Reg. Std 7.

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

SEP 9 1991

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: PP#8F3362/FAP#6H5493-Metalaxyl on Grapes (CB-1 Nos. 7646 and 7647)-Evaluation of Amendment Dated January 25,1991 MRID Nos. 41664503 thru 41664506)

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Registration Division (H7505C)

and

Toxicology Branch
Health Effects Division (H7509C)

Thru: Robert S. Quick, Acting Chief
Chemistry Branch 1 - Tolerance Support
Health Effects Division (H7509C)

Robert S. Quick

Ciba-Geigy has submitted this amendment containing a revised Section B and copies of five volumes of data which contain the new goat and poultry metabolism studies and associated references, which were reviewed in the CB-2 March 13, 1991 Metalaxyl Reregistration Standard Update. This amendment is in response to deficiencies cited in CB-1's September 27, 1990 review of the subject petition.

Conclusions

1. The revised Section B/label which as requested, includes a specific minimum spray volume, is acceptable.

2. For the purpose of the subject petition the nature of the residue in animals is adequately understood and consists of the parent and its metabolites containing the 2,6-dimethylaniline moiety, and N-(2-hydroxy methyl-6-methyl)-N-(methoxyacetyl)-alanine methyl ester, each expressed as metalaxyl equivalents.

3. For the subject petition the current analytical methodology for animal commodities, which includes acid hydrolysis and formation of 2,6-dimethyl aniline, is adequate.

4. In light of the current approved uses of metalaxyl, the proposed use on grapes will not increase the likelihood of secondary residues of metalaxyl in meat, fat, milk, poultry and eggs resulting from the feed commodities, grape pomace and raisin waste.

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Recommendation

TOX considerations permitting, CB-1 recommends for the proposed metalalaxyl tolerance on the RAC grapes at 2.0 ppm and the proposed FAT's on wet and dry grape pomace, raisins and raisin waste at 10.0, 6.0, and 10.0 ppm, respectively.

Present Submission

1. Section F - No Revisions

The tolerance proposal is the same as iterated in CB-1's September 27, 1990 review. In summary a tolerance on the RAC grapes at 2.0 ppm and FAT's on wet and dry grape pomace, raisins and raisin waste at 10.0, 6.0, and 10.0 ppm respectively, are proposed for 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 methylester, each expressed as metalaxyl

2. Revised Section B-Grapes

The revised Section B is the same as discussed in CB-I's September 27, 1990 review, except the label has been revised to recommend a minimum spray volume (i.e. 50 gallons/acre).

Detailed Considerations

The deficiencies listed in CB-I's September 27, 1990 review (i.e. Nos. 1,3,4 and 5) are iterated below followed by the Petitioner's Responses and CB-1's Comments/Conclusions.

Defiency No. 1

A revised label recommending a minimum spray volume is required.

Petitioner's Response to Deficiency No. 1

The Petitioner has submitted a revised Section B/label recommending a minimum spray volume of 50 gallons of water /acre.

CB-1's Comments/Conclusions re: Deficiency No. 1

This deficiency is resolved.

Defiency No. 3

The nature of the residue in animals is not adequately understood and new metabolism studies are required (see September 1988 Guidance Document for Metalaxyl).

Petitioner's Response to Deficiency No. 3

The petitioner has submitted new goat and poultry metabolism studies which were reviewed by CB-2 in the March 13, 1991 Reregistration Update.

CB-1's Comments/Conclusions re: Deficiency No. 3

The required new goat and poultry metabolism studies were submitted and reviewed by CB-2 in the March 13,1991 Metalaxyl Reregistration Standard Update (see Attachment 1 for conclusions). As discussed in Attachment 1, the nature of the residue in animals is not yet adequately understood, and additional data are required to resolve outstanding deficiencies. However, the petitioner has submitted the required new animal metabolism studies and accordingly appears to be attempting to resolve this deficiency.

Also, other metalaxyl tolerances including alfalfa, green hops, oats, and leafy vegetables were recently approved (see PP#8F3695, August 3,1989 memo of J. Garbus; PP#9F3712, April 11,1989 memo of S. Willet; PP#0E3826, February 20,1991 memo of S. Bacchus; PP#0F3893 January 21,1991 memo of S. Bacchus; respectively). Accordingly, for the puroposes of this petition on grapes, CB-1 considers the nature of the residues in animals to be adequately understood. However, the petitioner, at the earliest possible date, should resolve the deficiencies in the animal metabolism studies discussed in the March 13, 1991 Metalaxyl Reregistration Update (see Attachment 1).

This deficiency is tenatively resolved for the subject petition.

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Deficiency No. 4

A determination concerning proposed analytical methodology for determining residues of metalaxyl and its metabolites in in animal commodities is reserved pending submission of acceptable animal metabolism studies with radiolabeled validation of the enforcement analytical methodology.

Petitioner's Response to Deficiency No. 4

The petitioner has not responded to this deficiency.

CB-1's Comments/Conclusions re: Deficiency No. 4

As noted by CB-2 in the March 13, 1991 Metalaxyl Reregistration Update (see Attachment 1), no data were provided in the new metabolism studies to meet this requirement.

However, for purposes of this petition, the current analytical methodology for metalaxyl and its metabolites in animal commodities (which includes acid hydrolysis and formation of the 2,6-dimethyl aniline),is tenatively acceptable, and accordingly this deficiency is tenatively resolved, for the subject petition. Once the nature of the residue in animals is adequately understood , data on radiolabeled validation of the proposed enforcement methodology must be submitted.

Deficiency No. 5

The likelihood of secondary residues of metalaxyl in meat, fat, milk,poultry and eggs resulting from ingestion of the feed commodities, grape pomace and raisin waste, and the need for new feeding studies cannot be determined until acceptable animal metabolism studies are available.

Petitioner's Response to Deficiency No. 5

THe petitioner has made no response to this deficiency.

CB-1's Comments/Conclusions re: Deficiency No. 5

Currently, approved tolerances for metalaxyl (see 40 CFR 180.408(a) and (b)) include a variety of crops with animal feed commodities, such as peanut hay at 20.0 ppm, and rotational crop tolerances on alfalfa forage/meal at 10.0 ppm and alfalfa hay at 20.0 ppm. The proposed use on grapes and tolerances on the animal feed commodities (i.e. wet and dry grape pomace and raisin waste) should not increase the current animal dietary burden of metalaxyl.

Accordingly, this deficiency is resolved.

Other Considerations

International Residue Limits

An International Residue Limit Status Sheet is appended to this petition review as Attachment 2. Codex has a tolerance established for metalaxyl per se of 1.0 ppm. We note that Codex currently regulates metalaxyl residues in terms of parent only while the U.S. tolerance expression regulates the parent and metabolites containing the 2,6-dimethylaniline moiety and N-(2-hydroxymethyl-6- methylphenyl)-N-(methoxyacetyl) alanine methyl ester each expressed as metalaxyl. Therefore, there is a compatibility problem.

Attachment No. 1: March 13,1991 Metalaxyl Reregistration Standard Update; Qualitative Nature Of The Residue In Animals/Conclusions

Attachment No. 2: International Residue Limit Status Sheet

cc (with Attachment): PMSD/ISB, RF, Circu, Metalaxyl Registration Standard File, Reviewer-Otakie, E. Haeberer, J. Kariya (SACB), PP#6F3362/FAP#6H5493.

H7509c:CBTS:G.Otakie:CM#2:RM804:557-7484:
RDI:E. Haeberer,8/22/91; R. Loranger, 8/22/91.

ATTACHMENT NO. 1

MARCH 13, 1991 METALAXYL REREGISTRATION STANDARD UPDATE

QUALITATIVE NATURE OF THE RESIDUE IN ANIMALS

Conclusions:

The qualitative nature of the residue in animals is not adequately understood. The Metalaxyl Guidance Document dated 9/88 specified the need for metabolism studies on ruminants and poultry. In response to these requirements, Ciba-Geigy Corp. submitted data pertaining to the metabolism of metalaxyl in goats and poultry. Additional data is required from these studies. The deficiencies in the submitted data and the additional information required are summarized in the paragraphs that follow.

The data on lactating goats submitted by Ciba-Geigy Corporation (1990; MRID 41664503) are not adequate to delineate metabolism of metalaxyl in ruminants because the residues in milk and tissues were inadequately characterized. In milk, 40% (0.036 ppm) of the total radioactive residue is found as an unidentified metabolite "A". The registrant states that under mild base conditions the unidentified metabolite may be hydrolyzed to a known metabolite (CGA-107955). Additional data must be presented regarding the identity of this major component of the milk residue.

The following additional data are required:

- The registrant must submit additional information from the study described in MRID 41664503. Specifically, metabolite "A" isolated from milk of goat 2 needs to be characterized further.

The major portion of radioactivity analyzed in liver and kidney was found in metabolites CGA-107955 (13.5% and 31.5%, respectively), CGA-94689-isomer B (4.5% and 22.5%, respectively), and CGA-94689-isomer A (3.5% and 11.7%, respectively). The major portion of analyzed radioactivity in muscle was in metabolites CGA-107955 (18.4% and 17.4, respectively), CGA-62826 (10.9% and 9.1%, respectively), and CGA-67869 ((8.7% and 6.4%, respectively). The three major metabolites found in perirenal fat (goat 1) included two identified metabolites CGA-107955 (29.6%) and CGA-67869 (13.3%), and an unidentified metabolite "J" (11.6%). The three major metabolites found in perirenal fat (goat 2), extracted using an alternative scheme, were CGA-107955 (11.4%), CGA-94689 (5.8%) and CGA-67869 (4.8%). Milk samples from goat 1 and 2 were also extracted by two different extraction schemes. Similarly to perirenal fat (goat 1), milk samples from goat 1 contained the major portion of analyzed radioactivity as metabolites, CGA-107955 (7.3%) and CGA-67869 (4.8%), and the unidentified metabolite "J" (5.6%). Milk samples from goat 2 contained the greater portion of the analyzed radioactivity as metabolite "A" (40%), which is unidentified, and metabolites CGA-107955 (4.6%) and CGA-67869 (4.3%).

Metalaxyl in goats may be hydrolyzed to the ester alcohol and the acid alcohol which may then be N-dealkylated. Alternatively, oxidation can lead to either benzylic alcohol or phenolic compounds.

The data submitted regarding the metabolism of metalaxyl in hens (1990; MRIDs 41664504 and 41664506) are inadequate to fulfill data requirements for this topic because only 20% of the residue in liver, 30% in egg yolk, 9.3% in egg white, 2.4% in muscle, and none in skin/fat were identified. Components from protease digestion accounting for 32.9% of the total residue in egg whites were not resolved chromatographically and need further analysis. In addition, 45.7% of the egg white residue that was aqueous soluble should be identified. In egg yolk, radioactive components in the aqueous fraction (17.2%), the hexane fraction (21.8%), and insoluble residues (14.3% of the total) need to be characterized. Aqueous-soluble residues extracted after enzyme hydrolysis of whole liver should be characterized

along with the organosoluble residues (before hydrolysis) accounting for 17% of the total residue and the unextractable residues (ca. 20%). Unresolved residues in the organic fraction of muscle accounting for up to 60% of the residue and inidentified aqueous residues accounting for up to 34% need to be identified further. The following additional data are required:

- o The registrant must submit additional information from the poultry study described in MRID 41664504. The unextracted solid residue from the liver should be subjected to acid hydrolysis. The final aqueous fraction collected after collagenase treatment of liver requires further separation and identification of the radioactive components. Additional chromatographic techniques should be employed to resolve CGA-79353 and to identify the co-eluting unknown in extracts from liver, breast, and thigh muscles. The unknowns in the skin and attached fat, the breast, and thigh muscles should be characterized further. The unresolved metabolites in the breast muscle should be resolved and quantified.

The metabolism of metalaxyl, in the hen, seems to follow two major pathways. In the first pathway, sequential demethylation of the ether and the ester groups gives first the alcohol CGA-67869 and then the hydroxy acid CGA-107955. Oxidation of the alcohol moiety of CGA-107955 results in the formation of the diacid CGA-78532, which in turn cleaves to give CGA-68124. Alternatively, oxidation of the benzylic carbon of metalaxyl produces the benzylic alcohol isomers CGA-94689 (two isomers). The benzoic acid CGA-108905 also forms. The benzoic acid undergoes demethylation to give the diacid CGA-108906. The registrant also suggested a minor pathway which consists of the hydroxylation of the phenyl ring resulting in the formation of CGA-100255; GC/MS indicated the presence of this metabolites in excreta. In the second pathway, CGA-107955 undergoes lipophilic, amino acid, and glucuronic acid conjugation. The latter two routes of conjugation also occur with CGA-78532, CGA-68124, CGA-10896, and CGA-94689. In addition CGA-94689 also forms lipoprotein conjugates in the egg yolk.

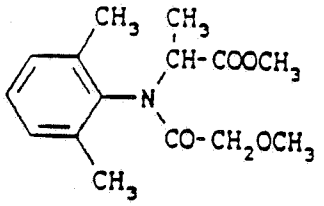
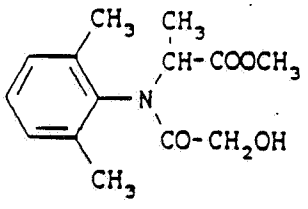
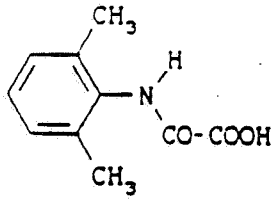
The Metalaxyl Guidance Document dated 9/88 specifically requests that representative samples from this test be analyzed by current enforcement methods to ascertain the validity of the method. No data were provided to meet this requirement; therefore, this test remains outstanding.

The molecular structures and chemical names of metalaxyl and known and suspected metabolites are given in Table 1.

References (used):

MRIDs: 41664503. 41664504. 41664506.

Table 1. Chemical names and molecular structures of metalaxyl and known and putative metabolites identified in animal tissues and used as standards in metabolism studies.

Company Code Chemical Name	Structure	Substrate	MRID
CGA-48988 (metalaxyl) N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-alanine methyl ester		**Poultry:** Liver Egg White Egg Yolk Breast Muscle Excreta Gizzard	 41664504 41664504 41664504 41664504 41664504 41664504
CGA-67869 N-(2,6-dimethylphenyl)-N-(hydroxyacetyl)-alanine methyl ester		**Ruminant:** Urine Tenderloin Milk Liver Kidney Leg Muscle Perirenal Fat **Poultry:** Gizzard Excreta Kidney Liver	 41664503 41664503 41664503 41664503 41664503 41664503 41664503 41664504 41664504 41664504 41664504
CGA-68124 [2,6-dimethylphenyl)-amino] oxoacetic acid		**Poultry:** Excreta[a] Heart[a] Gizzard[a] Liver[a] Breast Muscle[a] Thigh Muscle[a] Skin/Attached Fat[a] Egg White[a] Peritoneal fat[a] Kidney[a]	 41664504 41664504 41664504 41664504 41664504 41664504 41664504 41664504 41664504 41664504

[a]Unresolved residues considered putative.
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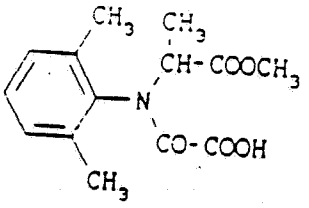
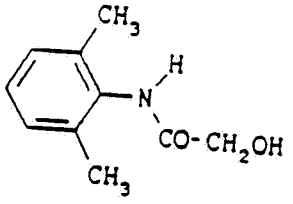
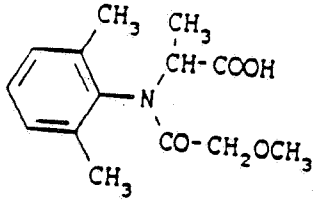
ble 1. Metalaxyl and metabolites (continued)

Company Code Chemical Name	Structure	Substrate MRID
CGA-79353 N-(carboxy- carbonyl)-N-(2,6- limethylphenyl) lanine methyl ster		**Poultry:** Excreta[a] 41664504 Heart[a] 41664504 Gizzard[a] 41664504 Liver[a] 41664504 Breast Muscle[a] 41664504 Thigh Muscle[a] 41664504 Skin/Attached fat[a] 41664504 Egg White[a] 41664504 Peritoneal fat[a] 41664504 Kidney[a] 41664504
CGA-37734 (2,6-di- thylphenyl)-2- droxyacetamide		**Ruminant:** Tenderloin[a] 41664503 Milk[a] 41664503 Liver[a] 41664503 Urine[a] 41664503 Kidney 41664503 Leg Muscle 41664503 Perirenal Fat 41664503
CGA-62826 2,6-dimethyl- nyl)-N-(meth- acetyl)-alanine		**Ruminant:** Tenderloin 41664503 Milk 41664503 Liver 41664503 Urine 41664503 Kidney 41664503 Leg Muscle 41664503 Perirenal Fat 41664503

olved residues considered putative.
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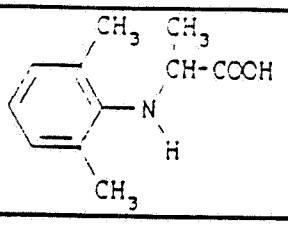
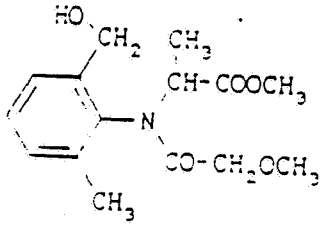
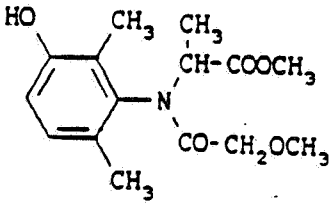
Table 1. Metalaxyl and metabolites (continued)

Company Code Chemical Name	Structure	Substrate MRID
CGA-67867 N-(2,6-di-methylphenyl) alanine		**Ruminant:** Urine 41664503
CGA-94689 N-[(2-hydroxy-methyl)-6-meth-ylphenyl]-N-(meth-oxy acetyl)-alanine methyl ester		**Ruminant:** Milk 41664503 Liver 41664503 Kidney 41664503 Leg Muscle 41664503 Perirenal Fat 41664503 Urine 41664503 Tenderloin 41664503 **Poultry:** Liver 41664504 Egg White 41664504 Egg Yolk 41664504 Breast Muscle 41664504 Thigh Muscle 41664504 Excreta 41664504 Gizzard 41664504 Kidney 41664504 Heart 41664504
CGA-100255 N-(3-hydroxy-2,6-dimethylphenyl)-N-(methoxyacetyl) alanine methyl ester		**Ruminant:** Milk[a] 41664503 Liver[a] 41664503 Tenderloin[a] 41664503 Urine[a] 41664503 Kidney 41664503 Leg Muscle 41664503 Perirenal Fat 41664503

[a]Unresolved residues considered putative.

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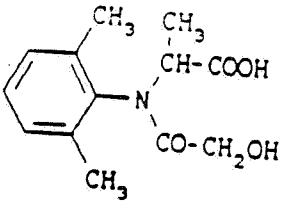
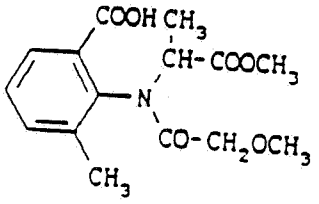
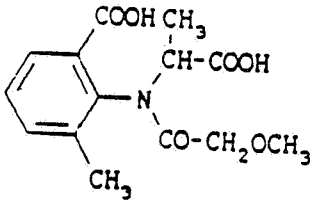
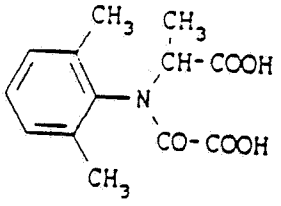
Table 1. Metalaxyl and metabolites (concluded)

Company Code Chemical Name	Structure	Substrate	MRID
CGA-107955 N-(2,6-dimethylphenyl)-N-(hydroxyacetyl)-alanine		**Ruminant:** Milk Liver Urine Tenderloin Kidney Leg Muscle Perirenal Fat **Poultry:** Excreta Kidney Peritoneal Fat Liver Gizzard Heart	 41664503 41664503 41664503 41664503 41664503 41664503 41664503 41664504 41664504 41664504 41664504 41664504 41664504
CGA-108905 2-[(methoxyacetyl)(2-methoxy-1-methyl-2-oxoethyl) amino]-3-methylbenzoic acid		**Poultry:** Excreta Gizzard Kidney	 41664504 41664504 41664504
CGA-108906 2-[1-carboxyethyl) (methoxy acetyl) amino]-3-methyl benzoic acid		**Poultry:** Excreta[a] Heart[a] Gizzard[a] Liver[a] Breast Muscle[a] Thigh Muscle[a] Skin/Attached fat[a] Egg White[a] Peritoneal fat[a] Kidney[a]	 41664504 41664504 41664504 41664504 41664504 41664504 41664504 41664504 41664504 41664504

Unresolved residues considered putative.

(continued)

Table 1. Metalaxyl and metabolites (concluded)

Company Code Chemical Name	Structure	Substrate	MRID
CGA-78532 N-(carboxy-carbonyl)-N-(2,6-dimethyl-phenyl) alanine		**Poultry:**	
		Excreta[a]	41664504
		Heart[a]	41664504
		Gizzard[a]	41664504
		Liver[a]	41664504
		Breast Muscle[a]	41664504
		Thigh Muscle[a]	41664504
		Skin/Attached Fat[a]	41664504
		Egg White[a]	41664504
		Peritoneal fat[a]	41664504
		Kidney[a]	41664504

[a] Unresolved residues considered putative.

ATTACHMENT NO. 4

INTERNATIONAL RESIDUE LIMIT STATUS

F. Nuss 5/20/91

CHEMICAL METALAXYL

CODEX NO. 138

CODEX STATUS:

☐ No Codex Proposal Step 6 or above

Residue(if Step 8): _____

Metalaxyl per se

Crop(s)	Limit (mg/kg)
Grapes	1

PROPOSED U.S. TOLERANCES:

Petition No. 6F3362/6H5493

RCB Reviewer G. OTAKIE

Residue: METALAXYL and its metabolites containing the 2,6-dimethyl aniline moiety and N-(2-hydroxy-methyl 6-methyl-phenyl)-N-methoxyacetyl alanine methyl ester

Crop(s)	Limit (mg/kg)
GRAPES	2.0 PPM
WET AND DRY GRAPE POMACE	10.0 "
RAISINS	6.0 "
RAISIN WASTE	10.0 "

CANADIAN LIMITS:

☑ No Canadian limit (as above)

Residue: _____

Metalaxyl

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

☑ No Mexican limit

Residue: _____

Crop(s)	Limit (mg/kg)

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NOTES:

Form revised 1986