



5/10/90

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 50534-114 Tuffcide 960
50534-7 Technical Chlorthaloni.
50534-24 Technical Daconi/278
50534-157 Bravo 90DG, 50534-195 Daconi/2787 WDG

FROM: William S. Woodrow LSW 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 Weisley Rd.
P.O. Box 8000
Mentor, OH 44061-8000

FORMULATION FROM LABEL:

Active Ingredient(s):		% by wt.
<u>Chlorthaloni (tetrachloroisophthalonitrile)</u>	<u>96.0</u>	<u>90.0</u>
<u>Inert Ingredient(s):</u>	<u>4.0</u>	<u>10.0</u>
Total	100.0%	

1

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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 Tuffide 960

Chlorothalonil 96.0%

Inerts 4.0%

50534-7 Technical Chlorothalonil

Chlorothalonil 96.0%

Inerts 4.0%

50534-24 Technical Dacnil 2787

Chlorothalonil 96.0%

Inerts 4.0%

50534-157 Bravo 90DG

Chlorothalonil 90.0%

Inerts 10.0%

50534-195 Dacnil 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 Tuttlede 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 antihistamines....".

50534-114 Tuttlede 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 antihistamines or steroid creams and/or systemic steroids" 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 (Bravo⁹⁰⁰⁹ 50534-157, 90.0% A.I.)

ACC. NO. 253856, May 16, 1983

Tox. Category IV

Cerc. Guidelines

Acute Dermal Study, using 90.0% Bravo 90 DG.

Acc. NO. 253856, May 16, 1983.

Tox. Category IV

Cote Guidelines:

Acute Inhalation study, using Technical Chlorothalonil

MRID NO. 00094942. This study listed as

acceptable in Chlorothalonil Reg. Standard (no

additional inhalation data needed). Tox. Category

or Cote Grade not given in Reg. Standard.

Eye Irritation study, using Bravo 90 DG (90.0% A.I.)

Jan. 15, 1980.

Toxicity Category I

Cote minimum -

Dermal Irritation study, using Bravo 90 DG

(90.0% A.I.), May 16, 1983.

Acc. NO. 253856

Tox. Category IV

Cote Guidelines

Dermal sensitization study, using Technical
Chlorothalonil (97.0% A.I.)

MRID NO. 144112, 4-15-82.

Not a contact sensitizer

Cote 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 Tuftade 960,
 50534-24 Technical Daconil 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.

7.

8) The label deletions and additions
shown under 5, 6, and 7) above concern
products: 50534-114 Tuffide 960
50534-7 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)

Reviewer: ~~M. Waller~~ ^{Woodward}

MRID No.: 144112

Report Date: 5-10-90

Testing Laboratory: Food & Drug Res. Labs., Inc.

Report No. FDRL 7020

Author(s): N.H.W. Ison, M.A. Gallo

Species: guinea pig, Hartley

Sex:

Weight: 300-500g

Source: Charles River Labs., MA

Test Material: Technical Chlorothalonil (TC)

Positive Control Material: dimethylchlorobenzene (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, & TC selected in physiological saline.

5 clipped, 2cm, areas on backs of 8 g. pigs were treated & 100% TC (.2g) mixed in saline, .2ml of 30%, 10%, 3%, and

Results: 1% dil. of TC in saline - all contained on 2cm sq. gauze patches. Patches occluded & Blendedown tape & bandage - 24hr contact. 100% TC - mixed slightly & 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

* Mixed slightly & 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). 24hr contact. Repeated 3x weekly to 10 applications - left scapular. All 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, T.C. & 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 chloroethanol - Some irritation was evident (0.3-0.7 scores) during induction #5 through #8 only. All challenge scores were 0.00.
- 2) DNCB-t-control - The average (8 animals and 10 applications @ 24 hours) = 0.86; for induction. The DNCB 24 hour challenge reading = 1.8; these DNCB did sensitivity g-p.
- 3) The animals treated with phys. saline alone (vehicle control) - induction and challenge scores were 0.00.

Conclusion: Technical chloroethanol diluted in phys. saline, or powder moistened saline did not sensitivity guinea pigs.

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

Product Manager: (21)

Reviewer: ^{Woodrow} M. Waller

MRID No.: 405460-01

Report Date: 5-9-90

Testing Laboratory: U. of Texas, Dept. of Dermatology

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

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: GTC minimum (see one liners) study

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 test - 14 different dermal

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

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 test'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
<u>Induction Phase</u>			
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
<u>Challenge Phase</u>			
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
<u>Rechallenge Phase</u>			
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 2-3 erythema @ 24 hrs; 0.00 @ 48 hours.

NOTE: inconclusive results.

Second G. P. Maximization Study - Protocol quoted from testator'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
<u>Induction Phase</u>			
Day 0	5m+5F	5m+5F	
- 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
<u>Challenge Phase</u>			
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	4m+4F Number of Guinea Pigs/Sex	Irritancy ^a Testing	Sensitization Testing	
			Induction ^b	Challenge ^c
Control	4 m+4F	NA	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)	0.01X 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)	0.1X 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)	1.0X TC in acetone (v/v)	0.000075, 0.00025, 0.00075, 0.0025, 0.0075, 0.025% TC in acetone (v/v)

^aOne 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.

^bTwenty applications using a dose volume of 0.1 ml/site, administered on weekdays during a four-week period.

^cOne application using a dose volume of 0.05 ml/site administered during the fifth week of the study.

^dAnimals in this group were not exposed to chlorothalonil during the irritancy testing.

Unquote

RESULTS: Acetone Controls:

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 Chlorothaloniol

Mean values: Challenge Scores
5m+5F induced (@ 24 hrs) Tech Chlorothaloniol (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
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 Chlorothaloniol (in acetone) conc. as low as 0.01% did induce sensitization in c.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 ~~was~~ 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) Why did the tester not use physiological saline for the main sensitization study??? (cote minimum).

Chem No. 215 B Chlorothalonil

File Last Updated

Current Date 5-11-90

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	TOX. CONC Grade/Cat, Doc. No.
Dermal sensitization, Guinea pig. FDR # 7020 4-15-82	97% Technical chlorothalonil	144112-	Technical Chlorothalonil did <u>not</u> sensitize G.pigs.	guide-lines
Dermal sensitization Guinea pig. U. of Texas Dept of Dermatology #1094-86-0034-TX-001 1-6-88	Technical Chlorothalonil	405-460-01	T. chlorothalonil <u>did</u> weakly sensitize G.P. only when dissolved in acetone. (A preliminary study showed "significant irritation" when T.C. dissolved in acetone, but <u>no</u> irritation when dissolved in saline. Tester used <u>acetone</u> T.C. dilution for main study) - should have used <u>saline</u> .	minimum

RIN 8587-93

EPA Reg II 50532-7

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. 215 B Chlorothalonil

File Last Updated _____

Current Date 5-11-90

Study/Lab/Study #/Date	Material	EPA Accession No.	LD50, LC50, PIS, NOEL, LEL	Results	TOX. CONC. Grade/Cat, Doc. No.
skin irritation, Rabbit Bio/Dynamics #4503-77	Bravo 500	87308	P.I. Induct = 1.3 72 hr AV. irritation score = 0.42	IV	Guide - lines
Dermal sensitization, guinea pigs # PDR # 7020 4-15-82	Technical chlorothalonil 97% A.I.	144112	T.C. did not react guinea pigs	-	Guide - lines
Dermal sensitization, guinea pigs # SDS- 2787 6-27-86	Bravo 720 54% A.I.	455460-02	Modified Buehler closed-patch - repeated in suit Bravo 720 24 hrs challenge 0.66 control 0.38 rechallenge 0.54 0.17 did sensitization (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.s.; 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

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Tox Chem No. 215 B Chlorothalonil

File Last Updated _____

Current Date 5-11-90

udy/Lab/Study #/Date	Material	EPA Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	TOX. CONC. Grade/ Cat, 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	11 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.	111 guidelines
Acute eye irritation, Rabbit. Bio/Dynamics # 4513-77. 9-19-77	111	87178	No iris involvement, Corneal involvement absent by day 7 - present at day 3.	111 guidelines
Acute eye irritation Rabbit. Wil Res Labs. # W11-11006. 1-30-86	Bravo 720	158493	Corneal involvement absent by day 4. Irritation present through day 10, absent by day 21.	11 guidelines

Tox Chem No. 215B Chlorthaloni

File Last Updated _____

Current Date May 11, 1990

udy/Lab/Study #/Date	Material	EPA Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	TOX. CONC. Grade/ Cat. Doc. No.
acute oral LD50, Rat. Bio/Dynamics # 4501-77 10-19-77	Bravo 500	87306	LD50 4.2 g/kg (2.9-6.1) g/kg	III guidelines
Acute dermal LD50, Rabbit. SDS Biotech. # SDS-2787. 2-7-86	Bravo 720	158494	LD50 > 2000 mg/kg	III guidelines
Acute dermal LD50, Rabbit. Bio/Dynamics. # 4502-77. 10-24-77	Bravo 500	87307	LD50 > 20.0 g/kg	IV guidelines
Acute inhalation LC50, Rat. Bio/Dynamics # 77-1946. 12-6-1977	Bravo 500	87310	LC50 > 1.072 mg/L - No particle size distribution, No mixed, GSD. Accuracy of cloud conc. questionable. Respirable particle fraction estimated	- Supplementary

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