57

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

SEP 22 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: PP# 2F04063, Metalaxyl in or on the grass forage, fodder, and hay crop grouping. Evaluation of analytical method and residue data (Ridomil®2E Fungicide, EPA Reg No. 100-607). CBTS# 9338, HED# 2-1271, DP Barcode D173024, MRID# 421345-00,-01.

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To: PM Team #21 (Benjamin Chambliss)
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Ciba-Geigy requests an increase in the established tolerance for the combined residues of metalaxyl and its metabolites in or on members of the grass forage, fodder and hay crop grouping to 10.0 ppm for grass, forage and to 20.0 ppm for grass, hay to allow for soil application of metalaxyl.

Tolerances are established for residues of the fungicide metalaxyl and its metabolites containing the 2,6-dimethylaniline (2,6-DMA) moiety and N-(2-hydroxymethyl-6-methylphenyl)-N-(methoxyacetyl)-alanine methyl ester, expressed as metalaxyl under 40 CFR §180.408 for various raw agricultural commodities including grasses, forage at 0.1 ppm, and for food and feed additive tolerances under 40 CFR §185.4000 and 40 CFR §186.4000, respectively. The established grass tolerance is for metalaxyl use as a seed treatment.

Metalaxyl is a List A chemical and there is a metalaxyl Registration Guidance Document (9/88) as well as a metalaxyl Product Chemistry and Residue Chemistry Registration Standard Update (4/92).

CONCLUSIONS

1. The manufacturing process of metalaxyl has been adequately described. The impurities are not likely to produce a residue problem.

2. A 60-day feeding restriction for range grasses is not practical. The petitioner must either

a) propose a 0-day feeding and grazing restriction supported by the appropriate residue data and feeding studies, or
b) amend the use so the label reads: "Apply Ridomil®2E to any grass Gramineae family (either green or cured)...that will be fed to or grazed by livestock, all **enclosed** pasture grasses, and grasses grown for hay or silage, such as bermudagrass, bluegrass, bromegrass, and fescue (the phrase "and range grasses" must be deleted). In addition, the restriction which begins "To avoid possible illegal residues..." should be amended to "...do not **graze,** feed green forage, or cut for hay for 60 days following application, and a restriction added which reads **"Do not apply to range grasses"**.

3. The proposed 14-day plant-back restriction for wheat, barley, and oats is appropriate and over-tolerance residues should not result from the proposed use on grass.

4a. The nature of the residue in plants is adequately understood. The residues of concern are 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.

4b. The nature of the residue in animals is not adequately understood. However, CBTS does not expect an increase in dietary burden of metalaxyl residues as a result of the proposed use. Therefore, CBTS considers the residues of concern to be 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 for the purposes of this petition.

5. Adequate methodologies are available for enforcement of the proposed tolerances of metalaxyl in or on grasses, forage and hay.

6. It appears that adequate methodologies are available for the purposes of data collection. However, this adequacy is contingent upon the petitioner submitting actual ppm of metalaxyl equivalents recovered from the samples during the validation studies, sample calculations for determining percent recoveries, and an explanation for the large number of control samples positive for metalaxyl.

7. Adequate storage stability studies are not available for grass forage and hay. The petitioner must submit relevant storage stability studies to CBTS in support of the proposed tolerances.

8a. The residue data appear to support the proposed 10.0 ppm tolerance on grass forage. However, the petitioner must submit a revised Section F proposing a tolerance of 25.0 ppm on grass hay.

8b. The adequacy of the tolerances of 10.0 ppm on grass, forage and 25.0 ppm on grass, hay are contingent upon the petitioner submitting actual ppm of metalaxyl recovered from the crop field trials and sample calculations of corrections made for recovery, and upon resolution of the questions raised regarding storage stability and the analytical method.

8c. Residues resulting from the combined seed and soil treatments of metalaxyl are not expected to exceed the 10 ppm and 25 ppm tolerances for grass and grass hay.

9. Established meat, milk, poultry, and egg tolerances will not be exceeded as a result of the proposed use. However, CBTS cannot determine whether the original ruminant feeding studies calculated dietary burden on an as-fed or a dry matter basis. Future petitions and amendments which include ruminant feed items with higher tolerances proposed for feed items must be accompanied by a letter stating which method was used and support the statement with calculations and an explanation of the procedure (as per the 6/12/93 memo on calculating dietary burden, D. Edwards and E. Zager).

10. Harmonization between U.S., Codex, and Canadian tolerances for metalaxyl in or on grass is not possible at this time since the Codex and Canadian tolerance expressions include only parent compound.

RECOMMENDATIONS

CBTS cannot recommend for the proposed tolerances for metalaxyl in or on grass, forage at 10.0 ppm and grass, hay at 20.0 ppm because of conclusions 2, 6, 7, 8a, and 8b. The petitioner must submit a revised Section B, a revised Section F, and the requested data outlined above.

DETAILED CONSIDERATIONS

Manufacturing Process and Formulation:

Ridomil® 2E (EPA Reg. No. 100-607, Ciba-Geigy Corporation, Greensboro, NC) is an emulsifiable concentrate containing 25.1% active ingredient and 74.9% inert ingredients (2.0 lbs. active ingredient per gallon).

The manufacturing process of metalaxyl (technical product) has been adequately described in the Chemistry Branch review of PP#1F2500 (P. Errico, 3/9/82). The TGAI is >95% pure and the impurities are not likely to produce a residue problem.

Proposed Use:

Apply Ridomil®2E to any grass, Gramineae family, (either green or cured) except sugarcane and those included in the group cereal grains, that will be fed to or grazed by livestock, all pasture and range grasses and grasses grown for hay or silage, such as bermudagrass, bluegrass, bromegrass, and fescue. Ridomil®2E applied to the soil at planting will provide control of seedling diseases caused by Pythyium spp.

For Stand Establishment: Apply up to 4 pints/A (1.0 lb. ai) as a broadcast surface spray at planting in a minimum of 20 gallons of water. Use 1-2 pints/A (0.25-0.5 lbs. ai) if grass seed was previously treated with a metalaxyl seed treatment. Use the higher rate of 2-4 pints/A (0.5-1.0 lbs. ai) in areas where there has been a history of Pythium disease.

*To avoid possible illegal residues, do not feed green forage or cut for hay for 60 days following application.
*Do not plant any crop which is not registered for use with metalaxyl in metalaxyl-treated soil for a period of 12 months, with the exception of wheat, barley, and oats (a 14-day plant-back restriction is specified).

The proposed directions indicate use on all pasture and range grasses and also include a 60 feeding restriction of treated green forage and hay. However, CBTS has determined that feeding and grazing restrictions for range grasses is not practical. Therefore, the petitioner must either (1) propose a 0-day feeding and grazing restriction, or (2) amend the use so the label reads: "Apply Ridomil®2E to any grass Gramineae family (either green or cured)...that will be fed to or grazed by livestock, all **enclosed** pasture grasses, and grasses grown for hay or silage, such as bermudagrass, bluegrass, bromegrass, and fescue (the phrase "and range grasses" must be deleted). In addition, the restriction which begins "To avoid possible illegal residues..." should be amended to "...do not **graze,** feed green forage, or cut for hay for 60 days following application, and a restriction added which reads **"Do not apply to range grasses"**. Based on conversations with Dr. William Dyer (Montana) and Dr. Ed French (Florida) pasture grasses are not likely to be fed before the 60-day interval. If option one is followed, the 0-day preharvest and/or grazing interval must be supported by the appropriate residue data, supporting data, and feeding studies.

Crop Rotation Restrictions: The proposed 14-day plant-back restriction for wheat, barley, and oats is appropriate and over-

tolerance residues should not result from the proposed use on grass.

Nature of the Residue:

Plant metabolism studies were not submitted with this petition. The Reregistration Standard, Residue Chemistry Chapter indicates the metabolism of metalaxyl in plants is adequately understood. The residues of concern are 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.

The nature of the residue in animals is not adequately understood. The Registration Standard Update indicates that additional identification of metabolites is necessary (memo, E. Zager, 3/13/91). However, the expected dietary burden as a result of feeding grass forage or hay will not increase over its present load and should not result in over-tolerance residues in meat, milk, poultry, and eggs. Therefore, CBTS considers the residues of concern for the purposes of this petition to be metalaxyl and its metabolites as regulated for plants.

Analytical Method-Enforcement:

The Registration Standard, Product Chemistry Chapter (4/92) indicates that the Ciba-Geigy analytical method AG-395 adequately recovers the residues of concern from various plant tissues and has undergone successful Agency validation (PP#3F2978, P. Jung memo of 7/9/84). Method AG-395 is a modification of Method I in PAM II. In addition, multiresidue methods are available for metalaxyl in PAM I (PESTDATA, FDA, 11/90). Therefore, adequate methodologies are available for enforcement of the proposed tolerances of metalaxyl in or on grasses, forage and hay.

Analytical Method-Data Collection:

Bluegrass, Bromegrass, Fescue, and Bermuda grass samples were analyzed with a modification of Ciba-Geigy method AG-395. The method determines total residues of metalaxyl and its metabolites containing the 2,6-DMA moiety and N-(2-hydroxymethyl-6-methylphenyl)-N-(methoxyacetyl)-alanine methyl ester as 2,6-DMA by gas chromatography.

Method AG-395 has been previously reviewed (PP#8F3617, memo, F. Griffith, 11/28/88) and has undergone a successful petition method validation (PP#3F2918, memo, P. Jung, 7/9/84). CBTS will compare the modifications to the previously reviewed method. Wet and dry samples were extracted by refluxing with 80% methanol/water (v/v) for two hours. Previously, only dry samples were refluxed whereas wet samples had been homogenized for one minute with a polytron in methanol/water. A two gram aliquot was

evaporated to just dryness, dissolved in water/methanesulfonic acid and refluxed for 15 minutes. The sample was cooled, basified, and hexane and water added. The volume of water and base was doubled at this step to generate more steam in the distillation process. Steam distillation continued for 15 minutes and the sample cleaned up on a SepPak silica cartridge. At this point in the previous method, the DMA was derivatized with trifluoroacetic acid in a 15°C water bath. The TFA derivatization was to minimize DMA loss as the sample was taken to dryness; however, Ciba-Geigy states that if the water bath exceeded 18°C, traces of TFA actually caused losses of DMA. The TFA derivatization step was eliminated for the current analyses. Samples were analyzed by gas chromatography with a N/P detector operating in the nitrogen specific mode. Results were expressed as metalaxyl equivalents with a limit of detection of 0.05 ppm. The changes made for the current analysis do not significantly change the procedure and do not warrant a new method tryout.

In a previous petition for metalaxyl in or on the grass forage, fodder, and hay crop group, analysis of various wet and dry grass commodities was with AG-395 but without the current changes (PP#8F3617, memo, F.Griffith, 11/28/88). At that time, the recoveries ranged from 66-134%, 7 out of 17 controls were positive for metalaxyl, and all of the grass hay controls were spiked at a concentration below the existing apparent residues. DEB could not conclude that this method was suitable to gather metalaxyl residue on the grass forage, fodder and hay crop group without additional supporting chromatographic data, additional validation data (either repeat recoveries or new data), and an explanation for all of the variably positive controls.

Ciba-Geigy has provided the actual ppm recovered of metalaxyl equivalents and percent recovery for only four forage and hay samples. From the information provided, CBTS cannot determine which method the petitioner has used in calculating the percent recoveries. It appears that different calculations were used for different samples. The percent recovery only was reported for the remaining samples. Recoveries for the modified procedure (63-120%) were slightly less variable as compared to the unmodified procedure (66-134%), and 20 out of 44 of the forage and hay controls were positive for metalaxyl. All but three of these fortified controls were spiked at a concentration greater than the existing apparent residues.

Because of the low concentrations of apparent residues in controls (0.07-0.79 ppm) versus the proposed tolerances of 10.0 ppm in forage and 20.0 ppm in hay, the apparent residues are not likely to interfere with the actual residues in the RACs. It appears that the modified AG-395 method is adequate for data collection purposes. However, the adequacy is contingent upon the petitioner submitting actual ppm of metalaxyl equivalents recovered, sample calculations for determining percent

recoveries, and an explanation for the large number of control samples positive for metalaxyl.

Storage Stability:

Storage stability data were not submitted with this petition. Grass forage and hay samples were stored frozen from 4 to 18 months. The petitioner has referenced previously submitted studies for metalaxyl in various raw agricultural commodities analyzed with method AG-395 for up to 12 months. In response to the metalaxyl Reregistration Standard, the registrant indicated that storage stability studies for longer than 12 months are in progress on various RACs (memo, R. Perfetti, 1/15/91). CBTS concludes that adequate storage stability data are not available for grass forage and hay. The petitioner should submit or reference relevant storage stability studies in their response to CBTS' review of this petition.

Magnitude of Residue-Crop Field Trials: (MRID# 421345-01)

Fifteen field trials were conducted with the four representative commodities of the grass forage, fodder and hay crop group. The data presented represent five Bluegrass trials (IL, NY, OR, IA, MD), five Bermuda grass trials (TX, OK, GA, AL, LA), four Bromegrass trials (IL, NY, WA, NE), and one Fescue trial (TN). Metalaxyl residues were measured in or on grass forage (first cutting) and grass forage and hay (second cutting) except for the Bromegrass (NY) trial in which only the second cutting forage and hay metalaxyl residues were measured.

Crops were treated at either the 1x (1.0 lb. ai/A) or the 2x rate, with an at-planting broadcast application of Ridomil®2E. Seeded grasses received a preemergence, broadcast, nonincorporated spray. For several sprigged Bermuda grass trials, the at-planting application was made as a preplant, broadcast, nonincorporated spray. Grasses were grown under normal agricultural practices. Soil, forage, and hay samples were collected for analysis. The first cutting grass forage samples were taken at preharvest intervals of 58-63 days; second-cutting forage and hay samples were taken at PHIs of 89-312 days.

Samples were collected at random from within the plots and shaken to remove the surface soil. After collection, samples were frozen and shipped on dry ice to Ciba-Geigy Corporation, Greensboro, NC. Upon arrival, samples were stored at -20°C. Samples were prepared according to standard operating procedures, returned to the freezer, and stored frozen until residue analysis.

Forage (first- and second-cutting) and hay (second-cutting) samples were analyzed for metalaxyl residues. A second-cutting forage-to-hay concentration factor was calculated to determine

the first-cutting hay values. Concentrations of metalaxyl equivalents were reported as corrected for percent recovery. Sample calculations and uncorrected residue values were not provided. Metalaxyl residues ranged from 0.13 ppm (60 day PHI) to 6.2 ppm (61 day PHI) for first-cutting forage, from <0.05 ppm (283 days) to 5.9 ppm (105 days) for second-cutting forage, and from 0.09 ppm (288 days) to 8.1 ppm (105 days) for second cutting hay. Control values ranged from 0.07 ppm to 0.79 ppm; 20/44 control samples were positive for metalaxyl residues. The average concentration factor for second-cutting forage-to-hay residues was 2.48. Ciba-Geigy applied this concentration factor to the maximum residue for first-cutting forage, predicted a maximum first-cutting hay residue of 15.4 ppm, and proposed a tolerance of 20.0 ppm on hay. However, the standard procedure to predict residues from a concentration factor is to apply the concentration factor to the proposed tolerance (10.0 ppm) rather than the maximum residue. Therefore, a tolerance of 25.0 ppm would be more appropriate and should be proposed.

The current tolerance of 0.1 ppm on grasses, forage (40 CFR §180.408) reflects a seed treatment use. Residue data was translated from soybean green forage and stalks, navy bean green forage and vines, and sweet corn green forage. Residues ranged from <0.031 to 0.071 ppm as a result of treatment at 0.5 oz ai/100 lbs. seed. Therefore, residues as a result of seed treatment will not significantly add to residues that result from soil, at-planting treatments. CBTS concludes that the combination of seed treatment and soil treatment residues on metalaxyl-treated grass should not exceed the proposed tolerances.

The proposed metalaxyl tolerances of 10.0 ppm for forage appears to be adequate; however, the petitioner should submit a revised section F which proposes a tolerance of 25.0 ppm in or on grass hay. Before CBTS can recommend for these tolerances, the petitioner needs to submit actual ppm of metalaxyl recovered and sample calculations of corrections made for recovery. In addition, the adequacy of the proposed tolerance is contingent upon the petitioner resolving the questions raised by CBTS pertaining to the analytical method and storage stability.

Meat, Milk, Poultry, and Eggs:

Animal feeding studies were submitted with PP#1F2500 (memo, P.V. Errico, 3/9/82). CBTS will address only the ruminant feeding studies since grass forage and hay are not poultry and swine feed items. Lactating dairy cows were fed metalaxyl at levels of 0, 1.5, 7.5, and 15.0 ppm for up to 40 days. Residues were detected in liver and kidney but not in any of the milk, meat or fat samples. However, the animal metabolism study indicated that transfer of metalaxyl residues to milk, meat, and fat could occur at levels lower than those detected in liver and kidney. The

registrant subsequently submitted an additional animal feeding study in which 3 lactating dairy cows were fed 75 ppm metalaxyl for 14 to 28 days. Maximum residues for the cows sacrificed 19-23.5 hours after the last dose were 0.14 ppm in liver and 0.13 ppm in kidney. On the basis of the 75 ppm feeding study and an estimated dietary burden of 22.7 ppm metalaxyl from feeding corn grain and tomato pomace, CBRS concluded that existing tolerances for metalaxyl on cattle liver, kidney, and fat (0.4 ppm), meat and meat by products (0.05 ppm) would not be exceeded (memo, J. Abbotts, 6/27/91).

Similarly, CBTS has calculated the dietary burden for cattle based on the 75 ppm feeding study. The dietary burden was calculated on a dry matter (DM) basis (memo, 6/12/93, D. Edwards and E. Zager). Assuming a hypothetical diet:

70% grass hay/88% DM	at	25 ppm =	19.9 ppm
25% tomato pomace, dry/92% DM	at	20 ppm =	5.4 ppm
5% citrus pulp, dry/91% DM	at	7 ppm =	0.4 ppm

the highest expected dietary burden would be 25.7 ppm.

Therefore, the predicted residues would be 0.048 ppm for liver and 0.045 ppm for kidney. These values are well below the 0.4 ppm tolerances for liver, kidney, and fat. For the purposes of this petition only, CBTS concludes that the tolerances for metalaxyl in or on ruminant meat, meat byproducts, fat, liver, and kidney will not be exceeded by the proposed use. However, CBTS cannot determine if the feeding studies submitted in conjunction with PP#2500 calculated the dietary burden on a dry matter or an as-fed basis. Therefore, future petitions and amendments which include ruminant feed items with higher tolerances proposed for feed items must be accompanied by a letter stating which method was used and support the statement with calculations and an explanation of the procedure.

Other Considerations:

The International Residue Limit Status sheet is attached. Codex and Canadian tolerances for metalaxyl in or on grass are for metalaxyl per se. Since the U.S. tolerance expression includes parent and metabolites, harmonization between Codex, Canadian, and U.S. tolerances is not possible at this time.

cc:RF, SF, Circ., PP#2F04063, M.Peters.
RDI:SecHead:RSQuick:9/20/93:BrSrScientist:RALoranger:9/21/93:BrChief:DEdwards:9/21/93.
H5709C:MHP:mhp:CM#2:Rm804S:703/305-6380:9/22/93.

I. Mees 8/13/93

Attachment:

Page 1 of 1

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL: Metalaxyl

CODEX NO. 138

CODEX STATUS:

[X] No Codex Proposal Step 6 or Above (on grass)

Residue (if Step 8): _____

metalaxy per se

Crop(s)	Limit (mg/kg)

PROPOSED U.S. TOLERANCES:

Petition No. 2F4063

DEB Reviewer M. Peters

Residue: Metalaxyl and its metabolites containing the 2,6-dimethylaniline moiety and N-(2-hydroxymethyl-6-methyl phenyl)-N-(methoxyacetyl) alanine methyl ester.

Crop(s)	Limit (mg/kg)
Grass, forage	10.0
Grass, hay	20.0

CANADIAN LIMITS:

[X] No Canadian Limit (on grass)

Residue: _____

Metalaxyl per se

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

[X] No Mexican Limit

Residue: _____

Crop(s)	Limit (mg/kg)

NOTES

Form Revised 1989