Ciba-Geigy has received conditional registration for Ridomil 2 E fungicide [a.i. N-(2,6-dimethylphenyl)-N-(methoxyacetetyl) alanine methyl ester, aka CGA 48988 or metalaxyl] on fields to be planted with tobacco.

An EUP is currently in effect for Ridomil on tobacco (E. Brittin, 5/7/79), covering 430 gal Ridomil on 430 acres of tobacco. A temporary tolerance of 0.05 ppm Ridomil on potatoes has been established (PP#8G2121, G. Makhijani, 3/29/79). There have been no permanent tolerance requests.

Conclusions

1. The directions for use should specify spray volume and method of application for all uses, rather than only for black shank on flue-cured tobacco.

2a. The nature of the residue in tobacco and cigarette smoke is adequately understood.

2b. The characterization of pyrolysis products is marginally adequate.

3. Adequate analytical methods are available to determine both total residues and residues of Ridomil per se.

4a. Maximum residues of parent Ridomil resulting from the proposed use are 31 ppm in lower cured bright leaves and 6.3 ppm in cured burley leaves.

4b. Maximum residues of Ridomil and its metabolites convertible to 2,6-dimethylaniline are 83 ppm in lower cured bright leaves and 6.1 ppm in cured burley leaves.
4c. Maximum total residues of Ridomil and metabolites in a typical one gram cigarette are estimated to be 151 micrograms.

4d. Maximum residues of Ridomil and its metabolites inhaled by a person smoking a typical one gram cigarette are estimated as 38 micrograms.

Recommendations

We defer to TOX concerning the safety of reported Ridomil residues in cigarette smoke.

We defer to EFB for their evaluation of whether the crop rotation restrictions are adequate to ensure that residues will not transfer to follow-up crops.

Tox and EFB considerations permitting, we recommend for this registration.

Detailed Considerations

Manufacturing Process

The manufacturing process was submitted with the EUP for tobacco and also in FP#8G2121 where it was reviewed. Briefly,

Formulation

Technical CGA-48988 is 90% pure, with the remaining 10% composed of

The formulated product, Ridomil 2E, contains 27.8% CGA-48988 technical, equivalent to 2 lb a.i./gal. All inerts in this formulation are cleared under 40 CFR§180.1001.
Proposed Use

Ridomil is a soil-applied systemic fungicide for use on the field before transplanting, for control of black shank on flue-cured tobacco and blue mold on all types of tobacco.

For flue-cured tobacco:

1. To control black shank, apply 1.0-2.0 lb a.i./A using conventional ground sprayer in at least 15 gals of water per acre. [Use 3.0 lbs a.i./A under very high disease levels (>60%)]. Incorporate product into top 2-4 inches of soil and form beds.

1. To control blue mold, apply 0.5-1.0 lb a.i./A broadcast and incorporate into top 2-4 inches of soil.

For burley and other tobacco, to control blue mold, apply 1.0 lb. a.i./A broadcast and incorporate into top 2-4 inches of soil.

A statement regarding rotational crops is included. Second applications of Ridomil are not permitted—tobacco may be replanted following application if necessary. Tobacco, corn or root crops may be planted the year following treatment. Small grain cover crops may be planted in the fall following treatment provided they are plowed down and not used for food or feed. Other crops may be planted eighteen months following application.

The directions for use should specify spray volume and method of application for all uses, rather than only for black shank on flue-cured tobacco.

We defer to EFB for their evaluation of whether the crop rotation restrictions are adequate to ensure that residues will not transfer to follow-up crops.

Nature of the Residue in Tobacco

The nature of the residue for both cured and uncured tobacco was reviewed in connection with the EUP on tobacco (E. Brittin, 5/7/79). The component-residue profiles of uncured bright and burley tobaccos are not significantly different. Residues were characterized as either non-extracted, organic (soluble in chloroform or methanol) or polar (soluble in water). A decline in extractability was noted in the cured tobaccos.
Name | % of Total
--- | ---
CGA-94689, benzyl alcohol of CGA-48988 | atropisomer A-4.7%
(N-[2-(hydroxymethyl)-6-methylphenyl]- (N-(methoxy acetyl)-alanine methyl ester) atropisomer A-10.6%
m-phenol of CGA-48988 | 14.7%
(N-(3-hydroxy-2,6-dimethylphenyl)- N-(methoxyacetyl)-alanine methyl ester)

CGA-62826 | 16.0%
(N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-alanine)

The other study submitted concerns uptake and balance of labeled Ridomil in field-grown bright tobacco. The soil was treated with 3 lb a.i./A ring-labeled Ridomil preplant. Residue levels were considerably lower than in greenhouse-grown tobacco, presumably due to decreased availability of Ridomil because of soil binding, and were also lower than in a previous study on field-grown burley tobacco treated with 6 lb a.i./A (discussed in the EUR memo, 5/7/79, Brittin).

Residue levels increased about threefold on curing (9 week-old leaves - 6.7 ppm green, 21.5 ppm cured). Cured bottom leaves contained higher levels (21.5 ppm) than did cured top leaves (7.3 ppm).

Balance data showed a decrease in organic radioactive solubles from 49.1% at 5 weeks to 31.0% at 16 weeks and an increase in aqueous soluble metabolites from 43.0% at 5 weeks to 61.5% at 16 weeks. These changes occur more rapidly in field grown tobacco than in greenhouse tobacco.

Nonextractable radioactivity was low before curing, but rose to 10-20% upon curing. Aqueous soluble polar metabolites are higher in middle and upper cured leaves than in lower ones, which suggests that age increases the amount of polar metabolites.

Additionally, it was found that labeled Ridomil is transferred from treated to untreated leaves during curing. The amount of transfer occurring is expected to be a function of temperature and air flow rate in the curing ovens.

Metabolites II, IV, V, VI, VII and XVI (see Metabolite Chart attached) each comprised >1% of the total radioactivity in the leaf, and 17 unknown metabolites, each <1%, <10% total. No parent Ridomil was found. The TLC patterns are qualitatively similar to greenhouse-grown bright and burley tobacco. Apparently metabolism occurs faster under field conditions than in the greenhouse.
Residues of $^{14}$C-Ridomil per se average 42.5 ppm in the cured tobaccos in that study, and total $^{14}$C-Ridomil residues are about 155 ppm. A standard cigarette prepared with either 10% or 40% of $^{14}$C-labeled tobacco would be expected to contain total residues of $^{14}$C-Ridomil of 17 or 68 μg. Cigarettes (1g) prepared with greenhouse-grown $^{14}$C labeled tobacco contained 19 μg (10% blend) and 82.2 μg (regular blend) when made with bright tobacco, and 68.7 μg (regular blend) when made with burley.

Based on the field residue studies submitted in the EUP application, 1.0 gm cigarettes prepared with bright tobacco treated with 3.0 and 6.0 lb Ridomil/A would contain residues of Ridomil per se of 31 and 68 μg, and total residues of about 100 and 250 μg.

Two new studies are submitted with this registration action. In the greenhouse study, bright tobacco slips were treated by a transplant water procedure at 0.5 lb ai/A with ring-labeled Ridomil, and the mature top leaves were harvested and cured after 19 weeks. Residue levels were 93.7 ppm. Previous studies at 12 weeks showed that polar metabolites could be converted to nine aglycones, six of which corresponded to unconjugated metabolites. Four of those aglycones have now been identified primarily by GLC/MS, GLC/Fourier Transform IR and two dimensional TLC. Collectively, these and the parent compound account for 61% of the radioactivity in the leaf.
Thus we see that metabolism of Ridomil in bright tobacco occurs by oxidation of one of the aromatic methyl groups, oxidation at the meta position of the ring, hydrolysis of the methyl ester or hydrolysis of the methyl ether. The metabolism is adequately understood for this use on tobacco.

Nature of the Residue in Cigarette Smoke

No new data are submitted for smoke and pyrolysis products. The residues in smoke were discussed in our review of the EUP (5/7/79, E. Brittin). Four batches of radiolabeled cigarettes (Kentucky 2R1 type) were prepared, 10 and 40% labeled material, either bright or burley tobacco using greenhouse-grown tobaccos. The greenhouse-grown tobacco significantly affects smoking characteristics at the 40% level. Parent Ridomil and 2,6-dimethylaniline were the only components identified, and approximately half the C activity present remained in the ash (1.8 g) and the butt end (23 μg), or was trapped as 14CO2 from the smoke.

For both bright and burley cigarettes, 75% of the radioactivity was found in sidestream smoke and 25% in mainstream smoke, and all radioactivity was calculated as parent, although most is not. Burley and bright cigarettes showed very similar profiles. For the bright tobacco, the following table shows amounts of various components in both mainstream and sidestream smoke.

<table>
<thead>
<tr>
<th></th>
<th>Mainstream</th>
<th>Sidestream</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total particulate matter (tar)</td>
<td>18.7 μg</td>
<td>14.8 μg (about the same percentage parent and DMA)</td>
</tr>
<tr>
<td></td>
<td>6 μg parent,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6 μg DMA</td>
<td></td>
</tr>
<tr>
<td>Volatiles</td>
<td>0.3 μg</td>
<td>3.9 μg (0.7 μg DMA)</td>
</tr>
<tr>
<td></td>
<td>(8 components)</td>
<td>(22 components)</td>
</tr>
<tr>
<td>14CO2</td>
<td>&lt;1 μg</td>
<td>18.9 μg</td>
</tr>
</tbody>
</table>

*DMA = 2,6-dimethyl aniline

Since a standard cigarette weighs approximately 1g, these μg values are equivalent to ppm values. Some components are found in smoke and tar and in cured tobacco; apparently both distillation and pyrolysis occur during smoking. The nature of the residue in cigarette smoke is adequately understood.
Pyrolysis Products

These were also reviewed in connection with the EUP (5/7/79, Brittin). No new data are submitted. One organic component and 2,6-DMA are definitely pyrolysis products. Three organic components in cured tobacco and smoke are probably distillation components. Unlabeled pyrolysis products were not determined, but their presence is indicated by the large proportion of $^{14}C-CO_2$ in the smoke.

We consider this characterization of the pyrolysis products of Ridomil and its metabolites to be marginally adequate.

Analytical Methods for Residues in Tobacco

Petitioner's method AG-325 for determination of parent Ridomil residues was discussed in our review of the EUP (Brittin, 5/7/79). The method employs methanol extraction, partitioning into dichloromethane and then hexane, cleanup on an alumina column. The purified residue is then taken up into acetone and quantitated by GC using an alkaline flame detector. The limit of detection is 1.0 ppm.

This method is adequate for determination of residues of Ridomil per se.

A method (AG-330) for determining total residues as 2,6-dimethylaniline (DMA) is submitted with this registration application. Residues are extracted with 4:1 methanol-water, then a measured aliquot is evaporated and refluxed overnight with phosphoric acid in the presence of cobalt chloride. After reflux, the solution is basified and the DMA steam distilled, derivatized with trichloroacetyl chloride, cleaned up on an alumina column and analyzed by GC using alkali flame ionization detector in nitrogen-specific mode. The limit of detection for residues in tobacco is 1.0 ppm (in Ridomil equivalents).

Compounds containing oxidized forms of DMA were not detected satisfactorily, but six standard compounds related to known metabolic products (containing DMA moiety) are shown to give satisfactory recoveries (85 to 104%).

Twelve fortification studies using green and cured, bright and burley samples fortified with 1 to 500 ppm parent compound gave recoveries of 65 to 87% (avg. 72%).

Analyses of tobacco leaves treated with $^{14}C$-labeled Ridomil show that from 36% to 68% of extractable radioactivity was detected with this method (52-68%, according to petitioner who disregards the low recovery sample as having abnormally low residue levels).
A comparison of parent and total residues (determined as DMA) in green and cured field-treated (either 50W or 2E formulation) gives total-to-parent ratios of 2.0 to 4.7, averaging 3.5.

This method is adequate for determination of total residues of Ridomil (as DMA) in tobacco.

Residue Data for Field Tobacco

Residue data from five studies are discussed in our review of the EUP (5/7/79, Brittin). Ridomil residues per se were determined after treatment with Ridomil 50W at 3 or 6 lb a.i./A, and one study was done in duplicate with the subject Ridomil 2E formulation to provide cross-reference between the two formulations, and no significant differences were found. Residues in lower, uncured leaves, at twelve week treatment-to-harvest interval (84 day PHI), were up to 3.5 ppm in bright tobacco from 3.0 lb a.i./A and up to 9.2 ppm from 6.0 lb a.i./A; residues in uncured composites burley leaves, at 109 days PHI, were <1.0 ppm.

Residues in lower, cured bright leaves at 12 week (84 day) PHI were 3-31 ppm from 3 lb a.i./A and 4.6-68 ppm from 6 lb a.i./A; residues from cured composites burley leaves at 109 days PHI were 6.3 ppm from 6 lb a.i./A.

Five new reports are submitted which contain results of analyses for total Ridomil residues (detected as derivative of 2,6-dimethylaniline) found in tobacco from the same locations for which residues of Ridomil per se were reported earlier. Total residues in green lower leaves treated at 3 and 6 lb a.i./A ranged from 1.2 to 25 ppm (2.9 ppm parent at 25 ppm total) and 2.0 to 35 ppm (11 ppm parent at 35 ppm) respectively. Residues in composites green leaves (upper, middle and lower) from one study were <1.0 ppm from treatment with either 3 or 6 lb a.i./A.

In the cured tobaccos, lower bright leaves (harvested 84 days after treatment) contained 7.9 to 83 ppm from 3 lb a.i./A and 15-179 ppm from 6 lb a.i./A. Middle bright leaves (122 days) contained 8.6 to 16 ppm and 8.1 to 50 ppm from treatment with 3 and 6 lb a.i./A, respectively. Upper bright leaves (154 days) contained 6.0 to 12 ppm and 8.1 to 45 ppm from treatment with 3 and 6 lb a.i./A, respectively. Composites burley leaves (109 days) contained <1.0 to 6.1 and 1.5 to 21 ppm, and composites bright leaves contained 44 to 49 ppm (13 ppm parent) and 199-228 ppm (53 ppm parent) from 3 and 6 lb a.i./A treatments, respectively. Samples were treated with either the 2E formulation or a 50W formulation.

Maximum residues in cigarettes are calculated using the tobacco with the highest residue levels, which were 83 ppm (residues
determined as DMA) in lower cured leaves. From the metabolism studies, the average ratio of label recovered as DMA to total label present was 55%. Thus, we estimate that 151 ppm is the maximum level of metalaxyl and all metabolites. For a standard 1g cigarette, that level represents 151 μg per cigarette.

In cigarettes prepared from greenhouse-grown tobacco treated with radiolabelled metalaxyl, 25% of residues in smoke were found in the mainstream smoke (see Nature of the Residue). Thus, 38 μg of metalaxyl residues would be in the mainstream smoke, and likely inhaled by the smoker of a 1g cigarette.
Figure 1. Chemical names and structures

Standard Code

1. \( R - N \)  
   \( \text{CH}_3 \)  
   \( \text{CH} - \text{COOCH}_3 \)  
   \( \text{CO} - \text{CH}_2\text{OCH}_3 \)
   CGA-48988
   \( N-(2,6\text{-dimethylphenyl})-N-(\text{methoxyacetyl})\text{-alanine methyl ester} \)

2. \( R - N \)  
   \( \text{CH}_3 \)  
   \( \text{CH} - \text{COOCH}_3 \)  
   \( \text{CO} - \text{CH}_2\text{OH} \)
   CGA-67869

3. \( R - N \)  
   \( \text{CH}_3 \)  
   \( \text{CH} - \text{COOCH}_3 \)  
   \( \text{CO} - \text{COOH} \)
   CGA-79353

4. \( R - N \)  
   \( \text{CH}_3 \)  
   \( \text{CH} - \text{COOH} \)  
   \( \text{CO} - \text{CH}_2\text{OCH}_3 \)
   CGA-62826

5. \( R - N \)  
   \( \text{CH}_3 \)  
   \( \text{CH} - \text{COOH} \)  
   \( \text{CO} - \text{COOH} \)
   CGA-78532
FIGURE 1. CHEMICAL NAMES AND STRUCTURES (Continued)
Figure 1. Chemical Names and Structures (Continued)