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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: November 27, 1978

SUBJECT: Request for EUP and temporary tolerance for Ridomil 2E used as systemic fungicide to control potato late blight. EPA Acc. No. 234 429, 2344281 097382.

FROM: W. Woodrow, Ph.D (1476)
Toxicology Branch/HED

TO: Dr. E. Wilson
Product Manager#21

BEST DOCUMENT AVAILABLE

Registration No.:

100-EUP-1 [redacted]

Ciba-Geigy Corp.
Agricultural Division
P.O. Box 11422
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Conclusions: **INERT INGREDIENT INFORMATION IS NOT INCLUDED**

1. [redacted]

2. Toxicology Branch position regarding proposed Ridomil 2E EUP and temporary tolerance for potatoes:

   a. If an EUP is granted for Ridomil 2E containing [redacted] a request for destruction of all treated crops should be made.

   b. If [redacted] contained in Ridomil 2E is satisfactorily resolved, or if [redacted] is delected from the Ridomil 2E formulation, an EUP could be granted without a request for crop destruction.

3. Prior to establishing a permanent tolerance for use of Ridomil 2E as a systemic fungicide on potatoes, additional required information shall include, but not be limited to:

   a. Chronic feeding studies in the rat.

   b. An oncogenic study in two species.

   c. A reproduction study.

   d. A metabolism study.

   e. A chronic toxicity study.

4. The ADI has not been exceeded by the proposed temporary tolerance; determined from subacute rat feeding studies and the MRC:

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a. MTRC of 0.0053 mg/day, does not exceed the MPI of 0.378 mg/day.

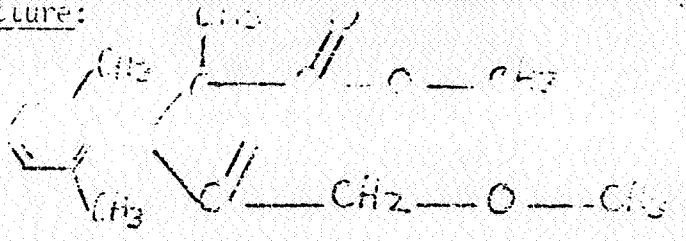
b. The MTRC on/kg basis: 0.0053 = 0.000088 mg/kg/day is less than the ADI of 0.0062 mg/kg/day.

Substance Identification

1. Chemical Name

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

2. Structure:



3. Purity of technical material

Component	% by weight
N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-alanine methyl ester	90.0%
[illegible] Impurities:	10.0%

[redacted]

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

4. 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%

Referenced petitions

No references petitions; a new chemical.

Formulation

1. Active ingredient

N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-alanine methyl ester 27.89

2. Inert ingredients - clearances

[redacted]

Uses proposed

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Foliar applications of Ridomil 2E are intended to control potato late blight and foliar blight.

Late blight - ½ to 1½ pts. Ridomil 2E/acre when plants are 6" high. Repeat 14 day intervals throughout season.

Early and late blight - Ridomil 2E mixed with other fungicides. Ridomil 2E at ¼ to ½ pt. mixed with label rates of Bravo 6E, Difolatan 4F, Dithane M-45, or Mangate 200. 7-10 day interval treatments.

Toxicology Studies

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

Acute Studies

1. Acute oral LD_{50}, rats = 1889.5 mg/kg.
   95% C.L. 1427.8-2500.4 mg/kg.
   Tox. Category III

2. Acute dermal LD_{50}, rabbit = 3,571.5 mg/kg.
   95% C.L. = 1,518.1 - 8,402.6 mg/kg.
   Tox. Category III

3. Primary eye irritation study, rabbits.
   Corneal opacity, conjunctival irritation persisting through day 7.
   Tox. Category [illegible] ← Woodrow, [illegible] ← Tox. Category III

4. Primary skin irritation, rabbit.
   Primary skin irritation score = 0.5/8
   Tox. Category IV

Teratology Study - Acceptable (technical chemical)

B. Submitted studies reviewed in present report:

1. Acute inhalation study, rats. Performed by Hazelton Labs. America. 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 µg/L air. Animals observed for mortality, toxic signs, abnormal behavior 14 days.

Results - 80% particles from nebulizer 5 µ. No mortality, no clinical signs. All M & F rats gained wt. during 14 days. Gross pathology findings [illegible] comparison.

Classification - Supplemental Data

a. No untreated control animals for comparison. It is doubtful if an accurate inhalation toxicity study using the product is possible;

(continue from last page)

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 be non-toxic by respiratory route in an acute test).

2. Acute intraperitoneal LD_{50}, rats. Performed by Ciba-Geigy, Basle, Switerland, June 28, 1976. Project No. Siss 5388. EPA Acc. No. 234428.

Results

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

mg/kg	dead/live
100	0/10
215	0/10
278	3/7
359	7/3
4..	10/0

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

I.P. LD_{50} = 312 mg/kg. 95% C.L. = 282-345 mg/kg.

Classification: Core Guidelines Data

3. Acute oral LD_{50}, technical chemical in rats:

Performed by Ciba-Geigy, Basle, Switerland, June 28, 1976. Project No. Siss 5388. EPA Acc. No. 234428.

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

mg/kg	dead/live
..	0/10
	3/7
464	7/3
775	7/3
1000	8/2
12.0	10/0
21.0	

Results

Acute oral LD_{50} rats = 669 mg/kg.
95% C.L. = 515-868 mg/kg.
Toxicity Category III
Classification - Core Guidelines Data

4. Acute dermal LD_{50} technical chemical, rabbits

[illegible], Basle, Switzerland, March 10, 1978. Project No. 408-378 Siss 6547. EPA Acc. No. 234428.

Results

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.

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

Acute dermal LD_{50} 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 ½.

5. Acute dermal LD_{50} technical chemical, rats.

Performed by Ciba-Geigy, Basle, Switerland, July 22, 1976. Project No. Siss 5388. EPA Acc. No. 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 LD_{50} technical chemical in rats = >3170 mg/kg. No signs or toxic

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 No. Siss 5388. EPA No. [illegible]

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 [illegible] 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 No. Siss 5388. EPA [illegible] No. [illegible].

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 III Tox Category III (corrected, 3-8-78)

Classification: Core Guidelines Data

8. Skin sensitization technical chemical in guinea pigs.

Performed by Ciba-Geigy, Basle Switerland, Sept. 13, 1976. Project No. Siss [illegible]

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

Results

Treatement	Reactions	P
DNCB	20/20	0.001
polvethylene gl[illegible] 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. No. 234428.

100 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:

A. Body wt. & brain studies

males	Weeks		
Group	0	6	13
1	[illegible]	[illegible]	[illegible]

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females	Weeks		
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 dose (1250 ppm). Food conversion in males 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 after 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 treatment 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 wts. These calculations did not reveal differences.

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 [illegible] cysts. The hypertrophy in parenchymal cells was considered "work hypertrophy"; cause of the cysts was unknown. No other changes attributed to treatment observed.

[illegible]

[illegible]

Performed by Hazelton Labs., Europe, LTD. submitted by Ciba-Geigy. Report No. 653/380/4, Jan., 1977. Technical chemical. EPA Acc. No. 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.

3M & 3 F dogs from 1250 ppm groups, or controls sacrificed at end of treatment [illegible] for one month without treatment.

Results

No moriality, no changes in animals behavior. Serum alkaline phosphatase slightly increased in high dose animals; 1 M & 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.

Classification: Core Minimum Data

11. Salmonella/mammalian microsome mutagenicity study - technical chemical

Performed by Ciba-Geigy, Basle, Switerland, March 14, 1978. Expt. No. [illegible], EPA Acc. No. [illegible]

25, 75, 225, 675, or 2025 µg/0.1 ml of the technical test chemical dissolved [illegible] was tested with and without mammalian microsomal activation, using 4 Salmonella typhimurium 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 µg/0.1 ml of phosphate buffer of N-methyl-N'-nitro-N-nitrosoguanidine.

Strain TA1537 - 9 (5) aminoacridine hydrochloride monohydrate.

[illegible] - 2.5, and 10 µg/0.1 ml of [illegible].

[illegible] - 0.125 and 0.25 µg/0.1 ml of nitrosodimethylamine.

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 [illegible].

Classification: Core-Guidelines Data

12. Mouse dominant lethal mutagenicity study

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

Single doses of 65 or 195 mg/kg were adminsitered 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.

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; however, one male treated with 195 mg/kg died. No evidence of test chemical mutagenicity was observed.

Classification: Core Minimum Data

No rationale was presented for highest dose used; should have used at least an MTD for the highest dose.

Evaluation of ADI

1. No prior, or pending tolerances.

2. ADI - The proposed temporary tolerance is 0.05 ppm on potatoes.

   A NEL of 250 ppm was determined in 90 day rat and 90 day Beagle feeding studies.

   The ADI is calculated from the rat data submitted. This study employed optimum dosing levels and numbers of animals, whereas the Beagle 90 day study ulitized < than an MTD high dose and < than desirable numbers of animals/dose level.

   1 ppm in rat food = 0.05 mg/kg/day

   $\frac{1}{.05} \sim \frac{250}{x}$ = 12.5 mg/kg/day of pesticide.

   Use a 2000 fold safety factor for temp. tol.

   $\frac{12.5 \text{ mg/kg/day}}{2000}$ = ADI of 0.0062 mg/kg/day

3. MPI = 0.0062 X 60 kg = 0.378 mg/day

4. MTRC 7% of diet attributed to potatoes.

   1 ppm in total daily diet ~ to 1 mg of residue in each kg of diet.

   proposed tol. is 0.05 ppm

   1 ppm ~ .05

   x = .05 mg/kg of diet

Therefore .07 X 1.5 kg X .05 mg/kg diet = 0.005 mg/day in diet = MTRC

Comparison:

ADI = 0.0062 mg/kg/day acceptable daily intake.

MPI = 0.378 mg/day maximum permissable intake.

MTRC = 0.0053 mg/day in diet for proposed tol. of 0.05 ppm.

The MTRC (0.0053 mg/day) is less than the MPI of 0.378 mg/day max intake.

The MTRC on a /kg basis = $\frac{0.0053 \text{ mg/day}}{60 \text{ kg}}$ = 0.000088 mg/kg/day,

is less than the ADI of 0.0062 mg/kg/day

Therefore, the 0.05 ppm proposed temporary tolerance is acceptable.

TOX/HED:th:GWhitmore:11-22-78