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

APR 30 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#8F3617/8H5554 - Metalaxyl on Sugar Beet Tops and Roots, Legume Vegetables (Dry and Succulent) Crop Group; Legume Vegetables Foliage Crop Group; Grass Forage, Fodder, and Hay Crop Group; and Non-grass Animal Feeds Crop Group.
Evaluation of the September 21, 1989 Amendment (MRID Nos. 412501-01 and 410552-03) [DEB Nos 5934, 5935, and 6545) [HED Nos. 0-0044 and 1010]

FROM: Francis D. Griffith, Jr., Chemist
Dietary Exposure Branch
Health Effects Division (H7509C)

TO: Susan Lewis, PM 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

and

Toxicology Branch - Herbicide, Fungicide and Antimicrobial Support
Health Effects Division (H7509C)

THRU: Robert S. Quick, Section Head
Tolerance Petition Section I
Dietary Exposure Branch
Health Effects Division (H7509C)

Ciba-Geigy Corporation, Agricultural Division, has submitted this amendment consisting of a cover letter dated September 21, 1989, a revised Section B (amended labels for three Ridomil® formulations), revised Section F (new tolerance proposals), and a supplementary Section D (multiresidue method validation data and additional enforcement method validation data) in response to several deficiencies outlined and summarized in our review of November 28, 1988 by F.D. Griffith, Jr. (which see). These deficiencies are repeated and listed in the body of this review in the order they appeared in that review followed by the petitioner's response, then DEB comments. Our conclusions and recommendation follow.

SUMMARY OF DEFICIENCIES REMAINING TO BE RESOLVED

None

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CONCLUSIONS

1. DEB Conclusion on **Directions for Use**

The petitioner has proposed new directions for use of Ridomil® by deleting all proposed uses of metalaxyl on the legume vegetables (succulent and dried) and foliage crop groups, the grass forage, fodder, and hay crop group, and the non-grass animal feeds crop group. The deficiency on plant back restrictions to have both Ridomil® labels in agreement becomes moot, and thus is resolved. The petitioner now has proposed an adequate set of directions for use of Ridomil® (metalaxyl) on sugar beets.

2. DEB Conclusion on **Nature of the Residue - Livestock**

Upon further consideration, DEB will not delay this petition while the petitioner completes the FRSTR livestock metabolism studies. This action is consistent with current Branch policy applied to other metalaxyl petitions involving major livestock feed items. Thus, the deficiency is resolved. The metalaxyl residues of concern in livestock are now as they were previously; i.e., metalaxyl per se, and metabolites containing the 2,6-dimethylaniline moiety and N-(2-hydroxymethyl-6-methylphenyl)-N-(methoxyacetyl)alanine methyl ester.

3. DEB Conclusion on **Residue Analytical Methods**

The petitioner has submitted multiresidue method recovery data following protocols I through IV for metabolites CGA-94689 and CGA-100255. The data have been forwarded to FDA. This part of the deficiency is resolved.

Since the petitioner has withdrawn proposed directions for use and tolerances for metalaxyl on non-grass animal feeds crop group, the grass forage, fodder, and hay crop group, the legume vegetables (succulent and dried) crop group, and the legume vegetables foliage crop group, the residue analytical method deficiencies relating to these crop groups becomes moot, and thus these parts of the method deficiency are resolved.

The petitioner has provided additional metalaxyl method validation data for levels from 2 to 15 ppm along with supporting chromatographic data. The method AG-395 is suitable to gather metalaxyl residue data on sugar beet tops and roots, and it is suitable to enforce the proposed metalaxyl tolerances. This part of the method deficiency is resolved.

The petitioner has supplied the additional supporting chromatographic data. We are now able to perform independent verification of the residue results. While numerous unidentified analytical responses (UARs) are present, the method in the hands

of a skilled residue analyst will not present a problem. This part of the deficiency is resolved.

The petitioner presented an explanation for the variably positive control samples. This is satisfactory. The petitioner pointed out the positive controls are low in relation to the proposed tolerance and the method's overall sensitivity. This part of the deficiency is resolved.

4. DEB Conclusion on **Storage Stability**

There are adequate storage stability data for metalaxyl to support the crop field trial residue data for metalaxyl in sugar beet tops and roots.

5. DEB Conclusion on **Magnitude Residue - Crop Field Trials**

Since directions for use and tolerances for metalaxyl have been withdrawn, deficiencies relating to the need for additional geographically representative crop field trial data on representative commodities of the legume vegetables foliage crop group, legume vegetables (succulent and dried) crop group, non-grass animal feeds crop group, grass forage, fodder, and hay crop group, and details of the legume vegetable processing study become moot and, thus, these parts of the deficiency are resolved.

Since analytical method concerns are resolved on sugar beets, DEB does not expect residues of metalaxyl to exceed the proposed tolerances of 10 ppm on sugar beet tops and 0.5 ppm on sugar beet roots when Ridomil® is used as directed. This part of the deficiency is resolved.

The petitioner has proposed the suggested food additive tolerance (FAT) on sugar beet molasses at 5 ppm metalaxyl. This part of the deficiency is resolved.

6. DEB Conclusion in **Magnitude of the Residue - Meat/Milk/Poultry/Eggs**

Since questions relating to animal metabolism, analytical methods, and additional crop field trial data have been resolved above, this deficiency is now resolved. Previously submitted and reviewed metalaxyl feeding studies are adequate to support the secondary metalaxyl tolerances for this petition only.

DEB points out that questions raised by the FSTR relating to the nature of the residue in livestock may engender the need for additional livestock metalaxyl feeding studies.

7. DEB Conclusions on **Harmonization of Tolerances**

An updated International Residue Limit (IRL) Status Sheet is attached to this review that shows there is no problem with harmonizing the proposed U.S. metalaxyl tolerance on sugar beets with Canadian or Mexican tolerances. The proposed U.S. metalaxyl on sugar beets tolerance cannot be harmonized with Codex at this time as Codex tolerances are set for the parent only, metalaxyl.

RECOMMENDATION

There being no further residue chemistry deficiencies associated with the revised petition, DEB makes the following recommendations, Tox Br considerations permitting.

Since residues are not expected to exceed the proposed tolerances under the proposed Ridomil® conditions of use, DEB recommends for the 10 ppm metalaxyl tolerance on sugar beet tops, 0.5 ppm metalaxyl tolerance on sugar beet roots, and for the feed additive tolerance of 5.0 ppm in sugar beet molasses.

DETAILED CONSIDERATIONS

DIRECTIONS FOR USE

Deficiency

The petitioner needs to revise the Ridomil® 5G label to make it in agreement with the Ridomil® 2E label for rotational uses and plant back restrictions relating to grass forages crop group and non-grass animal feeds crop group; i.e., a 60-day rotational interval.

Petitioner's Response

The petitioner has submitted amended labels for Ridomil® 5G (EPA Registration No. 100-628) containing 5% ai metalaxyl, Ridomil® 2E (EPA Registration No. 100-607) containing metalaxyl at 2 lbs ai/gallon or 25.1% ai, and Ridomil® MZ58 (EPA Registration No. 100-629) containing 10% ai metalaxyl.

DEB Comments

On the Ridomil® 5G and Ridomil® 2E labels, the petitioner has amended these labels by deleting all proposed metalaxyl uses on the legume vegetables (succulent and dried) and legume forages crop groups; the grass forage, fodder, and hay crop group; and the non-grass animals feeds crop group. Thus, the petitioner is now only proposing uses of metalaxyl on sugar beets. The deficiency on plant back restrictions relating to grass forages crop group and non-grass animal feeds crop group to have the two

labels in agreement becomes moot and is thus resolved. The plant back or planting time from last Ridomil® application for sugar beets is 0 days on both labels.

These labels have been previously reviewed for use of Ridomil® on sugar beets as a systemic fungicide to control fungi caused diseases such as damping off and downy mildew. Metalaxyl is proposed for soil application, preplant incorporation, or surface application at planting at a rate of 1 to 2 lbs ai/acre. Ridomil® 2E can also be applied by irrigation sprinkler, ground application in water at a 20 gallons/acre maximum application, or by air at 5 gallons/acre water minimum application.

Metalaxyl may also be used as a foliar spray at a rate of 0.15 to 0.2 lb ai/metalaxyl mixed with mancozeb. The repeat foliar application interval is 14 days for a maximum of four applications per sugar beet growing season and a preharvest interval of 7 days.

The petitioner has now proposed an adequate set of directions for use of metalaxyl on sugar beets.

NATURE OF THE RESIDUE - LIVESTOCK

Deficiency

Metabolism studies are needed utilizing ruminants and poultry in which animals should be dosed for a minimum of 3 days with ^{14}C-metalaxyl at a level sufficient to make residue identification and quantification possible. Milk and eggs should be collected twice daily during the dosing period. Animals should be sacrificed within 24 hours of the final dose. The distribution and characterization of residues should be determined in milk, eggs, liver, kidney, muscle, and in skin and gizzard for poultry. If the metabolism of metalaxyl in ruminants or poultry is different than that in rats or with each other, then a porcine metabolism study would be required.

Petitioner's Response

The petitioner did not submit the requested studies. Instead, in letters dated April 14 and September 21, 1989 signed by Karen J. Stumpf of Ciba-Geigy, the petitioner requests DEB reconsider the need for these animal metabolism studies in the interim period to comply with the FRSTR requests.

DEB Comments

Ciba-Geigy has committed to run the requested metalaxyl livestock metabolism studies. These studies are due to the Agency in April 1990. Subsequent to our November 1988 review of this petition DEB concluded in PP# 8F3698 (metalaxyl in leaves of root and tuber vegetables crop group and root and tuber vegetables crop group), and in PP# 8F3695 (alfalfa forage and

hay, and barley grain forage, fodder, and straw) that we should continue regulating metalaxyl and its metabolite residues in meat, milk, poultry, and eggs while the petitioner completes the FRSTR livestock metabolism requirement. Upon further consideration, DEB will apply this principle to this petition. The livestock metalaxyl metabolism is now resolved. For this petition only, the metalaxyl residues of concern in meat, milk, poultry, and eggs are as previously defined; i.e., the metalaxyl parent and metabolites containing the 2,6-dimethylaniline (DMA) moiety and N-[2-hydroxymethyl-6-methylphenyl]-N-(methoxy-acetyl)alanine methyl ester.

DEB points out that petitions for use of metalaxyl on feed items submitted after April 1990 will not be considered further until the metalaxyl livestock metabolism concerns are resolved.

ANALYTICAL METHOD

Deficiency

For the analytical method used to gather metalaxyl residue data on sugar beets, the petitioner needs to provide validation data at the 2 to 15 ppm range where residues are reported. Additional supporting chromatographic data, especially control and spike samples are needed. The petitioner needs to provide reasons for variably positive controls.

For the non-grass animal feeds crop group and the grass forage crop group, the petitioner needs to supply additional supporting chromatographic data, an explanation for the variable positive control values, and additional method validation data (either repeat the original work or provide new data).

For legume vegetable (succulent or dried) crop group and legume vegetable foliage crop, the petitioner needs to provide additional recovery data for all pea (pisum) commodities and an explanation for variable positive control values.

Multiresidue method data are still needed for the metabolite CGA-94689.

Petitioner's Response (See MRID Nos. 412501-01 and 410552-03)

In response to the multiresidue method data deficiency for metabolite CGA-94689 the petitioner presented a study titled "Determination of the Metalaxyl Metabolites CGA-100255 and CGA-94689 (A & B Isomers) By U.S Food and Drug Administration Multiresidue Procedures" by H. Lee Hubbard dated February 24, 1989. The 78-page study is assigned Laboratory Project ID No. ABR-88156 and EPA MRID No. 410552-03.

In response to the deficiencies on the analytical method used to gather metalaxyl residue data on sugar beets, the

petitioner submitted a study titled "Metalaxyl: Response to EPA Review of Metalaxyl on Sugar Beets" by M.W. Cheung, dated September 18, 1989. The 97-page study is assigned Laboratory Project ID No. ABR-89075 and EPA MRID No. 412501-01.

DEB Comments

The petitioner has presented MRM recovery data for metalaxyl metabolites CGA-94689 and CGA-100255 through FDA protocols I through IV, not A through E. Much of these data can be translated from the Roman numeral protocols to the alphabet designation protocols. The petitioner has presented GC determination data using the various columns designated in protocols I, II, and III for EC and N/P but not FPD-S detector. There is no S in the molecules, thus, no need to try for recovery data for that system as the metabolites could not be recovered for that system. The metabolites could not be recovered through Florisil using either elution system. Adequate detection could not be obtained for these metabolites using post-column OPA derivatization fluorescence detection. The metabolites can be recovered using the Luke Method, but not necessarily at low sensitivity levels.

These data have been forwarded to FDA (see letter from F.D. Griffith, Jr., EPA/DEB to L. Sawyer, FDA/DCC dated April 24, 1990. This part of the deficiency is resolved.

The petitioner has withdrawn metalaxyl tolerances and deleted directions for use on the non-grass animal feeds crop group, the grass forage, fodder, and hay crop group, the legume vegetable (succulent and dried) crop group, and the legume vegetable foliage crop group. The residue analytical method deficiencies relating to these crop groups becomes moot, thus all are resolved.

For the deficiencies relating to the method for metalaxyl residues on sugar beets, the petitioner has presented additional supporting data. Control sugar beet tops were spiked with metalaxyl at 5.0, 10.0, and 15.0 ppm. Recoveries ranged from 68 percent (at 5 ppm) to 93 percent (at 10 ppm or the proposed tolerance) with an average recovery of 78 percent ($X = 78\% \pm 13.2\%$, $n = 3$). The petitioner also supplied adequate additional supporting chromatographic data to help validate these recovery data. The method has now been validated to gather the metalaxyl on sugar beet tops residue data. This part of the deficiency is resolved.

The petitioner provided four possible reasons for the large number of positive controls. The petitioner maintains the nature or exact reason for the positive values is not clearly understood, but potential sources are spray drift during application, volatility due to weather and/or soil conditions, cross contamination during the trial or sampling, and the possibility of a naturally occurring compound in sugar beets.

These explanations are acceptable to DEB. The deficiency is resolved.

The petitioner presented chromatographic support to show that the metalaxyl is in the control samples, in the reagents. Reagent blanks were non-detected for metalaxyl.

The petitioner points out the blank or positive control values are low (maximum 0.3 ppm) in relation to the proposed tolerance (10 ppm) and the method's overall sensitivity is low (0.05 ppm) in relation to the control values and the proposed tolerance. DEB agrees. We note that 7 out of the 14 control sugar beet tops have metalaxyl or its equivalent above 0.1 ppm. When compared to the actual metalaxyl residues reported from the proposed use application rate the control value ranges from < 1 to 16 percent of the value in the treated crops with one value about 10 percent and only three trials with values of > 6 percent. DEB agrees that a majority of the positive control values in sugar beet tops are low and can now be considered insignificant. The petitioner points out that when various control values were subtracted in recovery experiments, method AG-395 had recoveries ranging from 61 to 108 percent ($\bar{X}$ = 83.7 $\pm$ 12.6%, n = 17) from the low level spikes of 0.1 to 2 ppm.

The petitioner points out the positive control problem is mainly in sugar beet tops, not roots, as only 2 out of 13 sugar beet root controls have positive low values. DEB agrees with the petitioner that positive controls are not a significant problem in the sugar beet roots metalaxyl analysis.

The petitioner has presented extensive additional supporting chromatographic data. Copies of chromatograms for all controls and all spikes were presented as well as all chromatograms for 6 out of 13 field trials. The petitioner took care to present these chromatograms in their sequence of analysis. DEB found this to be extremely helpful as we were able to perform an independent verification of the metalaxyl results in sugar beet tops and roots. These sets of chromatograms included the standards and the standard curves, controls, recoveries, and treated samples. The curves show numerous UARs but in the hands of a skilled residue analyst these UARs are not a problem. We also agree the positive controls do not present an enforcement problem for false positives as long as analysis of sugar beet tops and roots using method AG-395 is in the hands of a skilled residue analyst. This part of the deficiency is resolved.

DEB concludes the petitioner has used a validated method AG-395, to gather the metalaxyl residue data on sugar beet tops and roots. Since this method has completed a successful PMV it is suitable with the petitioner's additional recovery data to enforce the proposed tolerances. There are no remaining analytical method deficiencies for metalaxyl on sugar beets.

MAGNITUDE OF THE RESIDUE - STORAGE STABILITY

Deficiency

Adequate metalaxyl storage stability exist for 18 months. Metalaxyl storage stability data are needed for up to 3 years for non-grass animal feeds crop group and the grass forage, fodder, and hay crop group.

Petitioner's Response

The petitioner did not respond in this amendment.

DEB Comments

Since the petitioner withdrew the proposed tolerances and directions for use of metalaxyl on the non-grass animal feeds group and the grass forage, fodder, and hay crop group, the storage stability deficiency becomes moot; thus, is resolved. There are adequate storage stability data to support the metalaxyl on sugar beets residue data.

MAGNITUDE OF THE RESIDUE - CROP FIELD TRIALS

Deficiencies

DEB defers judgment on the proposed metalaxyl tolerances for sugar beet roots at 0.5 ppm and sugar beet tops at 10 ppm until the petitioner resolves analytical method concerns noted above. No additional metalaxyl sugar beet field trial data are required. It appears that residues will not exceed the proposed tolerance under the conditions of the proposed use.

For the FAT on sugar beet molasses, the petitioner needs to submit a revised Section F proposing total metalaxyl tolerances of 5 ppm (10X concentration factor x proposed metalaxyl sugar beet root tolerance). DEB reiterates FATS are not required for sugar, dried beet pulp, or the cossettes.

DEB defers judgment on the proposed metalaxyl tolerance on legume vegetable (succulent or dried) crop group and foliage of legume vegetables crop group until the petitioner resolves analytical method concerns relating to this crop group and provides additional geographically representative data for the representative commodities dry and succulent beans (phaseolus) and dry and succulent peas (pisum).

The petitioner needs to provide complete details of the legume vegetables processing study that generated the proposed 11 ppm metalaxyl tolerance on cannery waste.

DEB defers judgment on the proposed metalaxyl tolerance on the legume vegetable foliage crop group until the petitioner has resolved our analytical method concerns relating to this crop

group and has provided satisfactory additional geographically representative crop field trial data on all representative commodities of the group.

DEB defers judgment on both the proposed rotational crop tolerances for the grass forage, fodder, and hay crop group until the petitioner has resolved analytical method concerns for the crop group, provided adequate storage stability data for up to 3 years of sample storage, and provides satisfactory additional geographically representative crop field trial residue data for each representative commodity in this group.

DEB defers judgment on the proposed rotational crop tolerances for the non-grass animals feeds group until the petitioner has resolved our analytical method concerns, and provides adequate storage stability data for up to 3 years of sample storage.

Petitioner's Response

The petitioner has proposed the following revised metalaxyl tolerances in a new Section F:

"Tolerances 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, expressed as metalaxyl equivalents, in or on the following raw agricultural commodities:

Sugar beet (tops)	10.0 ppm
Sugar beet (roots)	0.5 ppm,

"A food additive tolerance 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 or on the following food additive:

Molasses	5.0 ppm"

DEB Comments

Since the petitioner has withdrawn the tolerance and directions for use of metalaxyl on legume vegetables (succulent and dried) crop group and legume vegetables foliage crop group, the deficiencies relating to the need for additional geographically representative crop field trial residue data on the representative commodities dry and succulent beans (phaseolus) and dry and succulent peas (pisum), complete details of the legume vegetables processing study, and additional geographically representative crop field trial residue data on representative commodities of the legume vegetable foliage crop group becomes moot; thus, all of these parts of the deficiency are resolved.

Likewise, since tolerances and directions for use of metalaxyl on the grass forage, fodder, and hay crop group; and non-grass animal feeds crop group have been withdrawn the deficiencies relating to additional geographically representative crop field trial residue data for each representative commodity becomes moot; thus, this part of the deficiency is resolved.

As noted above, the analytical method deficiency on sugar beets has been resolved. DEB now concludes the petitioner has presented adequate field trial crop residue data for metalaxyl on sugar beets. Residues of metalaxyl on sugar beet tops are not expected to exceed the proposed 10 ppm tolerance and the proposed 5 ppm tolerance on sugar beet roots under the conditions of the proposed Ridomil® use. This part of the deficiency is resolved.

The petitioner is proposing a FAT on sugar beet molasses as DEB had suggested. This part of the deficiency is resolved.

MAGNITUDE OF THE RESIDUE - MEAT/MILK/POULTRY/EGGS

Deficiency

Judgment is deferred on the appropriateness of the existing livestock feeding studies and secondary metalaxyl tolerances in meat/milk/poultry/eggs until questions relating to animal metabolism, analytical methods, and additional crop field trial data are all resolved.

Petitioner's Response

The petitioner did not respond in this amendment.

DEB Comments

Since questions relating to animal metabolism, analytical methods, and additional crop field trial data have all been resolved, this deficiency is resolved.

DEB recognizes that the livestock diets based on previously submitted feeding studies are artificial, but nonetheless maximizes possible exposure to metalaxyl residues. Based on feeding studies previously reviewed (see memorandum PP#8F3617 by F.D. Griffith, Jr., dated November 28, 1988), these studies have demonstrated the presence of low levels of metalaxyl in liver and kidney; thus any feed use of a metalaxyl-treated rac or its byproducts must necessarily be categorized within 40 CFR 180.6(a)(1) or (a)(2). Since real residues have been found in livestock tissues from feeding exaggerated levels of metalaxyl, DEB characterized the proposed use as (a)(2). DEB now concludes that previous metalaxyl feeding studies used to support the secondary metalaxyl tolerances are adequate for this petition only. DEB points out that questions raised by the FRSTR relating

to the nature of the residue in livestock may engender the need for additional livestock metalaxyl feeding studies.

OTHER CONSIDERATIONS - HARMONIZATION OF TOLERANCES

An International Residue Limit (IRL) Status Sheet is attached to this petition. There are no problems of compatibility with Canadian or Mexican metalaxyl tolerances in sugar beets as these countries have not established tolerances. There is a Codex tolerance for parent only metalaxyl on sugar beet roots at 0.05 ppm. Because the tolerance is expressed for residues of parent only, compatibility cannot be achieved at this time.

Attachment: International Residue Limit Status Sheet

cc: R.F.,Circu(7),Reviewer(FDG),PP#8F3617/8H5554,
FDA(Corneliussen, HFF-426),PIB/FOD(Furlow),
DRES/SCAB(Kariya).

H-7509C:DEB:Reviewer(FDG):CM#2:Rm814B:5570828:JOB:57275:I:C.Disk:
KENCO:04/18/90:de:sw:vo:de:ed:fdg:4/24/90.

RDI:Section Head:R.S.Quick:4/26/90:R.A.Loranger:4/26/90.

CHEMICAL Metalaxyl (Ridomil®)

F. Griffith 4/17/90

CODEX NO. 138

CODEX STATUS:

☒ No Codex Proposal Step 6 or above

Residue(if Step 8): _____

Metalaxyl per se

Crop(s)	Limit (mg/kg)
Sugar beet (roots)	0.05

PROPOSED U.S. TOLERANCES:

Petition No. 8F3617/8H5554

RCB Reviewer F.D Griffith, Jr. 17Apr90

Residue: Metalaxyl* and its metabolites

Crop(s)	Limit (mg/kg)
Sugar Beet (tops)	10.0
Sugar Beet (roots)	0.5
FAT	
Sugar Beet Molasses	50

CANADIAN LIMITS:

☒ No Canadian limit (on sugar beet)

Residue: _____

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

☒ No Mexican limit

Residue: _____

Crop(s)	Limit (mg/kg)

NOTES:

*N-(2,6-Dimethyl)-N-(methoxyacetyl) alanine methyl ester