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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

5-23-90

215B

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

50534-114 Tuffcide 960
50534-7 Technical Chlorothalonil

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 50534-24 Technical DACONIL 2787
50534-157 Bravo 90DG, 50534-195 Daconil 2787 WDG

FROM: William S. Woodrow WSW 5-18-90
Precautionary Review Section
Registration Support Branch
Registration Division (H7505C)

E 5/23/90

TO: Lewis/Stone (PM 21)
Fungicides-Herbicides Branch
Registration Division (H7505C)

APPLICANT: Fermenta Plant Protection Co.
5966 Heisley Rd.
P.O. Box 8000
Mentor, OH 44061-8000

50534-114
50534-7 50534-195
50534-24 50534-157

FORMULATION FROM LABEL:

	% by wt.	
Active Ingredient(s):		
Chlorothalonil (tetrachloroisophthalonitrile)	96.0	90.0
Inert Ingredient(s):	4.0	10.0
Total	100.0%	

1 F 5

BACKGROUND

The Fermenta ASC Corp. requested precautionary labeling changes and/or the addition of label use claims for the following chlorothalonil products; whose Confidential Statements of Formula are similar enough to utilize a single set of supporting acute toxicity data:

EPA 50534-114 Tuffcide 960

Chlorothalonil	96.0 %
Inerts	4.0 %

50534-7 Technical Chlorothalonil

Chlorothalonil	96.0 %
Inerts	4.0 %

50534-24 Technical Daconil 2787

Chlorothalonil	96.0 %
Inerts	4.0 %

50534-157 Bravo 90DG

Chlorothalonil	90.0 %
Inerts	10.0 %

50534-195 Daconil 2787 WDG

Chlorothalonil	90.0 %
Inerts	10.0 %

RECOMMENDATIONS

1) Precautionary labeling change requests:

a. Request to delete "may be a potential skin sensitizer", under Precautionary Statements for: 50534-114 Tuffcide 960;
50534-7 Technical Chlorothalonil, and;
50534-24 Technical Daconil 2787

RSB/PRS recommendation: This request is justified. Dermal Sensitization study conducted using Technical chlorothalonil (MRID 144112, Lab.# 7020, 4-15-82) indicated a non-sensitizer.

b. Fermenta Corp. is justified in removing all statements from the following labels referring to "chlorothalonil... or this product may produce temporary allergic side effects....", or "Note to Physicians: Persons having an allergic reaction respond to treatment with antihistimines...."
50534-114 Tuffcide 960;
50534-7 Technical Chlorothalonil;
50534-24 Technical Daconil 2787;
50534-157 Bravo 90 DG, and;
50534-195 Daconil 2787 WDG

c. Fermenta Corp. request to add:
"Note to Physician: Persons having temporary irritation symptoms may respond to treatment with antihistimines or steroid creams and/or systemic steriods" is acceptable to RSB/PRS.
NOTE TO PM: The Fermenta "Note To Physician is acceptable Provided "may" is inserted into the phraseology suggested by Fermenta.

The "Note to User: This product may produce mild bronchial irritation and temporary irritation of the skin characterized by redness or rash on exposed skin areas. Affected persons should call a physician", proposed by Fermenta is also acceptable to RSB/PRS, for the following product labels:

50534-114
50534-7
50534-24
50534-157
50534-105

2) The Fermenta Corp. requests permission to add "Prevents fungal growth on caulks, non-food grade sealants and adhesives", to the 50534-114 Tuffcide 960 product label.

The Fermenta Corp. request to add caulks, non-food grade sealants and adhesives to the 50534-114. Tuffcide 960 label is acceptable to RSB/PRS; a complete acute toxicity profile for 50534-114, as well as for the products listed below:

50534-114
50534-7
50534-24
50534-157
50534-195

The toxicity profile for the products listed above consists of:

Acute oral study (Bravo 50534-157, 90.0% A.I.) ACC. NO. 253856, May 16, 1983
Tox. Category IV Core Guidelines

Acute Dermal Study, using 90.0% Bravo 90DG.
Acc. No. 253856, May 16, 1983.
Tox. Category IV Core Guidelines.

Acute Inhalation study, using Technical Chlorothalonil.
MRID NO. 00094942. This study listed as acceptabl in Chlorothalonil Reg. Standard (no additional inhalation data needed). Tox. Category or Core Grade not given in Reg. Standard.

Eye Irritation study, using Bravo 90DG (90.0% A.I.)
Jan. 15, 1980.
Toxicity Category I Core minimum.

Dermal irritation study, using Bravo 90DG (90.0% A.I.), May 16, 1983.
Acc. NO. 253856
Tox. Category IV Core Guidelines

Dermal sensitization study, using Technical Chlorothalonil (97.0% A.I.)
MRID NO. 144112, 4-15-82.
Not a contact sensitizer Core Guidelines

LABELING : 50534-114, 50534-7, 50534-24, 50534-157, 50534-195

1) The DANGER signal word is appropriate.
2) The Precautionary Statements are acceptable
3) The Statement of Practical Treatment is acceptable.
4) Deletion of the "may be a potential skin sensitizer" from the 50534-114 Tuffade 960, 50534-24 Technical Dacomil 2787, and 50534-7 Technical Chlorothalonil labels is acceptable.
5) Deletion of statements regarding temporary allergic side effects, and Note to Physician as indicated on sample labels provided by the registrant is acceptable. The deletion of "Note to User" under Directions For Use is acceptable.
6) The addition of a Note to Physician, as indicated on sample labels, is acceptable provided the word "may" is inserted between the words ... symptom and respond ...
7) The addition of a "Note to User:", as shown on the Sample labels is acceptable.

?

8) The label deletions and additions shown under 5, 6, and 7) above concern products: 50534-114 Tuffside 960
50534-? Technical Chlorothalonil
50534-24 Technical Daconil 2787
50534-157 Bravo 90 DG, and
50534-195 Daconil 2787 WDG

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

Product Manager: (21)
MRID No.: 144112
Testing Laboratory: Food & Drug Res. Labs., Inc.
Author(s): N.H. Wilson, M.R. Gallo
Species: guinea pig, Hartley
Sex: ____ Weight: 300-500g
Source: Charles River Labs., MA
Test Material: Technical Chlorothalonil (TC)
Positive Control Material: dinitrochlorobenzene (DNCB)
Quality Assurance (40 CFR §160.12): adequate

Reviewer: ~~M. Walker~~ Woodrow
Report Date: 5-10-90
Report No. FDRL # 7020

Method: Open epicutaneous

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

Procedure (~~Deviation From §81-6~~): A preliminary dose range (irritation) study was conducted, c TC diluted in physiological saline. 5 clipped, 2cm, areas on backs of 8 G. pigs were treated c 100% TC (.2g) moistened c saline, .2ml of 30%, 10%, 3%, and ~~Results~~: 1% dil. of TC. in saline - all contained on 2cm sq. Gauze patches. Patches occluded c Blenderm tape & bandage - 24hr contact. 100% T.C. - moistened slightly c saline used for main study.

Induction:

Group	Treatment	Dose	10 animals
A	TC	0.2g (100%)+	10
B	DNCB (control)	0.2ml (0.07%)**	10
C	Phys-saline (vehicle control)	0.2ml	10

* Moistened slightly c saline
** 80% ETOH for induction; acetone for challenge

0.2g or 0.2ml on 2cm sq. Gauze patches applied to clipped dorsal areas and covered (as described above). 24 hour contact. Repeated 3x weekly to 10 applications - left scapular. Skin scoring (according to Draize) @ 24 & 48 hrs post dose. - 14 day rest following last

induction application.

Challenge:
Each animal received 0.2g or 0.2ml of appropriate material on gauze patches applied to clipped left flank area. In addition, TCA+control groups received 0.2g or 0.2ml to right flank areas; all patches secured + occluded as described above. Challenge sites were scored at 1, 24 & 48 hrs after removal of patches.

Results:
1) Technical chloroethalonil - Some irritation was evident (0.3 - 0.7 scores) during induction #5 through #8 only. All challenge scores were 0.00.
2) DNCB - +control - The average (8 animals and 10 applications @ 24 hours) = 0.86; for induction + the DNCB 24 hour challenge reading = 1.8; thus DNCB did sensitize S.P.
3) The animals treated with phys. saline alone (vehicle control) - induction and challenge scores were 0.00.

Conclusion: Technical chloroethalonil diluted in phys. saline, or powder suspended in saline did not sensitize guinea pigs.

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

Product Manager: (21) Reviewer: ~~M. Waller~~ Woodrow
MRID No.: 405460-01 Report Date: 5-6-92
Testing Laboratory: Univ of Texas, Dept of Dermatol Report No. 1094-Sc-0034-TX-001
Author(s): N.H. Wilson, J.C. Killeen
Species: Guinea Pigs, Hartley
Sex: M & F Weight: 350g
Source: Hazleton Dutchland, Denver, PA
Test Material: Technical Chlorothalonil
Positive Control Material: none mentioned
Quality Assurance (40 CFR §160.12): adequate
2 maximization studies;
Method: 1 - open Epicutaneous study
Summary: ① No +control test. ② acetone for main study - +results/ should have included TC dissolved in saline in main study
1. This product (is) / is not a dermal sensitizer.
2. Classification: Core minimum (see one liners)

Procedure ~~(Deviation From §81-6)~~: Three preliminary irritation studies were conducted using rabbits: saline (0.1% w/v chlorothalonil/saline), petrolatum, and acetone). 2nd irritation study, 0.001, 0.01 and, 0.1% (V/V) chlorothalonil in acetone Tested - 14 different dermal

~~Results~~: applications. During the 3rd irritation study, gross observation for edema and erythema & histopathologic skin changes were followed

Induction:

Three separate guinea sensitization studies were conducted; 2 - Maximization studies, & 1 - open epicutaneous study.

The procedures and results of the three sensitization studies are shown on the next 3 pages.

Quoted from the testers report:

First sensitization evaluation of Chlorothalonil:
Quoted from the Tox's report:

STUDY DESIGN FOR THE SENSITIZATION TESTING IN THE FIRST GUINEA PIG MAXIMIZATION STUDY WITH TECHNICAL CHLOROTHALONIL (TC)

	Material Administered		
	Test Group	Control Group	Dose
Induction Phase			
Day 0	5M+5F	5M+5F	
- six i.d. injections per animal:	0.5% (v/v) TC in acetone	acetone	0.1 ml/site x 2 sites
	+	+	+
	0.5% (v/v) TC in acetone/FCA (50:50)	acetone/FCA (50:50)	0.1 ml/site x 2 sites
	+	+	+
	acetone/FCA (50:50)	acetone/FCA (50:50)	0.1 ml/site x 2 sites
Day 7			
- one topical application per animal:	1.0% (w/v) TC in acetone	acetone	0.1 ml/site x 1 site
Challenge Phase			
Day 21			
- two topical applications per animal:	0.001% (w/v) TC in acetone	0.001% (w/v) TC in acetone	0.05 ml/site x 1 site
	+	+	+
	acetone	acetone	0.05 ml/site x 1 site
Rechallenge Phase			
Day 30			
- two topical applications per animal:	0.001% (w/v) TC in acetone	0.001% (w/v) TC in acetone	0.075 ml/site x 1 site
	+	+	+
	acetone	acetone	0.075 ml/site x 1 site

FCA - Freund's Complete Adjuvant unquote:)

RESULTS

1) Control Group 0 0 0 @ 24 & 48 hours

2) Test (0.075ml 0.001% solution Chlorothalonil in acetone
1-animal eliciting 2-3 erythema @ 24 hrs; 0.00 @ 48 hours.

NOTE: Inconclusive results.

Second G.P. Maximization Study - Protocol quotes from tester's depot:

STUDY DESIGN FOR THE SENSITIZATION TESTING IN THE SECOND GUINEA PIG MAXIMIZATION STUDY WITH TECHNICAL CHLOROTHALONIL (TC)

	Material Administered		
	Test Group	**Control Group**	**Dose**
Induction Phase	5M+5F	5M+5F	
Day 0			
- six i.d. injections per animal:	5.0% (v/v) TC in propylene glycol	propylene glycol	0.1 ml/site x 2 sites
	↓ 5.0% (v/v) TC in propylene glycol/ FCA (50:50)	↓ propylene glycol/ FCA (50:50)	↓ 0.1 ml/site x 2 sites
	↓ propylene glycol/ FCA (50:50)	↓ propylene glycol/ FCA (50:50)	↓ 0.1 ml/site x 2 sites
Day 7			
- one topical application per animal:	1.0% (v/v) TC in acetone	acetone	0.15 ml/site x 1 site
Challenge Phase			
Day 21			
- two topical applications per animal:	0.0125% (v/v) TC in acetone	0.0125% (v/v) TC in acetone	0.075 ml/site x 1 site
	↓ acetone	↓ acetone	↓ 0.075 ml/site x 1 site

FCA - Freund's Complete Adjuvant

Unquote:

RESULTS

1) Acetone vehicle alone: mean score = 0.00 (induction)

2) mean scores (10 animals)

	Test		Control	
	24	48	24	48
mean scores =	1.25	1.05	0.40	0.55

Conclusion: Chlorothalonil dissolved in acetone did sensitize guinea pigs

Open Epicutaneous sensitization study using Technical Chlorothalonil. The test protocol below is quoted from the tester's report:

STUDY DESIGN FOR THE OPEN EPICUTANEOUS STUDY WITH TECHNICAL CHLOROTHALONIL (TC)

Group	Number of Guinea Pigs/Sex	Irritancy Testing[a]	Sensitization Testing	
			Induction[b]	Challenge[c]
Control	4m+4F	[d]	acetone	0.0075, 0.025, 0.075, 0.25, 0.75, 1.25% TC in acetone (v/v)
Low Dose	4	0.0075, 0.025, 0.075 0.25, 0.75, 1.25% TC in acetone (v/v)	0.01% TC in acetone (v/v)	0.000075, 0.00025, 0.00075, 0.0025, 0.0075, 0.025% TC in acetone (v/v)
Mid-Dose	4	0.0075, 0.025, 0.075 0.25, 0.75, 1.25% TC in acetone (v/v)	0.1% TC in acetone (v/v)	0.000075, 0.00025, 0.00075, 0.0025, 0.0075, 0.025% TC in acetone (v/v)
High-Dose	4	0.0075, 0.025, 0.075 0.25, 0.75, 1.25% TC in acetone (v/v)	1.0% TC in acetone (v/v)	0.000075, 0.00025, 0.00075, 0.0025, 0.0075, 0.025% TC in acetone (v/v)

[a] One application using a dose volume of 0.025 ml/site and a second application, 24 hours later, using a dose volume of 0.05 ml/site.

[b] Twenty applications using a dose volume of 0.1 ml/site, administered on weekdays during a four-week period.

[c] One application using a dose volume of 0.05 ml/site administered during the fifth week of the study.

[d] Animals in this group were not exposed to chlorothalonil during the irritancy testing.

Unquote

RESULTS: Acute Contact:

Tech — mean scores

chlorothalonil challenge	1.25%	0.75%	0.25%	0.075%	0.025%	0.0075%
24 hrs →	0.43	0.06	1.5	0.18	0	0
48 hrs →	0.75	0.62	0.31	0.18	0	0

Results - Open Epicutaneous Sensitization study, using Technical Chlorothalonil

Mean values: Challenge Scores

5M+5F induced (@ 24hrs) Tech Chlorothalonil (TC)

		TC challenge 0.025%	0.0075%	0.0025%	0.00075%	0.00025%	0.000075%
	induced 1.0% TC	1.5	0.31	0.25	0.0	0.0	0.0
24hrs	" 0.1% TC	1.5	0.68	0.12	0.0	0.0	0.0
	" 0.01% TC	0.56	0.31	0.0	0.0	0.0	0.0
	induced 1.0% TC	1.80	0.0	0.0	0.0	0.0	0.0
48hrs	" 0.1% TC	1.68	0.35	0.18	0.0	0.0	0.0
	" 0.01% TC	0.85	0.35	0.0	0.0	0.0	0.0
	induced 1.0% TC	0.5	0.0	0.0	0.0	0.0	0.0
72hrs	" 0.1% TC	1.0	0.25	0.0	0.0	0.0	0.0
	" 0.01% TC	0.5	0.25	0.0	0.0	0.0	0.0

Conclusions:

1) A Technical Chlorothalonil (in acetone) conc. as low as 0.01% did induce sensitization in G.P. (topically); elicited by T.C. in acetone conc. as low as 0.0025%.

2) A preliminary irritation study using rabbits showed that "significant irritation was observed when the vehicle was acetone, less irritation when petrolatum was used and virtually no irritation was observed when phys. saline was used as the vehicle."

3) Would the tester not use physiological saline for the main sensitization study??? (Core minimum).