13544

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Chemical:	**Metalaxyl; D-Alanine, N-(2,6-dimethylphenyl)-N-(met**
PC Code:	**113501; 113502**
HED File Code	**11000 Chemistry Reviews**
Memo Date:	**09/13/2001**
File ID:	**DPD276001**
Accession Number:	**412-02-0006**

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: September 13, 2001

MEMORANDUM

SUBJECT: Metalaxyl/Mefenoxam Analytical Method Recovery Data in Plants.

DP Barcode:	D276001	PRAT Case:	819456
Submission No.:	S547725	Caswell No.:	None
PC Code:	113501 and 113502	Class:	Fungicide
Trade Name:	Not Applicable	EPA Reg. No.:	Not Applicable
40 CFR:	180.408 and 180.546		
MRID Nos.:	44208107		

FROM: Nancy Dodd, Chemist
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Health Effects Division (7509C)

THROUGH: Stephen Dapson, Branch Senior Scientist
Registration Action Branch 3
Health Effects Division (7509C)
09/14/2001

TO: Mary Waller/Thomas Ellwanger, PM Team #21
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Registration Division (7505C)

and

Betty Shackleford/Bentley Gregg, PM Team #53
Special Review and Reregistration Division (7508C)

INTRODUCTION

Syngenta (formerly Novartis Crop Protection, Inc. and formerly Ciba Crop Protection) submitted additional method validation data for the fungicides metalaxyl [*N*-(2,6-dimethylphenyl)-*N*-(methoxyacetyl) alanine methyl ester] and mefenoxam [(R)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]-propionic acid methyl ester; CGA-329351] in plants. The method validation data were requested under the metalaxyl reregistration process (D203675, S. Hummel, 10/17/94). Mefenoxam (CGA-329351) is the R isomer; metalaxyl (CGA-48988) is a mixture of the R and S isomers.

A time-limited tolerance (to expire on December 31, 2001) for mefenoxam and its metabolites containing the 2,6-dimethylaniline moiety, and *N*-(2-hydroxymethyl-6-methylphenyl)-*N*-(methoxyacetyl)-alanine methyl ester, each expressed as mefenoxam equivalents, in/on canola at 0.05 ppm has been established [*FR Vol. 65, 57550-57557*; 40 CFR § 180.546 (b)] in connection with a Section 18 emergency exemption for use of mefenoxam as a seed treatment on canola in ND. Tolerances are pending for the combined residues of (R)- and (S)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]-propionic acid methyl ester, its metabolites containing the 2,6-dimethylaniline moiety, and *N*-(2-hydroxymethyl-6-methylphenyl)-*N*-(methoxyacetyl)alanine methyl ester, each expressed as mefenoxam equivalents, on canola at 0.05 ppm (D254225, N. Dodd, 11/13/00), on the Herb Subgroup (D257785, N. Dodd, 4/20/01), and on globe artichoke and a number of minor/tropical fruits (D260093, N. Dodd, 3/13/01). No other tolerances have been established for mefenoxam.

Permanent tolerances have been established for the combined residues of metalaxyl and its metabolites containing the 2,6-dimethylaniline moiety, and *N*-(2-hydroxymethyl-6-methylphenyl)-*N*-(methoxyacetyl) alanine methyl ester, each expressed as metalaxyl equivalents, in/on a number of plant and livestock commodities [40 CFR § 180.408 (a, c and d)]. Tolerances have been established on plant commodities at levels ranging from 0.1 ppm in/on beets (sugar and garden), *Brassica* leafy vegetables, cereal grains, cottonseed, pineapples, sunflowers, and papaya to 25 ppm in/on grass hay. Tolerances have also been established on livestock commodities at levels ranging from 0.02 ppm in milk to 0.4 ppm in fat, liver, and kidney of cattle, goats, hogs, horses, poultry, and sheep.

Tolerances for residues of metalaxyl in/on raw and processed plant commodities and livestock commodities are currently expressed in the CFR in terms of the combined residues of metalaxyl [*N*-(2,6-dimethylphenyl)-*N*-(methoxyacetyl) alanine methyl ester] and its metabolites containing the 2,6-dimethylaniline moiety, and *N*-(2-hydroxymethyl-6-methylphenyl)-*N*-(methoxyacetyl)-alanine methyl ester, each expressed as metalaxyl equivalents. However, the HED Metabolism Committee (now called the Metabolism Assessment Review Committee) determined in a meeting on 9/8/93 that the residues to be regulated in livestock commodities are metalaxyl, metabolites that can be converted to 2,6-dimethylaniline (2,6-DMA), and those metabolites containing the 2-hydroxymethyl-6-methylaniline (HMMA) moiety (S. Hummel, 9/10/93).

The Metabolism Assessment Review Committee (D269910, N. Dodd, 10/27/00) discussed mefenoxam on 10/24/00 and concluded that the residues to be regulated for the tolerance expression and for dietary risk assessments would be the following:

Plants

(R)- and (S)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]-propionic acid methyl ester, its metabolites containing the 2,6-dimethylaniline moiety, and *N*-(2-hydroxymethyl-6-methylphenyl)-*N*-(methoxyacetyl)alanine methyl ester*, each expressed as mefenoxam equivalents

[* *N*-(2-hydroxymethyl-6-methylphenyl)-*N*-(methoxyacetyl)alanine methyl ester is CGA-94689.]

Livestock

(R)- and (S)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]-propionic acid methyl ester, its metabolites containing the 2,6-dimethylaniline moiety, and its metabolites containing the 2-hydroxymethyl-6-methylaniline moiety, each expressed as parent equivalents

Rotational Crops

(R)- and (S)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]-propionic acid methyl ester, its metabolites containing the 2,6-dimethylaniline moiety, and *N*-(2-hydroxymethyl-6-methylphenyl)-*N*-(methoxyacetyl)alanine methyl ester, each expressed as parent equivalents, except that 2-[(methoxyacetyl)(2-methoxy-1-methyl-2-oxoethyl)amino]-3-methylbenzoic acid (CGA-108905) and *N*-(3-hydroxy-2,6-dimethylphenyl)-*N*-(methoxyacetyl)alanine methyl ester (CGA-100255) will be considered in risk assessments involving the foliar use of mefenoxam.

Metalaxyl is a List A chemical. A Metalaxyl Reregistration Standard and Guidance Document was issued on 12/81. Product and Residue Chemistry Chapters of the Metalaxyl Registration Standard were issued on 6/22/87. The Metalaxyl Final Reregistration Standard and Tolerance Reassessment (FRSTR) Guidance Document was dated 9/88. The Metalaxyl Product Chemistry and Residue Chemistry Reregistration Standard Updates were issued on 3/13/91. There is a Metalaxyl Product Chemistry and Residue Chemistry Registration Standard Update dated 4/92. The Product and Residue Chemistry Chapters for the Metalaxyl Reregistration Eligibility Decision Document (DP Barcodes D197037 and D197066, CBRS #12906 and 12907) were issued on 6/16/94.

The structure of metalaxyl/mefenoxam is shown in Figure 1 below.

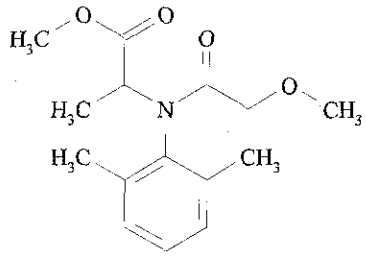


Figure 1. Metalaxyl/Mefenoxam

BACKGROUND

Adequate enforcement methods, Method I (Method AG-348) in the Pesticide Analytical Manual, Vol. II (PAM II) and Method AG-395 (MRID 00148440; sent to FDA for inclusion in PAM II as Method III), are available to determine regulated residues of metalaxyl/mefenoxam in plants. In AG-348, residues are converted to 2,6-dimethylaniline and analyzed by GLC with alkalki flame ionization detection (AFID). Gas-liquid chromatography/mass spectrometry in the chemical ionization mode with selected ion monitoring is used in the determinative step for samples that show interference in the GLC/AFID analysis. Method AG-395 is an improved modification of Method I in PAM II. Method AG-395 exhibits increased sensitivity for measurement of a metabolite and reduced time required for analysis. In AG-395, residues are converted to dimethylaniline and analyzed by gas liquid chromatography (GLC) with a nitrogen/phosphorus detector operating in the nitrogen-specific mode. Method AG-395 has undergone a successful EPA petition method validation with plant samples (PP#3F2918 and 3F2919, K.H. Arne, 8/2/84). Although recoveries of CGA-94689 were consistently less than 70%, the low recoveries of the hydroxy metabolite CGA-94689 were considered acceptable because it comprised less than 20% of the total residue in edible portions of plants (PP#3F2918 and 3F2919, K. Arne, 8/2/84). In the AG-395 method validation, peanuts and peanut hay were fortified with metalaxyl, CGA-94689, and a mixture of CGA-62826, CGA-67869, and CGA-107955. Acceptable recoveries were obtained in peanuts at 0.05 ppm and peanut hay at 0.5 ppm. Ciba-Geigy analytical method AG-395 has been forwarded to FDA for inclusion in PAM II as Method III (M. Bradley letter of 2/18/87 to A. Marcotte, FDA).

CONCLUSIONS

OPPTS GLN 860.1340: RESIDUE ANALYTICAL METHOD

1. Adequate recoveries were not obtained for CGA-94689 using Method AG-395 for tomatoes, corn grain, wheat straw, sugar beets, and head lettuce since 1) recoveries should lie between 70% and 120% and should not vary significantly from sample to sample and/or 2) control values should be reasonably low in relation to the proposed tolerance/spiking level, preferably less than 20% of the proposed tolerance/spiking level.

2. Adequate recoveries were generally not obtained for CGA-62826 using Method AG-395 for tomatoes, corn grain, wheat straw, sugar beets, and head lettuce since 1) recoveries should be at least 70% and should not vary significantly from sample to sample and/or 2) control values should be reasonably low in relation to the proposed tolerance/spiking level, preferably less than 20% of the proposed tolerance/spiking level. The exceptions may be CGA-62826 recoveries in tomatoes, corn grain, wheat straw, sugar beets, and head lettuce at the highest reported level (0.50 ppm), but only one recovery value was reported for each crop at that level.

3. The registrant should attempt to improve recoveries for CGA-94689 and CGA-62826 and provide recovery data for P1 and P2 in plants using Method AG-395.

4. In 1998, Enviro-Test Laboratories revised the analytical method used for analysis of CGA-329351 in the canola residue report designated MRID 44703530. The improved method for total residues of CGA-329351 as 2,6-dimethylaniline is based on the Ciba-Geigy Corporation analytical method AG-395. Improved recoveries for AG-395 were obtained because of the following modifications, which reduced losses of volatile DMA during the clean-up procedure: use of prechilled condenser water, improved glass ware, and insulation of the reflux flask with glass wool. The petitioner should submit this improved method so that it can be validated by EPA as an enforcement method and included in PAM II since the recoveries obtained are better than those obtained with the current enforcement method. An independent laboratory method validation would not be needed since the method is similar to the current enforcement method AG-395.

RECOMMENDATION

The registrant should be informed of the status of the validation data for Method AG-395 on plant commodities as stated in Conclusions 1, 2, 3, and 4 above.

DETAILED CONSIDERATIONS

See Attachment 1 for the chemical names and structures of metalaxyl/mefenoxam and its metabolites which are discussed in this review.

OPPTS GLN 860.1340: RESIDUE ANALYTICAL METHOD

Plant Commodity Method AG-395 (MRID 44208107)

Additional method validation data for method AG-395 for CGA-94689, CGA-62826, and P1/P2 in plants were requested under the metalaxyl reregistration process (D203675, S. Hummel, 10/17/94) to demonstrate that the method detects representative metalaxyl metabolites containing the DMA (2,6-dimethylaniline) and HMMA (hydroxymethyl methyl aniline) moieties. In response, method validation data for AG-395 for CGA-94689 and CGA-62826 on tomatoes, corn grain, wheat straw, sugar beets, and head lettuce were submitted (MRID 44208107, citation below). The registrant indicated that validation data on P1/P2 would be submitted later.

MRID 44208107 Eudy, L.W., PhD (1997) Method Validation Trial for the Determination of CGA-94689, P1/P2, and CGA-62826 in Crops Using Analytical Method AG-395, Laboratory Project Number ABR-96109, Study Number 174-95, unpublished study sponsored by Ciba-Geigy Corporation, 74 pp.

In Method AG-395, residues in wet crops are extracted by blending in 80% (v/v) methanol/water for one minute; dry crop samples are extracted by refluxing with 80% (v/v) methanol/water for two hours. An aliquot of the extract is dried and redissolved in water. The residue is refluxed with methanesulfonic acid for 15 minutes, and then basified after addition of water, converting the residues to 2,6-dimethylaniline (DMA). The DMA formed in the reaction is steam distilled and cleaned-up with a silica SepPak® cartridge prior to analysis by gas liquid chromatography (GLC) with a nitrogen/phosphorus detector operating in the nitrogen-specific mode. DMA residues are converted to metalaxyl equivalents.

In MRID 44208107, modifications to method AG-395 were as follows: Crop samples were extracted by refluxing with 80% (v/v) methanol/water for two hours as described in Section 5.4, "Extraction- Dry Crop." In Section 5.5.4, the water and sodium hydroxide were doubled in volume. In Sections 5.7.6 and 5.7.7, the trifluoroacetic acid addition step for the formation of DMA-TFA was found to be unnecessary and was omitted. DMA residues in dichloromethane from Section 5.7.5 were concentrated for GC analysis.

DMA results were calculated in ppm and converted to CGA-94689 or CGA-62826 equivalents by multiplying by the molecular weight ratios of 2.437 or 2.189, respectively. Control samples of tomatoes, corn grain, wheat straw, sugar beets, and head lettuce were fortified with either CGA-94689 or CGA-62826 at 0.05 ppm, 0.10 ppm, and 0.50 ppm. One control sample, a

reagent blank, and two controls fortified with metalaxyl (0.05 and 0.10 ppm) were included in each sample set. Recoveries for CGA-94689 and CGA-62826 are shown in the following tables.

Table 1. Recoveries using Method AG-395 for CGA-94689 and CGA-62826 on Tomatoes

Commodity	Chemical Added	PPM Added	PPM Found	% Recovery (corrected)[1]	% Recovery (uncorrected)[2]
tomatoes	CGA-94689	0.00	<0.05 (0.022)	NA[3]	NA
		0.05	0.047	50	94
		0.05	0.038	32	76
		0.10	0.062	40	62
		0.10	0.052	30	52
		0.50	0.154	26	31
	CGA-62826	0.00	<0.05 (0.013)	NA	NA
		0.05	0.050	74	100
		0.05	0.038	50	76
		0.10	0.098	85	98
		0.10	0.072	59	72
		0.50	0.399	75	80

[1] These recoveries were corrected for controls.

[2] These recoveries were not corrected for controls.

[3] Not applicable

Table 2. Recoveries using Method AG-395 for CGA-94689 and CGA-62826 on Corn Grain					
Commodity	Chemical Added	PPM Added	PPM Found	% Recovery (corrected)[1]	% Recovery (uncorrected)[2]
corn grain	CGA-94689	0.00	<0.05 (0.021)	NA[3]	NA
		0.05	0.026	10	52
		0.05	0.019	0	38
		0.10	0.034	13	34
		0.10	0.046	25	46
		0.50	0.120	20	24
	CGA-62826	0.00	<0.05 (0.043)	NA	NA
		0.05	0.068	50	136
		0.05	0.056	26	112
		0.10	0.092	49	92
		0.10	0.117	74	117
		0.50	0.384	68	77

[1] Recoveries were corrected for controls.

[2] These recoveries were not corrected for controls.

[3] Not applicable

Table 3. Recoveries using Method AG-395 for CGA-94689 and CGA-62826 on Wheat Straw

Commodity	Chemical Added	PPM Added	PPM Found	% Recovery (corrected)[1]	% Recovery (uncorrected)[2]
wheat straw	CGA-94689	0.00	0.060	NA[3]	NA
		0.05	0.051	0	102
		0.05	0.057	0	114
		0.10	0.055	0	55
		0.10	0.055	0	55
		0.50	0.096	7	19
	CGA-62826	0.00	0.052	NA	NA
		0.05	0.107	110	214
		0.05	0.102	100	204
		0.10	0.136	84	136
		0.10	0.129	77	129
		0.50	0.407	71	81

[1] Recoveries were corrected for controls.

[2] These recoveries were not corrected for controls.

[3] Not applicable

Table 4. Recoveries using Method AG-395 for CGA-94689 and CGA-62826 on Sugar Beets					
Commodity	Chemical Added	PPM Added	PPM Found	% Recovery (corrected)[1]	% Recovery (uncorrected)[2]
sugar beets	CGA-94689	0.00	0.110	NA[3]	NA
		0.05	0.105	0	210
		0.05	0.058	0	116
		0.10	0.068	0	68
		0.10	0.087	0	87
		0.50	0.128	4	26
	CGA-62826	0.00	<0.05 (0.044)	NA	NA
		0.05	0.095	102	190
		0.05	0.074	60	148
		0.10	0.113	69	113
		0.10	0.112	68	112
		0.50	0.387	69	77

[1] Recoveries were corrected for controls.

[2] These recoveries were not corrected for controls.

[3] Not applicable

Table 5. Recoveries using Method AG-395 for CGA-94689 and CGA-62826 on Head Lettuce					
Commodity	Chemical Added	PPM Added	PPM Found	% Recovery (corrected)[1]	% Recovery (uncorrected)[2]
head lettuce	CGA-94689	0.00	0.097	NA[3]	NA
		0.05	0.096	0	192
		0.05	0.099	4	198
		0.10	0.126	29	126
		0.10	0.136	39	136
		0.50	0.236	28	47
	CGA-62826	0.00	0.056	NA	NA
		0.05	0.106	100	212
		0.05	0.084	56	168
		0.10	0.133	77	133
		0.10	0.132	76	132
		0.50	0.320	53	64

[1] Recoveries were corrected for controls.

[2] These recoveries were not corrected for controls.

[3] Not applicable

Conclusions

Adequate recoveries were not obtained for CGA-94689 using Method AG-395 for tomatoes, corn grain, wheat straw, sugar beets, and head lettuce since 1) recoveries should lie between 70% and 120% and should not vary significantly from sample to sample and/or 2) control values should be reasonably low in relation to the proposed tolerance/spiking level, preferably less than 20% of the proposed tolerance/spiking level.

Adequate recoveries were generally not obtained for CGA-62826 using Method AG-395 for tomatoes, corn grain, wheat straw, sugar beets, and head lettuce since 1) recoveries should be at least 70% and should not vary significantly from sample to sample and/or 2) control values should be reasonably low in relation to the proposed tolerance/spiking level, preferably less than 20% of the proposed tolerance/spiking level. The exceptions may be CGA-62826 recoveries in tomatoes, corn grain, wheat straw, sugar beets, and head lettuce at the highest reported level (0.50 ppm), but only one recovery value was reported for each crop at that level.

The registrant should attempt to improve recoveries for CGA-94689 and CGA-62826 and provide recovery data for P1 and P2 in plants using Method AG-395.

In 1998, Enviro-Test Laboratories revised the analytical method used for analysis of CGA-329351 in the canola residue report designated MRID 44703530. The improved method for total residues of CGA-329351 as 2,6-dimethylaniline is based on the Ciba-Geigy Corporation analytical method AG-395. Improved recoveries for AG-395 were obtained because of the following modifications, which reduced losses of volatile DMA during the clean-up procedure: use of prechilled condenser water, improved glass ware, and insulation of the reflux flask with glass wool. The petitioner should submit this improved method so that it can be validated by EPA as an enforcement method and included in PAM II since the recoveries obtained are better than those obtained with the current enforcement method. An independent laboratory method validation would not be needed since the method is similar to the current enforcement method AG-395.

Attachment 1: Names and Structures of Mefenoxam, Metalaxyl, CGA-94689, CGA-62826, P1 and P2

cc: N. Dodd (810C), PM# 21, PM#53, M. Rust (810J)
RDI: ChemTeam: 7/18/01: S. Dapson:8/31/01
7509C:RAB3:CM#2:Rm810C:305-5681:N. Dodd:nd:9/13/01

ATTACHMENT 1

Table 6. Names and Structures of Mefenoxam, Metalaxyl, CGA-94689, CGA-62826, P1, and P2

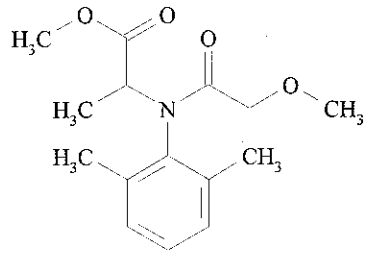
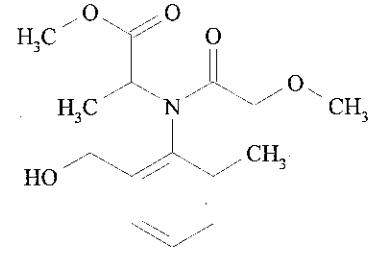
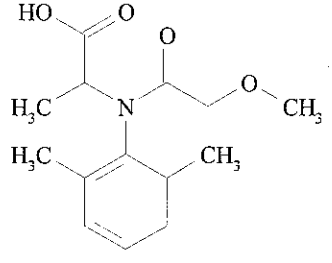
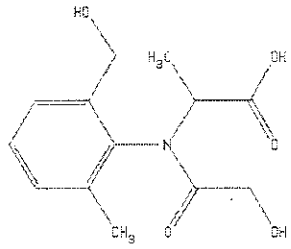
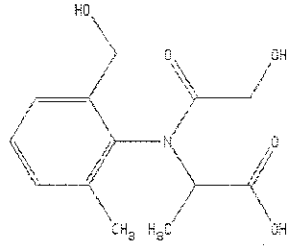
Chemical Name Common Name (Company Code)	Structure
(R)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]-propionic acid methyl ester mefenoxam (CGA-329351) and *N*-(2,6-dimethylphenyl)-*N*-(methoxyacetyl) alanine methyl ester metalaxyl (CGA-48988)	
N-(2-hydroxymethyl-6-methylphenyl)-N-(methoxyacetyl)alanine methyl ester (CGA-94689)	
N-(2,6-dimethylphenyl)-N-(methoxyacetyl)alanine (CGA-62826)	

Table 6. Names and Structures of Mefenoxam, Metalaxyl, CGA-94689, CGA-62826, P1, and P2	
Chemical Name Common Name (Company Code)	Structure
N-[2-(hydroxymethyl)-6-methylphenyl-N-(hydroxyacetyl)alanine[1] (P1)	
N-[2-(hydroxymethyl)-6-methylphenyl]-N-(hydroxyacetyl)alanine[1] (P2)	

[1] P1 and P2 are isomers.