the study)
Material and Methods :
Test substance : Metalaxyl, unlabelled.
3 groups of 15 hens were fed with oral doses of metalaxyl ad libitum for 28 days at rates of 10, 30 and 100 mg/kg in their diet (corresponding to about 1.43, 4.29, 14.3 mg/animal/day). The substance was incorporated in the ration.
Hens were sacrificed at 7, 14, 21 and 28 days intervals.
Eggs, muscle, skin, fat and liver were sampled and analysed for residues of total Metalaxyl.
Kidney was not taken for analysis.
Egg samples were collected at 0, 1,3,7, 14, 21 and 28 days after dosing.
Tissue samples were taken at 7,14, 21 and 28 days after dosing.
Residues of total metalaxyl were determined as 2,6-dimethylaniline in eggs and tissue samples according to the Analytical Methods AG-576 and expressed as metalaxyl equivalents.

Findings :
Table B.6.8-2 : Residues of total metalaxyl in poultry tissues and eggs after feeding with 1.43/4.29/14.3

mg/animal/day.

Dose level (mg/hen/day)	Tissue	Residues expressed as total metalaxyl equivalents (mg/kg)					
		1 day	3 days	7 days	14 days	21 days	28 days
1.43 4.29 14.3	Eggs	<0.05 <0.05 <0.05	<0.05 <0.05 <0.05	<0.05 <0.05 <0.05	<0.05 <0.05 <0.05	<0.05 <0.05 <0.05	<0.05 <0.05 <0.05
1.43 4.29 14.3	Muscle	- - -	- - -	<0.05 0.06 0.13	0.06 0.10 0.13	<0.05 <0.05 <0.05	<0.05 <0.05 0.12
1.43 4.29 14.3	Skin + attached fat	- - -	- - -	<0.05 <0.05 0.12	<0.05 0.07 0.32	<0.05 0.10 0.40	<0.05 0.08 0.34
1.43 4.29 14.3	Fat peritoneal	- - -	- - -	<0.05 <0.05 0.09	<0.05 0.07 0.27	<0.05 0.08 0.34	<0.05 0.07 0.17
1.43 4.29 14.3	Liver	- - -	- - -	<0.05 0.07 0.16	<0.05 0.07 0.10	<0.05 0.07 0.12	<0.05 0.1 0.11

<0.05 : below limit of determination of the analytical method.
- : Not sampled.

Conclusion :
In absence of intake calculations for livestock, no dose group could be chosen as representative of the likely highest residue level that may occur in the feedingstuff of chicken.
No MRL was proposed for animal products.

B.6.8.3 Livestock feeding studies in pigs

A metabolism study in pigs was not required as metabolic pathway in rat, goat and hen can be considered as similar. For the same reason, a livestock feeding study in pigs is not required.

B.6.9 Residues in succeeding or rotational crops (Annex IIA 6.6; Annex IIIA 8.5)

-Uptake of 14C-(Phenyl)-metalaxyl in potatoes grown in a field plot - preparation of rotational plots (Foster R.A., Fischer W.C. and Cassidy J.E., 1978)
- Uptake and characterization of ^{14}C-Phenyl-Metalaxyl and its soil metabolites in rotation Winter Wheat (Fischer W.C. and Cassidy J.E., 1978a)
- Uptake and characterization of ^{14}C-Phenyl-metalaxyl and its soil metabolites in rotation lettuce (Fischer W.C. and Cassidy J.E., 1978b)
- Uptake and characterization of ^{14}C-Phenyl Metalaxyl and its soil metabolites in field rotation spring Oats (Fischer W.C. and Cassidy J.E., 1979a)
- Uptake and characterization of ^{14}C-Phenyl Metalaxyl and its soil metabolites in field rotation Soybeans (Hamilton T.B., Fischer W.C. and Cassidy J.E., 1979a)
- Uptake and characterization of ^{14}C-Phenyl Metalaxyl and its soil metabolites in field rotation corn (Fischer W.C. and Cassidy J.E., 1979b)
- Uptake and characterization of ^{14}C-Phenyl Metalaxyl and its soil metabolites in field rotation sugar beet (Hamilton T.B., Fischer W.C. and Cassidy J.E., 1979b)

Guidelines :
Not specified.
GLP :
No.
Material and Methods :
Test substance : ^{14}C-(Phenyl) -metalaxyl.
Prior to seeding or planting the representative rotational crops (wheat, lettuce, oat, soybeans, corn plant and sugar beet), potatoes were planted and were sprayed over-the-top 6 times at 14 days intervals at a rate of 0.45 kg a.s./ha of metalaxyl. The first spray treatment was 6 weeks after plant emergence and subsequent treatments were at 14 day intervals.
Mature tubers were sampled one day and 14 days after the last spray treatment.
Soil and plant samples were dosed by combustion analysis and Liquid Scintillation Counting.
The level of radioactivity in mature tubers ranged from values <0.003 to 0.094 mg/kg.
At the mature potato harvest, the soil radioactive levels were respectively 1.82, 0.31 and 0.05 mg/kg of total metalaxyl for the 3 layers.

Findings :
Table B.6.9 -1 : Distribution of radioactivity equivalent to ^{14}C-Phenyl- Metalaxyl in field soil and in rotation Winter Wheat plant parts (expressed in mg Metalaxyl equiv./kg)

Total radioactive residues (mg Metalaxyl equiv./kg)	Rotation Winter Wheat
Field soil analysis at planting of rotation crop	
0-7.5 cm (12 weeks) 7.5-15 cm (12 weeks) 15-22.5 cm (12 weeks)	0.74 0.47 0.14
Plant part analysis	
Whole plant (17 weeks) Whole plant (47 weeks) Whole plant (51 weeks) Grain (55 weeks) Straw (55 weeks)	3.97 0.36 0.34 0.11 0.56

Numbers in parentheses indicated the elapsed time (weeks) since the first treatment with ^{14}C-Phenyl Metalaxyl on potatoes.

Conclusion :
The enrichment of edible plant parts of winter wheat installed as a succeeding crop, with metalaxyl or its metabolites was sufficient to reach measurable levels in monitoring.

Table B.6.9 -2 : Distribution of radioactivity equivalent to ^{14}C-Phenyl- Metalaxyl in field soil and in rotation Lettuce plant parts (expressed in mg Metalaxyl equiv./kg)

TRR (mg Metalaxyl equiv./kg)	Rotation Lettuce
Field soil analysis at planting of rotation crop	
0-7.5 cm (45 weeks) 7.5-15 cm (45 weeks) 15-22.5 cm (45 weeks)	0.30 0.40 0.23
Plant part analysis	
Leaves (51 weeks) Leaves (54 weeks) Leaves (56 weeks)	0.11 0.06 0.05

Numbers in parentheses indicated the elapsed time (weeks) since the first treatment with ^{14}C-Phenyl Metalaxyl.

Conclusion :
The residue levels in lettuce leaves at harvest didn't exceed the established MRL of 0.05 mg/kg. (See point B.6.4.)

Table B.6.9.-3 : Distribution of radioactivity equivalent to ^{14}C-Phenyl- Metalaxyl in field soil and in rotation Spring Oat plant parts (expressed in mg Metalaxyl equiv./kg)

TRR (mg Metalaxyl equiv./kg)	Rotation Spring Oat
Field soil analysis at planting of rotation crop	
0-7.5 cm (45 weeks) 7.5-15 cm (45 weeks) 15-22.5 cm (45 weeks)	0.33 0.36 0.16
Plant part analysis	
Whole plant (49 weeks) Whole plant (52 weeks) Whole plant (56 weeks) Grain (59 weeks) Straw (59 weeks)	0.33 0.17 0.21 0.09 0.19

Numbers in parentheses indicated the elapsed time (weeks) since the first treatment with ^{14}C-Phenyl Metalaxyl.

Conclusion :
The enrichment of edible plant parts of spring oat installed as a succeeding crop, with metalaxyl or its metabolites was sufficient to reach measurable levels in monitoring.

Table B.6.9.-4 : Distribution of radioactivity equivalent to ^{14}C-Phenyl- Metalaxyl in field soil and in rotation soybeans plant parts (expressed in mg Metalaxyl equiv./kg)

TRR (mg Metalaxyl equiv./kg)	Rotation Soybeans
Field soil analysis at planting of rotation crop	
0-7.5cm (48 weeks) 7.5-15 cm (48weeks) 15-20 cm (48 weeks)	0.34 0.23 0.17
Plant part analysis	
Whole plant (54 weeks) Whole plant (58 weeks) Whole plant (61 weeks) Leaves and stems (68 weeks) Beans (68 weeks)	0.40 0.81 0.74 0.59 0.17

Numbers in parentheses indicated the elapsed time (weeks) since the first treatment with ^{14}C-Phenyl Metalaxyl.

Conclusion :
The enrichment of edible plant parts of spring oat installed as a succeeding crop, with metalaxyl or its metabolites was sufficient to reach measurable levels in monitoring.

Table B.6.9.-5 : Distribution of radioactivity equivalent to ^{14}C-Phenyl- Metalaxyl in field soil and in rotation corn plant parts (expressed in mg Metalaxyl equiv./kg)

TRR (mg Metalaxyl equiv./kg)	Rotation corn
Field soil analysis at planting of rotation crop	
0-7.5 (47 weeks) 7.5-15 cm (47 weeks) 15-22.5 cm (47 weeks)	0.29 0.36 0.19
Plant part analysis	
Whole plant (52 weeks) Whole plant (56 weeks) Whole plant (61 weeks) Stalks (68 weeks) Cobs (68 weeks) Grain (68 weeks)	0.05 0.06 0.05 0.06 0.02 0.03

Numbers in parentheses indicated the elapsed time (weeks) since the first treatment with ^{14}C-Phenyl Metalaxyl.

Conclusion :
These data showed that rotation corn took up very little metalaxyl or its metabolites from soil.The level of residues at the time of harvesting didn't exceed the LOD of the analytical method for monitoring (0.05 mg/kg).

Table B.6.9.-6 : Distribution of radioactivity equivalent to ^{14}C-Phenyl- Metalaxyl in field soil and in rotation sugar beet plant parts (expressed in mg Metalaxyl equiv./kg)

TRR (mg Metalaxyl equiv./kg)	Rotation sugar beet
Field soil analysis at planting of rotation crop	
0-7.5cm (45 weeks) 7.5-15 cm (45 weeks) 15-22.5 cm (45 weeks)	0.33 0.30 0.19
Plant part analysis	
Whole plant (51 weeks) Whole plant (54 weeks) Tops (60 weeks) Roots (60 weeks) Tops (65 weeks) Roots (65 weeks)	0.16 0.07 0.06 0.03 0.02 0.02

Numbers in parentheses indicate the elapsed time (weeks) since the first treatment with ^{14}C-Phenyl Metalaxyl.

Conclusion :
These data showed that rotation sugar beet took up very little metalaxyl or its metabolites from soil. The residues at time of harvesting didn't exceed the LOD of the analytical method for monitoring (0.05 mg/kg).

-Uptake and metabolism of metalaxyl in greenhouse rotational crops following target tobacco grown in soil treated with ^{14}C-(phenyl)-metalaxyl (Mc Farland J.; 1992)
Guidelines :
Pesticide Assessment Guidelines - Subdivision N, EPA Guidelines No.165-1, Section 158.290.
GLP :
Yes.
Material and Methods :
Experimental design :
Tobacco plants were grown under controlled greenhouse conditions in soil treated with ^{14}C-(phenyl)-metalaxyl in order to provide amended soil to grow rotational crops following the mature tobacco harvest 226 days after soil treatment.
20 pails of soil samples were treated at a rate of 3.36 kg a.s./ha.
Rotational crops including lettuce, spring wheat, soybeans and sugar beet were successfully grown to maturity in greenhouse pails containing ^{14}C-(phenyl)-metalaxyl amended soil.
The rotational crops were planted 232 days after the application of the test substance to the tobacco soil.
The crops received nutrient and pesticide treatment as needed.
Soil samples were taken at planting and at the mature harvest time of each rotational crop.
Radioactivity in the soil and plant samples was determined using combustion radioanalysis and Liquid Scintillation Counting.
Extraction procedure :
Samples of rotational lettuce, wheat, sugarbeet and soybeans were extracted with methanol/water.
The extractable radioactivity in soil samples and in immature and mature samples from the tobacco target and the 4 rotational crops was fractionated by HPLC and the metabolites structures were elucidated by normal phase 2D-TLC and reverse phase 2D-TLC with reference standards.
Enzyme hydrolysis (β-glucosidase, cellulase and protease) and acid hydrolysis were performed on organic and aqueous fractions and also on unextractable residues resulting from solvent extractions to further characterize the glucose conjugates.
Characterization and identification of the metabolites in these fractions were accomplished by comparison with chemical standards using 2D-TLC and HPLC.
Additional experiments were conducted on mature wheat grain and stalks and on mature sugar beet root to characterize the nature of the non extractable residues using HPLC, Mass Spectrometry and NMR.

Derivatization of metabolites was conducted as an aid in mass spectral identification and also to confirm the presence of sugar conjugates.

Findings :

Table B.6.9-7 : Radioactive residue levels in rotational crops following tobacco grown in the ^{14}C-(phenyl)-metalaxyl treated soil (residues expressed as mg metalaxyl equiv./kg).

Sample commodity	Days after soil treatment	Total metalaxyl (mg metalaxyl equiv./kg)	Days post planting	Extractable (%)	Non-extractable (%)
Soil at rotational crop planting			Not relevant		
0-7.5*	232	1.054			
7.5-15	232	0.672			
15-20	232	0.594			
Mature Lettuce foliage	292	0.564	60	90.8	9.2
Mature Spring wheat stalks	323	7.171	91	79.2	20.8
Mature Spring wheat grain	323	0.593	91	22.0	78.0
Mature Spring wheat hulls	323	7.762	91	60.8	39.2
Mature Soybeans stalk	432	3.612	200	88.2	11.8
Mature Soybeans pods	432	1.061	200	81.6	18.4
Mature Soybeans	432	0.398	200	79.4	20.6
Mature Sugar beet foliage	411	1.102	179	88.1	11.9
Mature Sugar beet root	411	0.275	179	62.5	37.5

* : Soil layer depth in cm.

Relevant residues were present in lettuce leaves at maturity as they were 10 times higher than the MRL (0.05 mg/kg), 292 days after the soil treatment.
No MRL could be established for spring wheat, soybean and sugar beet in point B.6.6.
Residue values in rotational plant parts, at time of harvesting, ranged from 0.275 to up to 7 mg/kg of total metalaxyl with elapse time from the soil treatment of 323 to 432 days.

Table B.6.9-8 : Identification of metabolites in Wheat, Lettuce and Sugar beets rotational crops after soil treatment with ^{14}C-(Phenyl)-Metalaxyl

	Mature spring wheat stalks	50% mature lettuce foliage	Mature sugar beet root
Total residues (mg metalaxyl equiv./kg)	7.171	0.877	0.275
Extractable radioactive residues (% TRR)	79.2	91.7	62.5
Organosoluble phase (% TRR)*	10.5	23.4	23.9
Elucidation of radioactive residues (% of TRR)			
CGA-48988 (parent)	0.1	15.3	3.3
CGA-67869	0.1	-	-
CGA-62826	0.7	-	5.4
CGA-94689 A/B	1.9	0.5	-
CGA-100255	0.3	-	-

	Mature spring wheat stalks	50% mature lettuce foliage	Mature sugar beet root
CGA-107955	0.4	1.3	-
CGA-108905	1.0	-	2.3
CGA-67868	0.2	-	-
CGA-37734	1.0	-	-
N1a aglycone (benzyl alcohol of CGA-67868)	0.8	-	-
N1b aglycone (hydroxy phenyl ring of CGA-67868)	-	0.4	-
N4/5 : CGA-94689A/B glucoside	1.2	-	-
N7 : CGA-107955 glucoside	-	-	1.0
CGA-108905 + N7	-	0.9	-
CGA-100255+CGA-67868+CGA62826	-	0.9	-
CGA 94689A/B + CGA 107955	-	-	1.1
Unknown metabolites	<0.1	-	-
TOTAL	7.8	20.8	13.1
Aqueous soluble phase (% TRR)*	89.5	76.6	76.1
Elucidation of radioactive residues (% of TRR)			
CGA-94689 A/B	3.7	-	-
CGA-62826	0.5	-	20.1
CGA-100255	0.2	-	-
CGA-107955	0.7	-	-
CGA-108905	1.0	-	0.9
CGA-37734	0.2	-	-
CGA-119857	0.4	-	-
CGA-79353	-	-	8.1
N1a : benzyl alcohol of CGA-67868 glucoside	6.8	-	-
N1b: hydroxy phenyl ring of CGA-67868 glucoside	-	15.5	-
N2 : CGA-37734 glucoside	4.3	1.7	-
N3 : CGA-100255 glucoside	1.3	11.1	-
N4 : CGA-94689 A glucoside	12.2	0.2	-

	Mature spring wheat stalks	50% mature lettuce foliage	Mature sugar beet root
N5 : CGA-94689 B glucoside	18.4	1.9	-
N6a/6b: CGA-62826 glucoside	2.0	1.5	-
N7 : CGA-107955 glucoside	1.5	1.8	-
B1/B2 : benzyl alcohol of CGA-107955	4.6	-	-
P0 : benzyl alcohol of CGA-62826	2.6	-	-
Unknown metabolites	2.4	36.2	16.4
Total	62.8	69.9	45.5
Post extraction residues	20.8	9.2	37.5
Protease and β-glucosidase digestion (% TRR)			
Organosoluble residues released	7.9	-	-
Aqueous soluble residues released	10.3	-	-
Acid hydrolysis (% TRR)			
Organosoluble residues released	-	-	9.4
Aqueous soluble residues released	-	-	13.4
Final solid residue (% TRR)	2.6	-	14.7
Total recovery (extracted +unextracted phases)	100	101	100

- : Not radiodetected.
* : Fractions used for 2D-TLC or HPLC metabolites quantitation.

Most of the metabolites were characterized but their identification was not confirmed by a second analytical method.

A total of 76 % of the TRR in mature wheat stalks, 54 % of TRR in 50% mature lettuce and 55% of TRR in sugar beet root was characterized.
7 glucosides were isolated and identified by Mass spectral analysis.
The metabolites found back were qualitatively similar to residues previously identified in plants and in animals with a higher proportion of glucose conjugates.
The parent compound was extensively metabolized in the 3 selected rotational crops but still remained an important compound of the residues in the 50% mature lettuce foliage (15% of the TRR).
The metabolite CGA-67868 present in wheat stalks and lettuce foliage was not detected neither in plants nor in rat metabolism.
However, this latter didn't seem to be indicative of any particular degradation pathway.

Conclusion :
The metabolic pathway of metalaxyl in rotational crops is similar to that in target crops but with a greater proportion of sugar conjugates.
Regarding the important levels of residues found in the rotational crops, the following informations must be provided by the notifier in the view of the residue data obtained in this study.
-Waiting period between the application and sowing or planting the succeeding crops,
-Witholding period for animal feedingstuffs,
-Re-entry period for livestock.
It should also be advisable that the notifier submits residue trials in accordance with the proposed GAPs for these

rotational crops in order to propose MRLs.

B.6.10 Proposed pre-harvest intervals, re-entry intervals or withholding periods to minimize residues in crops, plants, plant products, treated areas or spaces (Annex IIA 6.8; Annex IIIA 8.7)

Table B.6.10-1 : Proposed pre-harvest intervals (days)

Crops	PHI (days)
Table and wine grape	15
Bulb vegetables (onion)	14
Tomato	3
Cucumber	6
Melon	3
Broccoli	14
Lettuce	14
Spinach	20
Globe artichoke	20
Potato	7

These PHI proposals were chosen on the basis of the critical GAPs.

B.6.11 Estimates of the potential and actual exposure through diet and other means (Annex IIA 6.9; Annex IIIA 8.8)

Adult consumer :

The following TMDI calculations are carried out using :
- the FAO/WHO cultural diet for European (August 1994),
- the estimated STMR for individual plant commodities and established in section B.6.6 (Residues resulting from supervised trials),
- the conversion factors to apply for assessment of consumer safety in section B.6.3 (Residue definition).
- the contribution of commodities of animal origin was not taken into account (insufficient data)

Table B.6.11-1 : Calculation of the TMDI

Commodity	Consumption (kg/day)	Exposure level (mg/kg)	Conversion factor	Intake (mg/kg)
Table and wine grapes	0.1137	0.1	2	0.02274
Onion	0.0278	0.02*	1	0.000556
Tomato	0.066	0.02*	1	0.00132
Cucumber	0.0045	0.15	1	0.000675
Melon	0.0183	0.02*	1	0.000366
Broccoli	0.027	0.02*	1	0.00054
Lettuce	0.0471	0.02	4	0.003768
Spinach	0.0021	0.02*	1	0.000042
Globe artichoke	0.0055	0.02*	1	0.00011
Potato	0.2408	0.02*	1	0.004816
TOTAL				0.03493

Taking into account a person of 60 kg body weight, the TMDI is 0.00057 mg/kg b.w./day. This represents 0.29 % of the ADI (0.2 mg/kg b.w./day).

German 4-6 years old girl :

The following TMDI calculations are carried out using :
-the German diet for a 4-6 years old girl,
-the estimated STMR for individual plant commodities established in section B.6.6 (Residues resulting from supervised trials),
-the conversion factors to apply for assessment of consumer safety in section B.6.3 (Residue definition).
- the contribution of commodities of animal origin was not taken into account (insufficient data)

Table B.6.11-2 : Calculation of the TMDI

Commodity	Consumption (kg/day)	STMR (mg/kg)	Conversion factor	Intake (mg/kg)
Table and wine grapes	0.0087	0.1	2	0.00174
Onion	0.0083	0.02*	1	0.000166
Tomato	0.0151	0.02*	1	0.000302
Cucumber	0.0115	0.15	1	0.001725
Melon	0.0005	0.02*	1	0.00001
Broccoli	0.001	0.02*	1	0.00002
Lettuce	0.0046	0.02	4	0.000368
Spinach	0.0021	0.02*	1	0.000042
Globe artichoke	0.0002	0.02*	1	0.000004
Potato	0.0711	0.02*	1	0.001422
TOTAL				0.005779

Taking into account a body weight of 13.5 kg, the TMDI of the German 4-6 years old girl is 0.000428 mg/kg b.w./day. This represents 0.214 % of the ADI (0.2 mg/kg b.w./day).

Children and infants from United Kingdom.

The following TMDI calculations are carried out using :
-the Pesticides Safety Directorate Consumer Exposure Model,
-the estimated STMR for individual plant commodities and established in section B.6.6 (Residues resulting from supervised trials).
-the conversion factors to apply for assessment of consumer safety in section B.6.3 (Residue definition).
-the contribution of commodities of animal origin was not taken into account (insufficient data)

Table B.6.11-3 : Calculation of the TMDI

Commodity	Child 30 kg bw		Infant 7.5 kg bw	
	'High level' intakes from single commodities			
	97.5th percentile consumption (kg/day)	TMDI for single commodity (mg/kg b.w/day)	97.5th percentile consumption (kg/day)	TMDI for single commodity (mg/kg b.w/day)
Grape table	0.0419	0.000279	na	na
Grape-wine	na	na	na	na
Onion	0.0222	0.000015	0.0111	0.00003
Tomato	0.0361	0.000024	0.0137	0.000037
Cucumber	0.0152	0.000076	na	na
Melon	na	na	na	na
Broccoli	0.0304	0.00002	na	na
Lettuce	0.0111	0.00003	na	na
Spinach	0.0155	0.00001	na	na
Globe artichoke	na	na	na	na
Potato-total with skin	0.1005	0.000067	na	na
	Total dietary intakes from combinations of commodities (total TMDI) (mg/kg b.w./day)			
	0.00037		0.000066	

na : Not applicable

The TMDI of UK children and infants are respectively 0.19 and 0.033 % of ADI (0.2 mg/kg b.w./day).

Conclusion :
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.

B.6.12 Community MRLs and MRLs in EU Member States (Document E-4)

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.

B.6.13 Proposed MRLs and justification for the acceptability of those residues (Annex IIA; Annex IIIA)

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.

Table B.6.13-1 : 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 assessed, the MRLs for commodities of animal origin can not be proposed. However, the expression of the residue could be established.

Table B.6.13-1 : Proposed MRLs for metalaxyl-M - commodities of animal origin

Expression of the residue	Products	MRL (mg/kg)	STMR (mg/kg)
Total metalaxyl (+ its metabolites with the 2,6-dimethylaniline moiety)	Cow milk	Not defined	-
Total metalaxyl (+ its metabolites with the 2,6-dimethylaniline moiety)	Meat, Kidney and Liver	Not defined	-
Total metalaxyl (+ its metabolites with the 2,6-dimethylaniline moiety)	Egg	Not defined	-
Total metalaxyl (+ its metabolites with the 2,6-dimethylaniline moiety)	Fat	Not defined	-

B.6.14 Storage stability of residue samples

Stability of metalaxyl in lettuce during frozen storage at -20°C (Büttler B.; 1979)
Guidelines :
Not specified
GLP :
No. Not required at the time the test was performed.
Material and Methods :
Samples of lettuce were fortified with 5.0 ppm metalaxyl. The spiked samples were divided into several portions and one portion was analysed immediately after preparation. The other samples were frozen at -20°C until analysis after approximately 3 and 6 months.
Field trial lettuce samples were directly frozen at -20°C until analysis for the parent compound at approximately 5, 8 and 12 months.
One method recovery test was made for each time point.
Levels of metalaxyl were determined according to the method REM 16/76.
Findings :
Recovery values (presented in the table herebelow) were generally acceptable. However, a previous analysis of a non fortified sample is strongly advisable to prevent interference with other substances (Doc. 7032/VI/95 rev.5-Appendix H).

Table B.6.14-1 : Percent recovery for method recovery test (%)

Plant commodity	Test substance	Fortification level (mg/kg)	Days					
			0	81	155	177	241	337
Fortified lettuce	Metalaxyl	5	106	92	-	102	-	-
Field trial lettuce	Metalaxyl	-	87	-	106	-	92	102

- : Result not available.

Table B.6.14-2 : Amount of metalaxyl found in the course of the frozen storage stability study (mg/kg)

Plant commodity	Test substance	Days					
		0	81	155	177	241	337
Fortified lettuce	Metalaxyl	5.2	4.8	-	5.7	-	-
Field trial lettuce	Metalaxyl	0.67	-	1.11	-	0.85	1.14

Conclusion :
Residues of metalaxyl are stable in lettuce for a minimum of 12 months under freezer storage conditions.

Stability of residues of metalaxyl and its metabolites under freezer storage conditions (Ross J.A., 1980)
This study was not taken into consideration as the analytical methods used for the determination of the parent compound and metalaxyl and its metabolites containing the 2,6-dimethylaniline moiety (AG-325 and AG-330) were not evaluated at point B.4 - Methods of analysis- of this monograph.

-Storage stability of total residues of metalaxyl in weathered crops under freezer storage conditions (Eudy L.W., 1993)
-Storage stability of total residues of metalaxyl in weathered crops under freezer storage conditions - Amendment 1 (Eudy L.W., 1994)
Guidelines :
Not specified.
GLP :
Yes, except the biological phase of the study.
Material and Methods :
Weathered samples of peppers, potatoes and spinach were stored for 39 months under freezer storage conditions at approximately -20°C and wheathered samples of cranberries were stored under identical conditions for 38 months. Samples of these crops were fortified with 0.05, 0.5, 1.0, 2.0, 3.0 and 4.0 ppm metalaxyl determined as 2,6-dimethylaniline.
Each sample set consisted of an unfortified control sample, 2 control samples fortified with parent metalaxyl immediately before extraction and 2 weathered crop samples.
These samples were analysed for total residues of metalaxyl determined as 2,6 dimethylaniline according to the analytical method AG-395. The results were reported as metalaxyl equivalents using the conversion factor 2.308.
One method of procedural recovery test of metalaxyl from control crop sample was made for each time point.
Residue results were corrected for average procedural recoveries<100%.
Findings :
Recoveries were generally acceptable with occasionally unexplained high and low values (underlined in the table).

Table B.6.14-2 : Percent recovery for method recovery test (%)

Plant commodity	Test substance	Months											
		0	1	2	6	8	9	12	18	24	31	38	39
Cranberries	Total Metalaxyl	71 83	87 <u>130</u>	- -	87 80	- -	- -	92 72	<u>45</u> 77	- -	79 66	96 77	- -
Peppers	Total Metalaxyl	91 89	- -	<u>50</u> 76	<u>154</u> 87	- -	60 74	96 94	60 95	62 82	- -	- -	83 65
Potatoes	Total Metalaxyl	98 86	- -	- -	85 79	- -	- -	80 71	80 79	65 80	- -	- -	93 79
Spinach	Total Metalaxyl	<u>122</u> 86	77 -	- -	- -	<u>58</u> 84	- -	64 -	65 91	67 77	- -	- -	82 86

- : Not applicable.

Table B.6.14-3 : Amount of total metalaxyl (determined as 2,6-dimethylaniline) found in weathered crops in the course of the frozen storage stability study (expressed as mg metalaxyl equiv./kg)

Plant commodity	Test substance	Months											
		0	1	2	6	8	9	12	18	24	31	38	39
Cranberries	Total metalaxyl	0.47 0.42	0.75 0.51	- -	0.54 0.54	- -	- -	0.54 0.46	0.66 0.60	- -	0.56 0.77	0.38 0.58	- -
Peppers	Total metalaxyl	0.48 0.48	- -	0.57 0.56	0.16 0.38	- -	0.52 0.55	0.49 * 0.47	0.57 * 0.61	0.49 0.54	- -	- -	0.44 0.54
Potatoes	Total metalaxyl	0.22 0.25	- -	- -	0.16 0.18	- -	- -	0.19 0.20	0.15 0.18	0.25 0.23	- -	- -	0.14 0.20
Spinach	Total metalaxyl	2.2* 2.1	- -	1.9* -	- -	2.8* 3.0	- -	3.0* 2.9	2.5* 2.1	2.1 2.2	- -	- -	2.1* 2.0

* : The control values were above the limit of determination (0.05 mg/kg) of the analytical method.

As far as the stability of the residues is concerned, the trend with all commodities was a stability of the residue level during the course of the study. One residue value (0.16 mg/kg) determined in peppers at 6 months was significantly lower than the corresponding replicate analysis or any of the other residue values determined over 2 years. This value was probably an outlier.

Conclusion :
Total residues of metalaxyl determined as 2,6-dimethylaniline are stable in peppers, potatoes and spinach samples stored for up to 39 months and in cranberries stored for up to 38 months when these crops are stored under freezer conditions.

B.6.15 Summary and evaluation of residue behaviour

Metabolism in plants and in livestock

The metabolism of metalaxyl was investigated in grapevines, lettuce, potato, tobacco, lactating goat and laying hen. The metabolic reactions on metalaxyl in plants and in animals are depicted in the figures 6.1 and 6.2 in appendix D to this section.

In plants, the parent compound is the major component of the residue and no metabolite of toxicological concern has been isolated.

In animals, metalaxyl undergoes an extensive metabolization.
All the metabolites detected in lactating goat and laying hen are also observed in rat, except the metabolite CGA-108906 identified in the hen study and covered by a toxicological study in the rat.

The degradation of metalaxyl in plants and in animals proceeds primarily via 4 independent pathways :
-oxidation of one of the ring methyl groups,
-ring hydroxylation,
-hydrolysis of the methyl ester and ether bonds,
-N-dealkylation.
The metabolites which are formed are then conjugated to sugars in plants and to glucuronic acid, fatty acids and amino acids in animals.

Supervised residue trials
Trials data under field conditions on grapes, onion, tomato, cucumber, melon, lettuce, spinach, artichoke, potato and tobacco for Northern and Southern Europe allowed MRL proposals.

A validated method of analysis of the parent metalaxyl-M enabled the enforcement of the proposed MRLs. However this method does not allow to distinguish between metalaxyl and metalaxyl-M.

Industrial or household processing studies - Livestock feeding studies
Data concerning the effects of industrial fruit processing on the residue level (grape wet or dry pomace) are required. These data would permit to perform the intake calculations for livestock, to generate feeding studies with the dairy cow and poultry at relevant dosage, and finally to determine the actual level of residue in commodities of animal origin.

Metalaxyl-M in animal products can be considered as non liposoluble.

Residues in rotational crops
Residues in the successive crops are considered as relevant and the fixing of MRLs for these crops is therefore necessary.
One metabolite (CGA-67868), not present in the rat metabolism, is observed in rotational wheat and lettuce.

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.