5-7-79

May 7, 1979

100-EUP-62; Experimental use permit for Ridomil on Tobacco.

Edward B. Brittin, Chemist, Residue Chemistry Branch,
Hazard Evaluation Division (TS-869)

Product Manager #21 (H. Jacoby) Registration Division (TS-767)

THRU: Acting Chief, Residue Chemistry Branch

Ridomil™ is a new active ingredient which Ciba-Geigy has proposed for use on tobacco. The company has submitted product chemistry and residue data in support of the following program.

PROPOSED EXPERIMENTAL PROGRAM

Experimental testing would start 2 February 1979, and continue for two years. A total of 430 acres of tobacco would be treated with 430-gallons of Ridomil 2E Fungicide (860 lb ai) each year. The following states and acreages are involved in the program:

Kentucky and N. Carolina (each, 100 acres), Tennessee (45), Georgia (40), South Carolina and Virginia (35), Florida, Maryland and Pennsylvania (20), and Connecticut (10).

Ridomil 2E would be applied either as a band application over a row, or broadcast, at rates of 1.0 qt to 6.0 qt of product per acre. The higher rates are recommended where the field history indicates higher disease levels. The broadcast rates are equivalent to 0.5 lb to 3.0 lb Ridomil per acre; the band applications over a row approximate 1.0 lb to 6.0 lb Ridomil per acre.

A second Ridomil application is not permitted for one year and then only for tobacco; other crops may be planted after 18 months.

CONCLUSIONS

Product Chemistry

1. Ridomil has been adequately identified in terms of chemical formula and physical properties. The composition of the technical product with the specified composition limits is acceptable. However, only the basic manufacturing reactions have been given; additional details are needed on the manufacturing process for full registration; see the recommendations.

2. The submitted analytical procedure for both the technical and formulated Ridomil appear acceptable, but the validation data which is required for the technical Ridomil procedure has not been submitted and will be needed for registration; see the recommendations.

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Special Chemistry (Residues)

NATURE OF RESIDUE IN TOBACCO & TOBACCO SMOKE

Following soil application, tobacco picks-up and extensively metabolizes the soil residues of Ridomil. The nature of the residue in both tobacco and tobacco smoke are adequately shown; see the summary Tables I and II.

RESIDUES MAXIMUM RATE OF APPLICATION

Following application at the maximum rate of 6 lb Ridomil per acre, the residues of Ridomil per se in tobacco, cigarette (1.0 gm), and cigarette smoke were respectively for the Bright tobacco: 68 ppm (total residue, ca 250 ppm); 68 micrograms (250 ug); 34 microgram (125 ug). The corresponding residues in burley were very much lower, approximately one tenth those of Bright tobacco. These lower residues resulted primarily from the practice of compositing the upper, middle, and lower leaves of Burley tobacco.

PYROLYSIS PRODUCTS

The only definite pyrolysis products were 2,6-dimethylanaline (3.8%) and the 2D-TLC fraction A, (2.8%). These two components, 6.6% of the total Ridomil residue in the cigarette (1.5 to 16.5 micrograms), were the only components present in smoke which were not also in the tobacco.

RECOMMENDATIONS

Residue Chemistry Branch defers to toxicology concerning the safety of the reported Ridomil residues in cigarette smoke, the need for further characterization of the pyrolysis products, and the need for Ridomil-residue-smoke inhalation studies.

CONCLUSION SUFFICIENT FOR EUP, BUT NOT FOR REGISTRATION

Sufficient chemistry data have been submitted to support the proposed EUP. However, the following additional data and information, as required by the Section 3 Regulations, will be needed at the time of Registration.

Product Chemistry

MANUFACTURING PROCESS

1. The applicant's discussion of the manufacturing process should be more thorough. It should reflect a diligent effort to anticipate unintentional toxic components in the product which are likely to pose a toxicity problem. In addition to the basic reactions, the discussion should consider the side reactions and factors such as temperature and reactant impurities. Consideration should also be given to the quality control measures and packaging material of both the technical and formulated product.

UNINTENTIONAL IMPURITIES

Quantitative procedures will be needed for the unintentional impurities, nitrosoamines for example, if such impurities are present in the product.

ANALYTICAL METHODS

2. The Method PA-173-T appears adequate for the formulated product; Method PA-172-T may also be adequate for the technical product, but validation data will be needed to establish its reliability. Also, at the time of registration, the applicant will need analytical results by Method PA-172-T for five or more samples of the technical product which are representative of the manufacturing process.

3. Representative samples of technical Ridomil with a product specification sheet, the proposed analytical procedure, and appropriate standards should be submitted to EPA:

Environmental Protection Agency
Penefits and Field Studies Division
Chemical and Biological Investigation
Branch (TS-768)
ARC Bldg. 306
Beltsville, MD 20705

4. The octanol-water partition coefficient for Ridomil should be reported. References for this determination and other data requirements are in the appendix to the Product Chemistry Guidelines,

5. In addition to the decomposition temperature, the stability data for Ridomil should include the effects of metallic contaminants and other probable impurities in the technical product.

6. The viscosity data should be given in common units, for example in Centistokes or Saybolt units; we are not familiar with the Cannon-Fensky unit.

7. The component of the technical product (CGA-48988) indicated as solvent 0.0-2.0% should be identified. Information is also needed concerning the solvent medium for the second and third manufacturing reactions.

8. The applicant should report the CAS (Chemical Abstracts Service) registry numbers of Ridomil, its related compounds, and the significant toxics in the technical product. Registry numbers (CAS) are also needed for the inerts of both the formulated and technical products.

PRODUCT-CHEMISTRY DETAILS

Ridomil™ Formula and Names

Chemical Abstracts nomenclature:

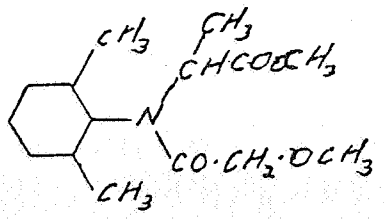
N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-alanine methyl ester

Common name - none metalaxyl

Company code: CGA-48988

Molecular weight: 279.34 ($C_{15}H_2NO_2$)

Structure:



Manufacturing Peactions

See RCB's review of PP# 8G2121 dated 3/29/79 for details of the manufacturing process.

Formulating Process*

Ridomil-2E Fungicide:

Component	% by Weight	Purpose in Formulation
ZGA-48988 Technical (90% ai)1/	27.9	Acting Ingredient
[redacted]		
	100	

1/ CIBA-GEIGY Corporation, Greensboro, NC

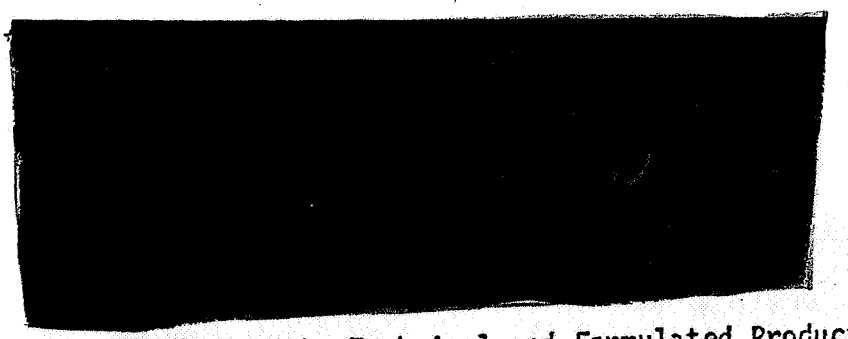
[redacted]

PRODUCT INGREDIENT SOURCE INFORMATION IS NOT INCLUDED

INERT INGREDIENT INFORMATION IS NOT INCLUDED

*The product is formulated with 2.0 pounds active per gallon; ingredients are heated, mixed, filtered, and packaged. The inerts in this revised (1/9/79) composition statement are tolerance exempted (40 CFR 180 1001).

Inerts →



Impurities in the Technical and Formulated Products

IMPURITIES MANUFACTURING PROCESS

At the time of registration additional information will be needed concerning the toxicologically significant components and impurities present in these products. The applicant's discussion of the manufacturing process should be more thorough and cover the factors related to the amounts of these components and impurities in the technical product.

Analytical Methodology (Products)

A. Ultraviolet, also IR, MS, and NMR spectra are included in this data section.

Analytical Methods

B. Method PA-172-T; determines CGA-48988, its related compounds, and impurities in the technical product:

Methyl sterate is used as an internal standard. The column (1.8m x 2 mm is prepared with OV-101(10%) on Gas Chrom Q. A flame ionization detector nitrogen flow, and acetone solution of both the sample and standards are recommended. The sensitivity of the procedure should approximate 1.0 manogram; see also the method AG-325 for residues in crop samples.

The procedure appears adequate, but validation data should be submitted for both Ridomil and the related products in the technical product.

C. Method PA-173-T, determines Ridomil in formulations:

The samples are dissolved in acetone. Ridomil is then quantified on the same GLC column used for the analysis of CGA-43983. The validation data which was reported only for the parent-compound indicates a standard deviation of ca 1.32%. If the Method PA-172-T is shown adequate for the technical product the Method PA-173-T would be suitable for product chemistry enforcement programs.

Physical-Chemical Properties

PHYSICO-CHEMICAL PROPERTIES

Except for the following properties the data are acceptable; we will need for full registration:

- Stability: only the decomposition temperature has been submitted; see the recommendations.
- Octanol-Water Partition Coefficient: the data as required by the guidelines.

. Viscosity: the report(ed) figures 2.31±0.05 in Cannon-Fensky units for the formulated product should be given in common units (Centistokes or Saybolt units).

SPECIAL CHEMISTRY

Nature of the Residue in Tobacco with Data Summary - Table I

One greehhouse-metabolism study (ABR-78036) is reported. In this study Bright and Burley cultivars, when six weeks old, were transplanted into a Georgia-sandy-loam soil. Ridomil (U-Ring-14C) was added to the transplant water; but only for the Bright tobacco, in an amount approximating either 0.25 lb or 0.50 lb ai/acres. The 14C-Ridomil (U-Ring-14C) application to Burley was soil incorpoaporated at approximately 6.0 lb ai/acre.

The resulting residues of Ridomil, present in the leaf of both Bright and Burley plants, were separated on the basis of their solubility into three groups: (a) non-extracted residues; (b) organic residues, soluble in chloroform or methanol; (c) and polar residues, soluble in water. Further analyses, by 2D-TLC, of the organic and polar groups provided component-residue profiles for the Ridomil residues in tobacco.

The component-residue profiles of the uncured tobaccos, Bright and Burley, are not significantly different. Although the curing procedures are different, Bright is oven cured and Burley is air dried; the increase in residue levels by the two procedures is comparable and approximately 10 fold. A decline in the extractability of the residues, averaging 6.6 (7.5 and 5.7%) is the most noticeable effect of curing. There are other differences, all rather small, between the residue profiles for these tobaccos.

The following table summarizes this data for both the cured and uncured tobacco.

TABLE I:

ANALYTICAL DATA	BRIGHT TOBACCO		BURLEY TOBACCO	
Rate(lb. ai/A)	0.50 Transplant Water Lower Leaves		6.3 ppi Lower Leaves	
THI[2] (weeks)	12UC	12C	12UC	12C
PPM	14.1	147.7	15.0	161.8
Balance	Percent of Total ^{14}C in Plant Sample			
Organic	56.2	31.3	49.4	43.6
Aqueous	46.8	49.6	44.6	44.7
Nonextractable	2.4	9.9	2.1	7.8
TLC Characterization				
Organic CGA-48988	34.7 (4.9 ppm)	26.9 (40 ppm)	32.9 (4.9 ppm)	28.1 (45 ppm)
7 Unknown Met.[3]	--	(12.5)	--	(12.5)
Aqueous CGA-62826[4]	1.5	<0.3	0.7	
Major Unknown Polar Met., each >3% in Cured Tobacco				
IV	4.7	6.5	5.4	5.4
V	2.5	3.2	2.2	3.0
VI	13.5	6.9	12.0	7.5
VII	3.3	2.3	4.7	3.1
VIII	3.2	3.0		
XIII	2.9	3.2		
Minor Unknowns, ca 20 Polar Met., each from 0.3 to 3.0% in cured Tobacco	12.1	19.6	16.8	17.3

Notes:

1. These data are from Tables I and II of the Report ABR-18036, Acc #234431.

2. TMI, the treatment to harvest interval. UC, the uncured; and C, the cured tobacco.

3. The 12.5% figure, although determined for tobacco treated at the 0.25 lb. ai/A rate, is assumed representative of the residues at these higher rates.

4. CGA-62826 has been identified as:

   N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-Alanine.

The metabolism of Ridomil by tobacco has been delineated with sufficient detail to support the proposed use. Based on the data, soil residues of Ridomil are picked-up and extensively metabolized. The major pathway appears to be conversion of a Ridomil ring methyl group to methoxy and conjugation of Ridomil with glucose through this methoxy group. A second and minor pathway is a conjugation with glucose through the alanine carboxyl group of the Ridomil metabolite CGA-62826 (N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-alanine).

As can be seen from Table I, residues of 14C-Ridomil per se in the cured tobaccos averaged 27.5% or ca 42.5 ppm; total 14C-Ridomil residues calculate to ca 155 ppm. A standard cigarette, weighing ca 1.0gm and prepared with either 10% or 40% of the 14C-labelled tobacco, would therefore be expected to contain total residues of 14C-Ridomil of either 17 or 68 microgram.

The 14C-Bright cigarettes used for this work contained total Ridomil residues, based on 14C-Analyses, of about 19 micrograms (10% blend) and 82.2 micrograms (regular blend) per cigarette. Similarly, 14C-Burley (regular blend) cigarettes contained 68.7 microgram per cigarette.

Based on the field residue studies, cigarettes (1.0 gm) prepared with Bright tobacco treated with 3.0 lb and 6.0 lb of Ridomil per acre would have Ridomil Residues per se of 31 ug and 68 ug or total residues of about 100 ug and 250 ug.

Nature of the Residue in Cigarette Smoke with Summary-Table II

Most of the data (ABR-78040) is based on work with four batches of 14C-cigarettes prepared according to an accepted standard, the Kentucky 2R1 specifications. Two batches were prepared with blended Bright Tobacco, using regular Bright and either 4% or 40% of the 14C-Bright tobacco. Two batches were similarly blended with regular Burley and 14C-Burley. The greenhouse grown 14C-tobaccos from the metabolism study ABR-78036 were used in these cigarettes.

There are differences between greenhouse and field grown tobacco that affect significantly its smoking characteristics. These differences are shown negligible for the 10% blended (4%), but were definite for the regular blended cigarettes. That is, the MS/SS (mainstream/sidestream) distribution of tar residues, measured in milligrams, was for the TPM-volatiles of the Standard and the 10% blend cigarettes approximately the same, 40.2/26.4 versus 39.2/27.2 for the 10% blend. For the regular blended Bright and Burley cigarettes the respective ratios were 19.9/32.7 and 23.7/26.6.

The Vapor Phase Volatiles, volatiles which passed the inline Cambridge filter, are the smoke residues that would probably be inhaled through a cigarette filter. The 10% blend Bright (4%) 14-cigarettes were the source for these Ridomil residues; they were the only residues characterized by GLC. The regular blend (40%) 14C-cigarettes, Bright and Burley, provided TPM-Volatiles with sufficient 14C-Ridomil residue for co-chromatographic characterization by 2D-TLC and HPLC. The reported 14C-carbon dioxide 26.7 (0.7 MS/26 SS)%, and the calculated Ridomil (14C) remaining in the ash and butt, 2.7% and 20% respectively, was also determined with these cigarettes.

The registrant's data for the Ridomil residues in the cigarette smoke are presented in several tables (5) with considerable detail; the following Table II summarizes this data.

TABLE II: Summary of the Residue Data for Cigarette Smoke

Component(s)	TPM-Volatiles 44% MS(28%)	TPM-Volatiles 44% SS(16%)	VP-Volatiles 6% MS(0.36%)	VP-Volatiles 6% SS(4.74%)
Ridomil	7.5	5.2	0.07	0.38
2,6-DMA	0.7	2.2	<0.01	0.90
Polar (3)	2.0	2.2	-	-
Organic (4)	4.2	3.9	-	-
Other (22)	-	-	0.15 (6)	0.42 (22)
Total	14.4%	13.5%	0.13%	1.60%
% of the volatiles recovered	63%		34%	

Notes

- The regular blended(40%) Bright cigarettes provided the TPM-volatiles (tars). These components were characterized by 2D-TLC and HPLC (Tables IV, V, and VI). The 10% blended (4%) Bright cigarettes provided the VP-volatiles (Vapor phase tars) which were characterized by GLC (Table VII). The data are from tables in Report ~~ABR-18040~~, 18040 Acc. #234431.
- 2,6-DMA, (2,6-dimethylanaline) and Ridomil *per se* were the only components identified.
- Approximately 50% of the 14C-activity present in these cigarettes remained in the ash and butts, or was trapped as 14C-carbon dioxide in the smoke.
- In view of the similar residue profiles for the tobaccos, only the smoke profile of the Bright tobacco was prepared.

- About 100 micrograms is the total Ridomil residue expected in cigarettes prepared with Bright tobacco treated with 3.0 lb of Ridomil per acre. For such cigarettes, the percentage figures in Table II are also equivalent to the microgram quantities of the components in the smoke; i.e., the factor is ca 1.0. Similarly, for cigarettes prepared entirely with Bright or Burley treated at the maximum rate, 6.0 lb ai per acre, the respective factors are about 2.5 and 0.23. These factors are based on the reported maximum residues of Ridomil per se which were reported in the field studies, and data from Table I, indicating Ridomil residues per se averaging about 27.5% of the total residue. The average cigarette weighs ca 1.0 gram.

Analytical Methods (Residue)

The report residues of parent Ridomil in field tobacco were determined by Method AG-325. The recoveries from green and cured tobacco samples which were fortified with 1.0-50 ppm of Ridomil averaged 87%. The samples were macerated in methanol (80%), clear aliquots were evaporated, the residue was acidified and partitioned into DCM (dichloromethane), a second partition was made to hexane and the sample was further cleaned-up on an alumina column. The cleaned-up sample was then transferred to acetone and quantified by GLC.

The procedure (AG-325) employs a 10% OC-200 column (2m by 4mm) prepared on Gas Chrom Q. With a column temperature of 220°C, retention time was 3.5 minutes. The method with an alkaline flame detector has a lower detection limit of 1.0 ppm.

Residues in Field Tobacco Ciba-Geigy Corp. (1978) 0127

The data are from test plots in North Carolina, Virginia, Tennessee, Maryland, and Georgia. Bright or Burley tobacco, as appropriate, was grown and harvested according to the cultural practice of the respective areas. The reported residues vary considerably.

Plots at all locations were treated with Ridomil-50W at rates of either 3.0 lb or 6.0 lb of Ridomil per acre. In order to obtain cross-over data, plots in Maryland were also treated with Ridomil-2E (the EUP-formulation) at these same rates. Differences between the formulations based on this data did not significantly affect the Ridomil residue in tobacco. Growing conditions, field versus greenhouse, do affect the residue profile. These differences are considered; see the preceeding section on the Nature of the Residue in Cigarette Smoke.

Only Ridomil residues per se were determined in these studies; the following high residues (from Table IV, Acc. #234430) are reported.

A. Bright Tobacco:

o Lower, uncured leaves-12 week (THI). The residues ranged from <1.0 ppm (Md) to ≥3.5 ppm (N.C.) following applications of 3.0 lb Ridomil per acre.

With application at the maximum rate of 6.0 lb Ridomil per acre, the residues ranged from <1.0 ppm (Md) to 9.2 ppm (N.C.).

o Lower, cured leaves - 12 week (THI).

The residues ranged from 3.0 ppm (Md) to 31 ppm N.C.) at an application rate of 3.0 lb Ridomil per acre.

With applications of 6.0 lb of Ridomil per acre, residues of Ridomil per se ranged from 4.6 ppm (Md.) to 68 ppm (N.C.)

B. Burley Tobacco:

The much lower residues are due to the common practice of compositing the upper, middle, and lower leaves of Burley.

o Uncured, composited leaves - 109 days (THI)

With application at the maximum rate, 6.0 lb Ridomil acre, the residues were <1.0 ppm

o Cured, composited leaves- 109 day, (THI)

Residues were 6.3 ppm following applications at a rate of ca 6.0 lb Ridomil per acre.

Pyrolysis Products

The applicant's data indicates both the distillation and pyrolysis (6.6%) of Ridomil tobacco metabolites into smoke as a result of the smoking process. Since 2,6-DMA (3.8%) and one organic component A (ca 2.8%) were not found as components of the cured tobacco, but were smoke components, these two components are definitely pyrolysis products. Three 2D-TLC organic components (D_1, D_2, and E; ca 5.3%) present in the cured tobacco and also in the smoke are probably distillation components.

Unlabelled (14C) pyrolysis products were not determined; the possibility of such components is indicated by the relatively large amount of 14C-carbon dioxide (ca 27%) in the smoke.

Edward B. Brittin
TS-769:EBBRITTIN:mer:Rm 108:WSME:X62610:5/8/79