5/10/90

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

50534-114 Tuffcide 960
50534-7 Technical Chlorothaloni.

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 50534-19
50534-24 50534-157

FORMULATION FROM LABEL:

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

1

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 antihistimes 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
50534-195

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

5

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

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

Eye Irritation study, using Bravo 90DG (90.0% A.
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
Chlorothaloni (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 indicate 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 Tuffide 960
50534-? Technical Chlorothaloni l
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)
Reviewer: Woodrow ~~M. Waller~~
MRID No.: 144112
Report Date: 5-10-90
Testing Laboratory: Food & Drug Res. Labs., Inc.
Report No. FDRL # 7070
Author(s): N.H. Wilson, M.A. 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

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, w TC diluted in physiological saline. 5 clipped, 2cm, areas on backs of 8 g. pigs were treated w 100% TC (.2g) moistened w saline, ~2ml of 30%, 10%, 3%, and ~~Results~~: 1% dil. of TC. in saline - all contained on 2cm sq. Gauze pads. Pads occluded w Blenderm tape & bandage - 24hr contact. 100% T.C. - moistened slightly w saline used for main study.

Induction:

Group	Treatment	Dose	NO 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 w saline
** 80% ETOH for induction; acetone for challenge

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

9

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 chlorothalonil - 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 chlorothalonil diluted in phys. saline, or powder moistened w 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: 5-9-90
Testing Laboratory: U. of Texas, Dept. of Dermatol. Report No. 1094-86-0034-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
Method: 2 maximization studies; 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: (see 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 applications. During the 3rd irritation study, gross observation for edema and erythema & histopathologic skin changes were followed.

~~Results~~: Induction:

Three separate G.P. 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 tester'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% (v/v) TC in acetone	acetone	0.1 ml/site x 1 site
Challenge Phase			
Day 21			
- two topical applications per animal:	0.001% (v/v) TC in acetone	0.001% (v/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% (v/v) TC in acetone	0.001% (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) Control Group 0.00 @ 24 & 48 hours

2) Test (0.075ml 0.001% solution Chlorothalonil in acetone
1-animal exhibited 2-0 erythema @ 24hrs; 0.00 @ 48 hours.

NOTE: Inconclusive results.

12

Second G.P. Maximization Study - Protocol quoted from tester's report:

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 dose: 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

13

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[a] Testing	Sensitization Testing	
			Induction[b]	Challenge[c]
Control	4 M + 4 F	NA[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: Acetone Control:

Tech chlorothalonil challenge	mean scores 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 (@ 24 hrs) Tech Chlorothalonil (TC)

	TC challenge	0.025%	0.0075%	0.0025%	0.00075%	0.00025%	0.00008%
	induced 1.0% TC	1.5	0.31	0.25	0.0	0.0	0.0
24 hrs	" 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
48 hrs	" 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
72 hrs	" 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 evidence 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).

Tox Chem No. 215 B Chlorothalonil File Last Updated _____ Current Date 5-11-90

udy/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX. Cat.	CORE Grade/ Doc. No.
Dermal sensitization, guinea pig. FDRL # 7020 4-15-82	97% Technical chlorothalonil	144112-	Technical Chlorothalonil did not sensitize g.pigs.	-	guidelines
Dermal sensitization guinea pig. U. of texas Dept of Dermatology #1044-86-0034-TX-001 1-6-88	Technical chlorothalonil	405-460-01	t. chlorothalonil did weakly sensitize g.p.'s only when dissolved in acetone. (A preliminary study showed "significant irritation" when t.c. dissolved in acetone, but no irritation when dissolved in saline. tester used acetone t.c. dilution for main study) - should have used saline.	-	minimum

9/16

RIN 8587-93 EPA Reg II 50537-7

Page_____ is not included in this copy.

Pages 17 through 37 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

__✓__ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Tox Chem No. 215B Chlorothalonil File Last Updated _____ Current Date 5-11-90

udy/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, IC_{50}, PIS, NOEL, LEL	TOX. Cat.	GDRE Grade/ Doc. No.
skin irritation) Rabbit Bio/Dynamics #4503-77	Bravo 500	8T308	P.I. Index = 1.3 72 hr AV. irritation score = 0.42	IV	Guide-lines
Dermal sensitization, g.p. pigs. # FDRL # 7020 4-15-82	Technical chlorothalonil 97% A.I.	144112	T.C. did not sensitize guinea pigs.	—	guide-lines
Dermal sensitization, guinea pigs # SDS-2787 6-27-86	Bravo 720 54% A.I.	405460-02	Modified Buehler closed-patch-repeated insult challenge: Bravo 720 0.66, 24 hrs control 0.38; rechallenge 0.54, 0.17; did sensitize g.p. (very weak)	—	guide-lines
Dermal sensitization) guinea pigs. U. of Texas, Dept. of Dermatology # 1094-86-0034-TX-001 1-6-88	Technical chlorothalonil	405460-01	T.C. did sensitize g.p.; when dissolved in acetone (Preliminary study showed: # significant irritation when T.C. dissolved in acetone & Virtually no irritation when dissolved in phys. saline?) did not main study use	—	Cote minimum

Tox Chem No. 215 B Chlorothalonil File Last Updated _____ Current Date 5-11-90

udy/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX. Cat.	CORR Grade/ Doc. No.
Acute eye irritation, Monkey. Bio/Dynamics # 6436-80. 4-17-81	Bravo 500	87177	Corneal opacity through day 14, absent day 21. Irritation absent day 14	II	guidelines
Acute eye irritation). Rabbit. Bio/dynamics # 6504-80. 4-17-81	Bravo 500	87177	No iris involvement. Corneal involvement absent by day 4, Conjunctival irritation absent by day 7.	III	guide-lines
Acute eye irritation, Rabbit. Bio/Dynamics # 4513-77. 9-19-77	"	87178.	No iris involvement, Corneal involvement absent by day 7 - present at day 3.	III	guide-lines
Acute eye irritation) Rabbit. Wil Res Labs. # Wil-11006. 1-30-86	Bravo 720	158493	Corneal involvement absent by day 4. Irritation present through day 10, absent by day 21.	II	guidelines

29

Tox Chem No. 215B Chlorothalonil File Last Updated _____ Current Date May 11 1990

udy/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX. Cat.	CORE Grade/ Doc. No.
acute oral LD_{50}, Rat. Bio/Dynamics # 4501-77 10-19-77	Bravo 500	87306	LD_{50} 4.2 g/kg (2.9-6.1) g/kg	III	guidelines
Acute dermal LD_{50}, Rabbit. SDS Biotech. # SDS-2787. 2-7-86	Bravo 720	158494	LD_{50} > 2000 mg/kg	III	guidelines
Acute dermal LD_{50}, Rabbit. Bio/Dynamics. # 4502-77. 10-24-77	Bravo 500	87307	LD_{50} > 20.0 g/kg.	IV	guidelines
Acute inhalation LC_{50}, Rat. Bio/Dynamics # 77-1946. 12-6-1977	Bravo 500	87310	LC_{50} > 1.072 mg/L : No particle size distribution, No mmaD, GSD. Accuracy of cloud conc. questionable. Respirable particle fraction could estimate	—	Supplementary