JUNE 15 1979

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

375AA

DATE: June 15, 1979

SUBJECT: Ridomil-2EG Request for EUP and temporary tolerance at 0.05 ppm on potatoes to control potato late blight.

FROM: William Woodrow, Ph.D
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WSW

TO: Mr. Henry Jacoby
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THRU: Dr. Adrian Gross, Chief
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8/3/79

Registration No.
100-EUP-1
8G2121

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Chemistry Branch Considerations

Memo of 3/29/79 from G.P. Makhijani recommends for establishment of the requested temporary tolerance.

Recommendations

1. The requested EUP and temporary tolerance can be toxicologically supported. Data previously reviewed and currently submitted are summarized below:

A. Previously reviewed by W. Woodrow Nov. 8, 1978., Ridomil-2EG for control of tobacco black shank.

formulation, containing [redacted] (See explantation below)

a. Acute Oral LD50, rats INERT INGREDIENT INFORMATION IS NOT INCLUDED
male = 2341.9 mg/kg
female = 1520.4 mg/kg
Tox. Category III
Classification - Core-Minimum Data

b. Acute Dermal, Rabbits = 3571.5 mg/kg
Tox. Category III
Classification - Core-Minimum Data

c. Primary Eye Irritation, rabbits
Corneal opacity and conjunctival irritation persisting through 7 days.
Tox. Category I
Classification - Core-Guidelines data

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d. Primary Skin Irritation Score = 0.5
Tox. Category IV
Classification - Core-Guidelines Data

technical chemical

Teratology study, rat - not teratogenic
Classification - Core-Minimum Data

B. Studies reviewed in present report formulation, Without [redacted]

[redacted]

INERT INGREDIENT INFORMATION IS NOT INCLUDED

a. Acute Inhalation Study, rats
LC50 not determined
Classification - Supplemental Data

b. Acute Intraperitioneal LD50, rats
I.P. LD50 - 312 mg/kg
Classification - Core-Guidelines Data

technical chemical

a. Acute Oral LD50, rats = 669 mg/kg
Toxicity Category III
Classification - Core-Guidelines Data

b. Acute Dermal LD50, rabbits = >6000 mg/kg
Toxicity Category III
Classification - Core-Minimum Data

c. Acute Dermal LD50, rats = >3170 mg/kg
Toxicity Category III
Classification - Core-Minimum Data

d. Skin Irritation, rabbits
Primary Skin Irritation Index
= 0.1/8 animals; mild skin irritant.
Toxicity Category IV
Classification - Core-Guidelines Data

e. Primary Eye Irritation, rabbits
Corneal involvement, completely clearing 3 days post-treatment.
Toxicity Category II
Classification - Core-Guidelines Data

f. Skin Sensitization, guinea pigs
negative; no skin sensitizer potential
Classification - Core-Minimum Data

g. Three-Month Dietary Study, rats
NOEL = 250 ppm
Classification - Core-Guidelines Data

h. 91-Day Dietary Study, dogs
NOEL = 250 ppm
Classification - Core-Minimum Data

i. Salmonella/mammalian microsome
mutagenicity study - not mutagenic
Classification - Core-Guidelines Data

j. Mouse Dominant Lethal Mutagenic Study - not mutagenic
Classification - Core-Minimum Data

*Significance of acute toxicity data from studies using formulation containing [redacted] INERT INGREDIENT INFORMATION IS NOT INCLUDED

Ciba-Geigy submitted separate requests for EUP's and temporary tolerance for Ridomil-2E to control tobacco black shank and potato plate blight, respectively, based on a formulation containing [redacted] which is presently on the Pre-RPAR review compound list.

On January 9, 1978, Ciba-Geigy submitted a change of formulation for Ridomil-2EG which eliminated [redacted] and certain of the inert compounds; however, the amount of active ingredients for the two formulations remained almost identical.

It is the opinion of this reviewer that the acute studies on Ridomil-2E containing [redacted] will reflect approximately the same acute toxicity profiles as the new Ridomil-2EG formulation without ehtylene dichloride, therefore a request for additional acute toxicity studies using the new formulation will not be necessary.

2. Prior to establishing a permanent tolerance for use of Ridomil-2EG on potatoes, additional required information shall include, but not be limited to:

a. A chronic feeding study in the rat.

b. Oncogenic studies in the rat and the mouse.

c. A 2-generation reproduction study in the rat.

d. A metabolism study in the rat.

e. A teratology study in a second mammalian species.

3. No prior or pending tolerances.

4. The ADI is based on the three month rat feeding study with a NOEL of 250 ppm (12.5 mg/kg/day). This study employed optimum dosing levels and numbers of animals. The 90 day Beagle study used < than a MTD and < than desirable numbers of animals/dose level. A 2000 fold safety factor is used to calculate the human ADI:

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$$ADI = NOEL \times \frac{1}{2000} = 12.5 \text{ mg/kg/day} \times \frac{1}{2000}$$

The MPI for a 60 kg person is 0.38 mg/kg

5. All actions on Ridomil-2E utilize 1.09% of the ADI (computer printout is attached).

Review of Data

The Company proposes the establishment of a temporary tolerance for the fungicide N-(2,6-dimethylphenyl)-N(methoxyacetyl)-alanine methyl ester, CGA-48988 (trade name Ridomil-2EG) in or on r.a.c. potatoes at 0.05 ppm.

CGA-48988 (Ridomil-2EG) is a new pesticide.

The proposed experimental program will use a total of 772 gallons (1543 lb. a.i.) of CGA-48988 to treat 1340 acres in 25 states over a period of 2 years (1979 & 1980).

1. Ridomil-2EG formulation

Active Ingredient	% by weight
CGA-48988 technical, (90% a.i.)	27.9
Inert Ingredients	
[redacted]	
	100.0

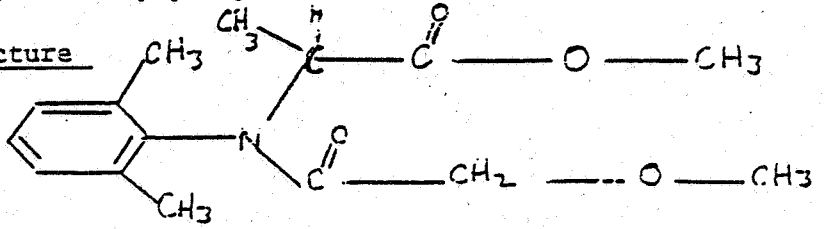
INERT INGREDIENT INFORMATION IS NOT INCLUDED

2. Substance Identification

Chemical Name (CGA-48988 technical)

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

Structure



Purity of technical material

Component	% by weight
N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-alanine methyl ester	90.0%
Other Ingredients:	10.0%

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INERT INGREDIENT INFORMATION IS NOT INCLUDED

[redacted]

3. Other physical/chemical data:

a. Density 1.21 g/cm^2 @ 20°C

b. Color/physical state white to beige, crystalline state

c. Vapor pressure 2.2 X 10^{-6} Torr. @ 20°C

d. Solubility
Water 0.7%
Methanol 65%
Benzene 55%
Hexane 0.9%
Isopropanol 27%
Methylene Chloride 75%

4. Referenced petitions

No referenced petitions; a new chemical.

5. Toxicology Studies - EPA Acc. No. 234429, 2344281, 097382

A. Submitted studies previously reviewed. See toxicology review by W. Woodrow, dated Nov. 8, 1978.

Acute Studies (formulation contained ethylene dichloride)

1. Acute Oral LD50, rats = 1889.5 mg/kg
95% C.L. 1427.8 - 2500.4 mg/kg
Tox. Category III

2. Acute Dermal LD50, rabbit = 3,571.5 mg/kg
95% C.L. = 1,518.1 - 8,402.6 mg/kg
Tox. Cateogry III

3. Primary Eye Irritation study , rabbit
   Corneal opacity, conjunctival irritation persisting through day 7.
   Tox. Category I

4. Primary Skin Irritation, rabbit
   Primary Skin Irritation Score = 0.5/8
   Tox. Category IV

Teratology study in the rat (technical chemical)

Technical chemical was found not teratogenic.

B. Submitted studies reviewed in present report (when used, formulation did not contain [redacted]).

1. Acute Inhalation study rats. Performed by Hazelton Labs. Amercia. Submitted by Ciba-Geigy. June 23, 1978 - Project No. 483-152. EPA Acc. No. 234429.

   6 male & 6 female rats exposed to one concentration of 3.38 mg/L for 4 hours. Analytical concentration of formulation was 6.35 ug/L air. Animals observed for mortality, toxic signs, abnormal behavior 14 days.

   Results - 80% particles from nebulizer 5 u. No mortality, no clinical signs. All M & F rats gained weight during 14 days. "Untreat control animal pathology reports were not available for comparison with test animal reports."

   Classification - Supplemental Data

   a. No untreated control animals for comparison. It is doubtful if an accurate inhalation toxicity study using the product is possible; it is a crystalline solid with V.P. of 2.2 X 10^{-6}.

   b. Only one dose level used.

   c. Active ingredient dose level too low, no mortality (may he non-toxic by respiratory route in an acute test).

2. Acute Intraperitoneal LD50, rats. Performed by Ciba-Geigy, Basle, Switzerland, June 28, 1976. Project No. Siss 5388. EPA Acc. No. 234429.

   Results - 5 male & 5 female rats/dose level injected I.P. with formulation, observed 14 days.

mg/kg	dead/live
100	0/10
215	0/10
278	3/7
359	7/3
464	10/0

No substance related gross organ changes seen. Survivors recovered within 10-12 days.

I.P. LD50 = 312 mg/kg. 95% C.L. = 282 - 345 mg/kg

Classification - Core-Guidelines Data

3. Acute Oral LD50, technical chemical in rats: Performed by Ciba-Geigy Basle, Switerland, June 28, 1976. Project#Siss 5388. EPA Acc.#234428.

5 male & 5 female rats/dose treated with technical chemical suspended in 2% carboxymethylcellulose, observed 14 days.

mg/kg	dead/live
215	0/10
464	3/7
775	7/3
1000	7/3
1200	8/2
2150	10/0

Results - Acute Oral LD50 rats = 669 mg/kg
95% C.L. = 515 - 868 mg/kg
Toxicity Category III

Classification - Core-Guidelines Data

4. Acute Dermal LD50 technical chemical rabbits. Performed by Ciba-Geigy Basle, Switerland, March 10, 1978. Project#408-378 Siss 6547. EPA Acc.#234428.

Administered as 50% Solution in poly-ethylene glycol and saline. 2 groups of 3 male and 3 female rabbits. Treatment sites occluded 24 hrs., animals observed 14 days.

Results

mg/kg	dead/live
1000	0/6
6000	0/6

Acute dermal LD50 technical in rabbits > 6000 mg/kg. No toxic symptoms, slight erythema after uncovering sites in 6000 mg/kg group.

Toxicity Category III

Classification - Core-Minimum Data

Only 3 animals/sex/dose level, only 2 dose levels, test material diluted 1/2.

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5. Acute Dermal LD50 technical chemical, rats. Performed by Ciba-Geigy Basle, Switerland, July 22, 1976. Project#Siss 5388. EPA Acc.#234428.

Technical chemical suspended with 2% carboxy methyl cellulose. 3 male and 3 female rats/dose level treated under occluded sites 24 hrs., observed 14 days.

Results

mg/kg	dead/live
2150	0/6
3170	0/6

Acute dermal LD50 technical techmical in rats = > 3170 mg/kg. No signs or toxic symptoms, no local skin irritation seen.

Toxicity Category III

Classification - Core-Minimum Data

Only two dose levels, more animals/sex/dose levels should have been used.

6. Skin Irritation, rabbits. Performed by Ciba-Geigy, Basle, Switerland, May 13, 1976. Project#Siss 5388. EPA Acc.#234428.

0.5 g technical chemical placed under occluded intact and abraded skin sites, each of 3 male and 3 female rabbits for 24 hours. Skin irritation scored through 72 hours.

Results

Primary skin irritation index = 0.1/8; a mild skin irritant.

Toxicity Category IV

Classification - Core-Guidelines Data

7. Primary Eye Irritation technical chemical, rabbits. Performed by Ciba-Geigy, Basle, Switerland, May 13, 1976. Project#Siss 5388. EPA Acc. No. 234428.

100 mg technical chemical placed in conjunctival sac, left eyes, 3 male and 3 female rabbits.

Results

No effect on eyes of female rabbits. Corneal involvement in 3 male rabbits tested, complete clearing 3 days post-treatment.

Primary eye irritation index technical chemical = 9.5/110 - a mild eye irritant.

Toxicity Category II

Classification - Core-Guidelines Data

8. Skin Sensitization technical chemical in guinea pigs. Performed by Ciba-Geigy, Basle, Switerland, Spet. 13, 1976. Project#Siss 5388. EPA Acc. No. 234428.

10 male and 10 female guinea pigs treated with 0.1 ml of 0.17 suspension of vehicle alone, vehicle and Dinitrochlorobenzene (DNBC), or vehicle and technical chemical. I.C. = every other day, 10 injections. Animals challenged 14 days post last injection.

Results

Treatment	Reactions	P
DNCB	20/20	0.001
polyethylene glycol and saline	1/20	0.01
technical chemical	7/20	0.02

P of 0.01 considered significant difference. Results considered negative; no skin sensitizing potential in guinea pigs.

Classification - Core-Minimum Data

Dosage employed was excessively low; 0.1 ml of a 0.1% suspension.

9. Three-Month Dietary Study technical chemical in rats. Performed by Geigy Pharmaceuticals, Toxicology Dept., Winslow, Cheshire, England. EPA Acc.#234428.

180 rats - 2 groups of 25 male and 25 female each, and 2 groups of 20 male and 20 female each.

Group	Diet Dosages
1	untreated control
2	50 ppm
3	250 ppm
4	1250 ppm

Test material was 99% technical chemical. Blood and urine samples taken at 5, 9, 13, and 17 weeks. Clinical symptoms - daily, body wts. - weekly, opthalmic examination on 10 male and 10 female from group 1 and 4 during weeks of 5, 9, and 13; Recovery animals during week 17. Terminal studies; autopsies, % organ/brain wt., or body wt. Histopathological examinations made:

(continue on next page)

A. Body weight gain summary

Males	Weeks (gram)		
Group	0	6	13
1	176	405	523
2	174	421	534
3	174	426	549
4	172	401	507

Females	Weeks (grams)		
Group	0	6	13
1	147	255	300
2	145	258	303
3	147	265	310
4	144	254	297

Females showed lower wt. gain than males, however, no real discrepancies occurred within treatment groups.

B. Food Consumption

A slight decline in food consumption by male rats occurred in animals treated with highest does (1250 ppm). Food conversion in male rats treated with highest dose (g/food/kg b. wt.) was unchanged from control animals, reflecting food intake reduction.

C. Hematology

Hematology values for the 3 treatment groups almost identical to controls, and were considered unaffected ater 5, 9, and 13 weeks of treatment.

D. Clinical Chemistry

Clinical chemistry exhibited by treated animals remained normal.

E. Urine Analysis

No differences were noted between control and treated animals for specific gravity, protein content, on phosphates.

F. Autopsy Findings

All treatments groups showed a slight increase in absolute or relative liver weights at a p of < 0.05. All other organs normal.

G. Organ Weights

a. Organ weights as % brain wts. Treatment group values did not differ from untreated control values.

b. Organ wt. as % body weights. These calculations did not reveal differences between treatment groups and untreated controls.

H. Histopathology

20 M & 20 F rats were examined for each of groups 1 & 4.

Results

Minimal cellular hypertrophy in parenchymal cells observed in 5 female rats receiving highest dosage. 5 female rats contained ovarian cysts. The hypertrophy in parenchymals cell was considered "work hypertrophy"; cause of the cysts was unknown. No other changes attributed to treatment observed. NOEL = 250 ppm

Classification - Core-Guidelines Data

10. 90-Day Dietary Study in beagle dogs. Performed by Hazelton Labs., Europe, LTD. Submitted by Ciba-Geigy. Report#653/380/4, Jan. 1977. Technical chemical. EPA Acc.#234428.

Technical chemical administered to 3 M & 3 F dogs/each of 2 groups; 50 or 250 ppm. Two additional groups of 4 M & 4 F each treated/group with 1250 ppm, or served as untreated controls.

3 M & 3 F dogs from 1250 ppm groups, or control sacrificed at end of treatment period. 1 remaining M and 1 female from these groups further observed for one month without treatment.

Results

No mortality, no changes in animal behavior. Serum alkaline phosphatase slightly increased in high dose animals; 1 M and 1 F at 4, 8, and 12 weeks. 1 additional F slight increase in serum alkaline phosphatase. Values normal in recovery animals at week 16. NEL = 250 ppm.

Macroscopic findings were not treatment related. Organ wts. no dose related trends in organ wts., organ wt./body wt. ratios, or organ wt./brain wt. ratios.

Microscopic findings - No dose related necropsy or microscopic findings. Blood chemistry, hematology, and urine analysis indicated no treatment related findings. Opthalmoscopy examinations did not reveal treatment related findings.

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Classification - Supplementary Data

"Only 3 animals/sex used, < than a MTD employed."

11. Salmonella/mammlian microsome mutagenicty study - technical chemical. Performed by Ciba-Geigy, Basle, Switerland, March 14, 1978. Expt. No. 78-2514. EPA Acc.#234428.

25, 75, 225, 675, or 2025 ug/0.1 ml of the technical test chemical dissolved in DMSO was tested with and without mammalian microscomal activation, using 4 Salmonella typhimunium histidine auxotrophic isolates in a mutagenicity test to detect point mutations. Controls consisted of:

1. DMSO negative control
2. Positive controls:

strain TA1535 - 3 & 5 ug/0.1 ml of phosphate buffer of N-methyl-N^1-nitro-N-nitrosoguanidine.

strain TA1537 - 9 (5) aminoacridine hydrochloride monohydrate.

strain TA-98 - 2.5, 5 & 10 ug/0.1 ml of daunoblastin.

strain TA-100 - 0.125 and 0.25 ug/0.1 ml of nitroquinoline-N-oxide.

The activation mixture consisted of rat liver microsomes plus co-factors.

Results

A doubling of plate colonies of the 4 different Salmonella strains to histidine prototrophy was evidence of mutagenic induction.

No significant differences in numbers of histidine prototrophs were found in experiments with and without microsomal activation between tests with the technical test chemical and the negative control.

Classification - Core-Guidelines Data

12. Mouse dominant lethal mutagenicity study - technical chemical.

The study was designed to evaluate cytotoxic or mutagenic effects on male germinal cells.

Single doses of 65 or 195 mg/kg were administered to groups of 20 male mice/group; carboxy methyl cellulose (CMC) served as a vehicle. Each treated male was placed in cage with 2 different untreated females during each of 8 consecutive weeks, to span spermatozoon development period.

Females were autopsied on the 14th day of pregnancy. The no. of live embryos, embryonic deaths, and uteri without visible implantations were noted. The total numbers of implantation sites indicating pre-implantation losses in test and control dams were compared, using a Student's t test.

Total numbers of mated and pregnant dams or embryonic deaths were compared using the X^2 test. Numbers of implantations and embryonic deaths were also compared with spontaneous or naturally data from untreated controls.

Results

The data on mating ratios, the number of implantations, and embryonic deaths were comparable for all groups. No adverse toxicity was seen in treated males; howver, one male treated with 195 mg/kg died. No evidence of test chemical mutagenicity was observed.

Classification - Core-Minimum Data

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