(3-16-92)

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 100-TGT
Tilt Gel Fungicide

FROM: William S. Woodrow (WSW 1-13-92
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C)
E 3/16/92

TO: S. Lewis / Sidney Jackson (PM 21)
Fungicide - Herbicide Branch
Registration Division (H75-05C)

APPLICANT: Ciba-Geigy Corp.
Agricultural Division
P. O. Box 18300
Greensboro, NC 27419-8300

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Propiconazole: 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-H-1,2,4-triazole	41.8
Inert Ingredient(s):	58.2
Total	100.0%

BACKGROUND

Ciba-Geigy submitted acute oral, acute dermal, acute inhalation, primary eye and skin irritation, and dermal sensitization studies to support registration of Tilt Gel Fungicide (EPA Reg. No. 100-TGT). MRID NOS. used were 421170-03 through 421170-08.

RECOMMENDATION

The acute toxicity studies submitted by Ciba-Geigy are acceptable. All studies were classified Guideline Data.

LABELING

1) The WARNING signal word is appropriate.
2) The Precautionary Statements are acceptable.
3) Under Statements of Practical Treatment, add "Get medical attention" to the "If inhaled:" statement. (IF NOT BREATHING, GIVE ARTIFICIAL RESPIRATION, PREFERABLY MOUTH-TO-MOUTH.) E
5) Current acute toxicity profile for Tilt Gel Fungicide (EPA Reg. NO. 100 TGT):

4) DELETE THE PHRASE "IF IRRITATION PERSISTS" FROM THE IF ON SKIN STATEMENT OF PRACTICAL TREATMENT. E

Tilt Gel accepted acute toxicity studies continued:

Study		Classification	Tox. Category
acute oral LD_{50}	2745 (1912-3940) mg/kg	Guideline	III
acute dermal LD_{50}	> 2020 mg/kg	Guideline	III
acute inhalation LC_{50}	0.733 mg/L	Guideline	III
eye irritation	Opacity thru 7 days	Guideline	II
skin irritation	P.I. Index 2.6	Guideline	IV
dermal sensitization	neta sensitizer	Guideline	—

5) No additional acute toxicity studies are required.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§81-1)

Product Manager: (21) 7-18-91 Reviewer: ~~M. Waller~~ Woodrow
MRID No.: 421170-03 Report Date: 1-9-92
Testing Facility: Stillmeadow, Inc. Report No. 8201-91
Author(s): J. O. Kuhn
Species: Rat, HSD (SD)
Age: young adult Observation Days (Post Exposure): (14); other ( )
Weight: M 216-276, F 180-213g
Source: Harlan Sprague Dawley, Houston Density 1.0 ~~gm~~ g/ml
Test Material: CGA-64250 41.3% (GEL A FL-910993 Batch 491-23, liquid
Quality Assurance (40 CFR §160.12): yes (Q.A. + G.L.P.)

Conclusion:

1. LD_{50} (mg/kg): Males = 3565 (2408-5278) mg/kg ; Females = 1852.6 (1272.7-2696.1) mg/kg ; Combined = 2745 (1812.5-3940.0) mg/kg
2. The estimated LD_{50} is
3. Tox. Category: III. Classification: Guideline

Procedure (~~Deviations From §81-1~~): Animals guaranteed prior to test. 5M x 5F/each of 3 dose levels + 5M for one additional dose level - all fasted at least 16 hrs prior to test. Dosing by oral intubation. Animals observed for mortality and signs of pharmacotoxicity 3 x day first week + 1 time daily to 14 Days.

Results:

Reported Mortality

DOSAGE (Mg/kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
750 mg/kg	0/5	0/5	0/10
2000 mg/kg	0/5	3/5	3/10
3500 mg/kg	—	3/5	3/10
5050 mg/kg	4/5	5/5	9/10

~~Symptomology & Gross Necropsy Findings:~~

Gross necropsies conducted on all animals. Bodyweights recorded days 0, 7 & 14.

Clinical: in life - activity decrease, ataxia, bradypnea, gasping, lacrimation, nasal discharge, piloerection, polyuria.

Necropsy: discolored anal discharge, diarrhea, lacrimation, nasal discharge, polyuria, salivation, liver discoloration (several). Dead → Diarrhea, lacrimation, nasal discharge, polyuria, salivation, discoloration of G.I. tract, G.T. Tract distended 2 gas.

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DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager: (21) 7-11-91
MRID No.: 412170-01
Testing Laboratory: Stillmeadow, Inc.
Author(s): V. O. Kuhn
Species: Rabbit, NZ White
Sex: 5M & 5F
Test Material: CGA-64250-41.3GR GEL A PL 910493
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Reviewer:- ~~M. Waller~~ Woodrow
Report Date: 1-9-92
Report No. 82-02-91

Wt.: M: 2.425-2.475 F: 2.175-2.925

Summary:

1. LD_{50} (mg/kg): Males = ; Females = ; Combined = ;
2. The estimated LD_{50} is > 2020 mg/kg
3. Tox. Category: III. Classification: Guideline

Procedure (~~Deviations From §81-2~~): Animals quarantined prior to test. Day prior to treatment, dorsal area of rabbits clipped free of hair to approx. approx. 10% of body surface. 10x10 cm gauze applied to dorsal trunk & secured. Trunk then wrapped

Results: = some pasmalle dressing & secured = Tape. 14 test

Reported Mortality

DOSAGE (mg/kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
2020 mg/kg	0/5	0/5	0/10

~~Symptomology & Gross Necropsy Findings~~:

~~wrapped~~ then introduced under wrapping by means of a syringe and spread evenly over exposure area. Tape resealed. 24 hrs exposure. Test sites rinsed, wiped. Observations for mortality/toxic signs made at ½, 1, 2, 3, 6 hrs and at 1 x daily to 14 days. Body weights recorded days 0, 7 & 14. Gross necropsies conducted on each animal.

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Results

No animals died.

Clinical: In life observations included decreased defecation and diarrhea.

Necropsy: Signs of diarrhea, desiccation of stomach contents, G.I. tract distended with gas.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (21) 9-3-91 Reviewer: W. Woodrow
MRID No.: 421170-05 Report Date: 1-9-92
Testing Laboratory: Stillmeadow, Inc. Report No. 8203-91
Author(s): M.S. Albert
Species: Rat, HSD (SD)
Sex: 10M+10F Weight: M 229-320, F 215-249g
Source: Harlan Sprague Dawley, Houston
Test Material: CGA-64250 418 GEL-A FL-910993 Batch 471-23
Quality Assurance (40 CFR §160.12): yes (G.A. & G.L.P.)

Summary:

1. LC_{50} (mg/kg): Males = ____; Females = ____; Combined = ____
2. The estimated LC_{50} is > 0.733 mg/mL
3. Mean Concentration: ____
4. Tox. Category: III. Classification: Guideline

Procedure (~~Deviations From §81-2~~): Animals were quarantined prior to testing. 6M & 5F/each of two dose levels were exposed to test material for 4 hours. Observations for mortality and or toxic signs frequently day of exposure,

Results:

Exposure Concentration (mg/L)	Reported Mortality (NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
0.2482 mg/L	0/5	0/5	0/10
0.733 mg/L	0/5	0/5	0/10

~~Symptomology & Gross Necropsy Findings:~~

and at least once daily thereafter for 14 days. Body weights recorded days 0, 7 & 14. A gross necropsy was performed on all animals.
The aerosol at the higher dose level was generated by pumping test material into pressure

Tox. Cat. III :→ 0.5 thru 5 mg/liter

operated operated Spraying Systems Co. air atomizer (¼ JSS) and then passing through a baffling chamber. Aerosol generated at the lower dose level generated by a pressure operated Spraying System Co air atomizer (¼ JSS) which aspirated the test material directly from its reservoir & then distributing resulting aerosol through baffling chamber. At both dose level(s) aerosol was diluted with dried and filtered air. Chamber concentrations determined analytically once/hour (samples collected from animal breathing zone. Analytical measurements made using Tracor Model 560 gas chromatograph.

Particle size determined 2 x during each exposure (samples collected from breathing zone), using an Andersen Cascade Impactor, at 28.3 L/min. for 3-10 min. MMAD calculated.

Results:

1) Chamber Concentration (average of 8 samples each dose)

high dose: 0.733 mg/L Nominal 42.9 mg/L
(analytical)

low dose: 0.2482 mg/L Nominal 35.9 mg/L
(analytical)

NOTE approximately a 3 fold difference in dosage levels (analytical)

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Results (Cont.)

2) Particle Size Distribution

Low dose

1 hr sample: μ

stage	size range	% in size range	Cum. % size range
4	2.1–3.3	17.68	20.49
5	1.1–2.1	12.08	8.40
6	0.7–1.1	2.27	6.12
7	0.4–0.7	0.35	5.77

MMAD 3.318μ, GSD = 2.469

2 hr sample

4	2.1–3.3	17.56	21.55
5	1.1–2.1	12.57	8.98
6	0.7–1.1	3.19	5.78
7	0.4–0.7	0.97	4.79

High Dose MMAD 3.245 μ, GSD 2.386

1 1/4 hr sample

4	2.1–3.3	28.47	38.26
5	1.1–2.1	35.30	2.96
6	0.7–1.1	0.45	2.50
7	0.4–0.7	0.91	1.59

3 1/4 hr sample MMAD 2.532 μ, GSD = 1.835

4	2.1–3.3	21.17	42.41
5	1.1–2.1	39.44	2.96
6	0.7–1.1	0.85	2.11
7	0.4–0.7	0.52	1.58

MMAD 2.502 μ, GSD = 1.516

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Clinical symptoms: On life observation included activity decrease, corneal opacity, nasal discharge, palpebration, polyuria, ptosis, respiratory ganglia and salivation.

Gross necropsy: No gross abnormalities.

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager: (21) 3-15-91 Reviewer: Woodrow
MRID No.: 421170-06 Report Date: 1-13-92
Testing Laboratory: Stillmeadow, Inc. Report No. 7820-91
Author(s): J. O. Kulin
Species: Rabbit, NZ White
Sex: 3M & 6F Weight: not given
Source: Ray Nichols Rabbitry, TX
Dosage: 0.1 ml
Test Material: CGA-61250 GEL-RKP FL-910065, liquid
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Summary:

Tox. Category: II Classification: Guideline

Procedure (~~Deviation From §81-4~~): Animals acclimated at least one week. Both eyes each animal examined 24 hrs prior to test, using 0.2% fluorescein (for defects). 0.1 ml (undiluted) placed in conjunctival sac right eye each animal. Lids held

Results: Together 1 sec. Three eyes washed, remainder unwashed. Treated eyes examined & scored for irritation (Draize),

Observations (number "positive"/number tested)

Unwashed eyes only (6 eyes)	Hour	Days								
	1	1	2	3	4	7	10 ~~14~~	14 ~~21~~	17	21
Cornea Opacity →	0/6	6/6 1	6/6 1	6/6 1	6/6 1	3/6 1	1/6 1	1/6 1	1/6 1	0/6
Iris	2/6 1	2/6 1	1/6 1	1/6 1	1/6 1	0/6	0/6	0/6	0/6	0/6
Conjunctivae Redness	6/6 V	6/6 V	6/6 V	6/6 V	6/6 V	6/6 1	3/6 1	1/6 1	1/6 1	1/6 1
Chemosis	6/6	6/6	6/6	5/6 1	3/6 1	0/6	0/6	0/6	0/6	0/6
Discharge	6/6 V	6/6 V	6/6 V	6/6 V	6/6 V	1/6 1	1/6 1	1/6 1	1/6 1	0/6

~~Comments~~: at 1, 24, 48, 72 hrs, and at 4, 7, 10, 14, 17 and 21 days post treatment. Corneal involvement absent by 21 days, conjunctival redness persisting through 21 days (1/6 animals); however, according to the guidelines, 1 redness is not to be considered a positive effect.

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DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager: (21) 7-9-91
MRID No.: 422170-07
Testing Laboratory: Stillmeadow, Inc.
Author(s): V.O. Kuhn
Species: Rabbit,
Age: 3 to 6 months
Sex: 3M + 3F
Weight: not given
Dosage:
Test Material: CGA-64260 41-3 GEL-A, PL-910993, liquid
Quality Assurance (40 CFR §160.12): yes (G.A. + G.L.P.)

Reviewer: ~~M. Waller~~ (contractor)
Report Date: 1-13-92
Report No.: 8204-91

Summary:

The Primary Irritation Index = 2.6

Toxicity Category: IV

Classification: Guideline

Procedure (~~Deviations From §81-5~~): Animals acclimated at least 1 week prior to test. Day before Test, dorsal areas clipped free of hair (8x8 cm) = 1 intact site. Each site (6 animals) treated with 0.5 ml undiluted test material "by introducing beneath gauze patch - 2.5x2.5 cm." Patches secured with tape. Entire trunks ~~Results:~~ wrapped with semi-occlusive material, secured w tape. Exit hour after exposure. (Wrappings, patches removed, sites wiped, scored for erythema/edema @ 1/4, 24, 48, 72 hours) and days 7, 10, 14, 17 and 21 Draize system.

Results: Primary Irritation Scores; 6 rabbits =

P.I (overall)	2.75
1 day	13.00
= 2.6	3.00
	3.25
	2.25
	1.25

Special Comments:

Draize scoring system - 0.5 1-3.0 scoring "Mildly irritating"

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DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager: (21) 8-1-91 | Reviewer: Woodrow
MRID No.: 421170-08 | Report Date: 1-13-92
Testing Laboratory: Stillmeadow | Report No: 8205-91
Author(s): J. O. Kuhlen
Species: Guinea Pig, Hartley
Sex: (2 M & 2 F | Weight: M 325-370, F 295-365 g
Source: Harlan Sprague Dawley, Houston, TX
Test Material: CGA-64250 41.8% GEL-A FL-910993 Batch 471-23, liquid
Positive Control Material: 1-chloro, 2-4 dinitrobenzene (DNBC)
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Method: Modified Buehler

Summary:
1. This product is / (is not) a dermal sensitizer.
2. Classification: Guideline

Procedure (~~Deviation From §81-6~~): Animals acclimated at least 5 days. A pre-test screening test to determine a maximum, non-irritating concentration to use for the main study. Four animals used for this purpose, 2 males and 2 females - 5, 20, 50, and 100% test material was screened. 0.5ml doses were applied - 2 concentrations per animal. Doses covered with patches, animals wrapped with polyethylene film - 6 hour exposure. Based on this range finding study

~~Results~~: Induction:

Based on the range finding study, 50% test material v/v solution in 95% ethanol was used for induction. 20.0% V/V solution in 95% ethanol used to challenge animals. 5M & 5F animals (Group 1) remained untreated until challenge. 5M & 5F were treated once weekly to total three inducting treatments, using 0.5ml of 50% v/v solution of test material in 95% ethanol. Induced animals treated by introducing test material beneath 3.8 x 5cm patch gauze pad secured with tape (known as a Coverlet adhesive dressing (left front quadrant). Entire trunks of animals

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wrapped with clear poly ethylene film secured with tape. (24 hrs prior to Treatment, dorsal area of each animal clipped free of hair). Following Treatment each animal placed in a restrainer for 6 hours. Wrappings, patches removed. Animals evaluated weekly, using same test sites. Two weeks following last induction application, animals challenged in same manner as before, on the right rear quadrant using 20% v/v solution of T.M. in 95% ETOH. Observations for skin reactions made @ 24 hours post patch removal. Also, observations for skin reactions made approx. 48 hrs following patch removal, after induction Treatments 1 and 3, and after the challenge. SM & SP challenged simultaneously with the induced animals (challenge only for the naive animals). Application and scoring procedures same (Naive animals also challenged with the 20% preparation).

Results

Recalled from tester's report:

treatment	Day	Group	test site	Virgin test site (challenge)
initial	1	naive control	NA	NA
challenge	29	naive control	NA	0.0
initial	1	Test	0.2	NA.
challenge	29	Test	NA	00.

NA = not applicable

Unquote —

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Discussion of tabular information presented above:

1) Note that the naive animals challenged (only) with 20% test material exhibited 0.00 scoring.

2) For the test animals, the 0.2 represents the average induction score - induced & 50% test mat.

3) Note that the induced test site - was not challenged.

4) The naive test site on the induced animals exhibited no sensitization, scoring was 0.00

Conclusion: The test material did not sensitize guinea pigs.

Positive Controls: 5M #5F induced 3x at weekly intervals (in same manner as test animals), and challenged two weeks following final induction. 5M #5F naive control animals challenged only. (0.6% W/V in 95% EtOH). DNBC. The test portion of materials and methods states "DNCB tested periodically to confirm sensitivity of guinea pigs."

Tox Chem. No. | File Last Updated | Current date

323EE Propiconazole | | 1-13-92

Study/Species/Lab/Study# Date	Material	MRID No.	Results	Tox. Cat.	Core Grade
acute oral LD_{50}, Rat stillmeadow, inc. #8201-91 7-18-91	Propiconazole Tilt Gel Fungicide	421170 -03	LD_{50} = 2745 (1912-3940) mg/kg	III	Guideline
acute dermal LD_{50}, Rabbit stillmeadow, inc. # 8202-91 7-11-91	"	421170 -04	LD_{50} > 2020 mg/kg	III	Guideline
acute inhalation LC_{50}, Rat stillmeadow, inc. # 8203-91	"	421170 -05	LC_{50} > 0.733 mg/L	III	Guideline
eye irritation, Rabbit stillmeadow, inc. # 7820-91 3-15-91	"	421170 -06	1/6 rabbits 1.0 @ 21 days (1.0 not considered positive	II	Guideline
skin irritation, Rabbit stillmeadow, inc. # 8204-91 7-9-91	"	421170 -07	P.I. Index 2.6 0.51-3.0 = Tox. IV	IV	Guideline
dermal sensitization, guinea pigs stillmeadow, inc. # 8205-91 8-1-91	"	421170 -08	Not a dermal sensitizer	-	Guideline

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