6-4-90

215B

008953

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 50534-ROT
Tuffcide 500

FROM: Lucy D. Markarian 5/24/90
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C)

E 6/9/90

TO: Susan Lewis (PM 21)
Fungicide Herbicide
Registration Division (H75-05C)

APPLICANT: Fermenta ASC Corporation
5966 Heisley Road
P.O. Box 8000
Mentor, Ohio 44061-8000

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
96% Chlorothalonil	50
Inert Ingredient(s):	50
Total	100.0%

1-3

008953

BACKGROUND: Fermenta ASC has submitted six studies in support of Trifficide 500 for registration consisting of an oral, acute dermal, acute dermal irritation, acute eye irritation dermal sensitization Toxicity and a study evaluating the possibility of the aerosolization of the test product That would make an acute inhalation toxicity study feasable.

RECOMMENDATION:

1. The acute oral Toxicity, dermal Toxicity and eye irritancy studies are rated core guideline and accepted
2. The acute dermal irritation Test is acceptable but is rated core minimum, because The evaluation of the irritation does not fully follow the Draize scoring System as indicated.

   In calculating the primary irritation index the 48 hour readings were disregarded Therefore the index in the report is lower Than calculated by the reviewer.
3. The dermal sensitization test is classified as supplimental for The following reasons:

   a. The range finding studies on The results of which the core study was based did not accurately determine the minimum irritating levels for induction or the

maximum non-irritating levels for the challenge

b. The origin, weight, sex, or age of the animals that were used for the range finding studies is unknown. It is not certain that they were representative of the colony of animals used for the actual study.

c. The elicitation of high degree of irritation at the induction phase precluded the possibility of concluding decisively if the test material was truly a sensitizer

d. The scoring of the elicited irritation especially during induction did not follow Buehlers method as the protocal dictated. ~~This resulted in breaking of S.C.P regulations~~ E 6/1/95

e. The applications of Test material and the positive control were in different volumes. Buehler recommends that both test and control materials be of the same volume. Tuftcide 500 was applied in 0.3 ml aliquots while DNCB was applied in 0.4 ml aliquots

It is recommended that:

1. The applicant present new ~~chronic~~ Sensitization studies or explain the inconclusive results and less than perfect scoring of the skin irritation

2. Present an application for waiver for submission of inhalation toxicity support in behalf of Tuftcide 500 ~~WE SUBMITTED NEGATIVE STUDY~~ E 6/4/95

LABELING: The signal word is "Danger" based on the eye irritancy being in Catagory I

Precautionary Statement should read as at now

Corrosive - causes severe eye damage and skin irritation, harmful or fatal if swallowed or inhaled. Do not get in eyes or skin or on clothing. Wear goggles, face shield or safety glasses. Wash Thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse. May be skin Sensitizer.

Statements of practical treatment:

If in eyes flush with gentle stream of water for 15 minutes, call physician.

If swallowed - Drink a large quantity of milk, egg whites and gelatin solution, or if not available drink large quantities of water. Avoid alcohol. Induce vomiting by Touching back of Throat with finger. Do not induce vomiting or give anything by mouth to an unconscious person. Call physician

If on skin Wash with plenty of soap and water. Get medical attention

DUE TO EYE IRRITATION THIS PRODUCT HITS THE TRIGGER FOR RESTRICTED USE. PM TEAM SHOULD DECIDE IF THERE IS ALTERNATIVE LABELING LANGUAGE SUFFICIENT TO OFFSET THIS HAZARD AND NOT REQUIRE RESTRICTED USE CLASSIFICATION. ~~E~~ change

008953

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

Product Manager: (21)
MRID No.: 412060-11
Testing Facility: Ricerca Inc. Painesville, Ohio
Author(s): Steven K. Shultz, Nelson H. Wilson, James C. Killeen
Species: Rat, Sprague Dawley
Age: Not specified
Weight: ♂ 213-245g ♀ 219-240g
Source: Zivic Miller Laboratories, Inc., Allison Park, Pennsylvania
Test Material: Tuffcide 500, SDS-2787-0998-2101 Ricerca Code T-232-1
Quality Assurance (40 CFR §160.12): included

Reviewer: Lucy D. Markarian
Report Date: 5/24/90
Report No. 88-0051
Observation Days (Post Exposure): (14); other ( )

Conclusion:

1. LD_{50} (mg/kg): Males = 4740 mg/kg (*); Females = 4310 mg/kg (2460-6720) mg/kg; Combined = 4520 mg/kg (3230-5760) mg/kg
2. The estimated LD_{50} is
3. Tox. Category: III. Classification: Core Guideline

Procedure (Deviations From §81-1): Fasted rats were intubated at three levels, after initial range finding. Animals were observed frequently on the day of dosing, and daily thereafter. Body weights were recorded on days 0, 7, 14 or at death. All animals were subjected to gross necropsy at termination and at death.

Results:

Reported Mortality

DOSAGE (mg /kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
3150	1/5	1/5	2/10
5000	3/5	3/5	6/10
7950	4/5	5/5	9/10

Symptomology & Gross Necropsy Findings:

All deaths occurred within 48 hours after dosing. Signs of toxicity included: decreased activity; labored respiration; salivation; chromorhinorrhea; staining around eyes, nose, mouth and front paws; soft feces; decreased amount of feces. Most signs of toxicity disappeared after day 5, but anogenital staining persisted to day 11 in two and to termination with the surviving high dose male.

* The probit model did not fit the mortality data for male rats well enough for the calculation of confidence limits.

Necropsy findings in the lowest dose level were nonremarkable for the ones that succumbed to treatment. The findings in the survivors included Thickening of the glandular portions of the stomach (3/10) and adhesion of internal organs to each other or surrounding tissue.

In the group treated at 5000 mg/kg Thickened glandular portion of the stomach, adhesion of internal organs to each other and/or surrounding tissue and mottled Thymus. The survivor at 7950 mg/kg showed the same. The animals succumbing to treatment at these dose levels showed no gross pathology other than mottled black Thymus glands.

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

Product Manager: (21)
MRID No.: 412060-12
Testing Laboratory: Ricerca Inc. Painesville, Ohio
Author(s): Maria-Louise Ackers, Steven K. Shultz, Julian H. Wilson, James C. Killeen
Species: Rabbit, New Zealand White, King's Wheel Rabbitry, Mount Vernon, Ohio
Sex: 5♂ + 5♀ Wt.: ♂ & ♀ 2300-2650g
Test Material: Tuffcide 500. SDS-2787-0992-2101, Ricerca Code T-232-1
Quality Assurance (40 CFR §160.12): Included

Reviewer: Lucy D. Markarian
Report Date: 5/24/90
Report No. 88-005a

Summary:

1. LD_{50} (mg/kg): Males = _____; Females = _____; Combined = _____;
2. The estimated LD_{50} is Greater Than 2000mg/kg
3. Tox. Category: III. Classification: Core Guideline

Procedure (Deviations From §81-2): Test material was spread in 4x6 inch area on clipped skin, wrapped in gauze and elastic Vetrap. Plastic collars were worn by the animals for the 24hr exposure. At 24hrs bandages were removed & sites wiped with wet paper towels. Observations were frequent on day 1 and daily thereafter. Body weights were taken on days 0, 7 & 14. There was terminal necropsy.

Results:

Reported Mortality

DOSAGE (mg/kg)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
2000	0/5	0/5	0/10

Symptomology & Gross Necropsy Findings:

Symptoms of systemic toxicity in the males were decreased feces, soft feces, anogenital staining and thin appearance. In the females nasal discharge was observed during exposure. Dermal toxicity manifestations included moderate to marked erythema, moderate to severe edema, Desquamation, fissures and crusting.

One male showed weight loss at 7 days, but returned to his

original weight at 14 days.

AT necropsy Two males showed dark red lungs and one female showed focal indentation of the surface of the right kidney. There were no other gross findings.

8

008953

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

Product Manager: (21)
Reviewer: Lucy D. Markarian
MRID No.: 412060-13
Report Date: 5/24/90
Testing Laboratory: Ricerca, Inc., Painesville, Ohio
Report No. 88-0054
Author(s): Steven K. Shults, Nelson H. Wilson, James C. Killeen
Species: Rabbit, New Zealand white
Sex: 3♂ + 3♀
Weight: 2.3 - 2.5 kg
Source: King's Wheel Rabbitry, Mount Vernon, Ohio
Dosage:
Test Material: Tuffcide 500, ID# SDS 2787-0442-2101 Ricerca ID code T 233.1
Quality Assurance (40 CFR §160.12): included

Summary:

Tox. Category: I Classification: Core Guidelines

Procedure (Deviation From §81-4): 0.1 ml of Test material was instilled in the Test eyes. Observations at 1, 24, 48, 72 hrs and days 4, 7, 10, 21. Fluorescein stains at 72 hrs & days 7, 14, 21, as well as all pre-test examinations. Graded according to Draize.

Results:

Observations (number "positive"/number tested)

	Hour	Days						
	1	1	2	3	4	7	14	21
Cornea Opacity	*	*	6/6	6/6	6/6	6/6	6/6	6/6
Iris	*	*	*	6/6	**	**	**	**1/6
Conjunctivae Redness	6/6	6/6	6/6	6/6	6/6	6/6	4/6	1/6
Chemosis	6/6	6/6	6/6	6/6	6/6	6/6	1/6	0/6
Discharge	6/6	6/6	6/6	6/6	6/6	6/6	5/6	3/6

Comments: * Severe chemosis and purulent discharge precluded observations of opacity and iritis in all or some of the eyes

** Severe opacity and vascularization of cornea and the presence of purulent material precluded the grading of the iris in all or some of the eyes.

Damage to the eye was extremely severe. At seven days There was complete opacity of the eye in all animals accompanied by vascularization conjunctival blanching and petechia, conjunctival blistering. At 21 days in addition to persistent severe opacity, vascularization, eyelid irritation and purulent discharge were still noted. In 2/4 animals Conjunctival Tissue incursion were present

008953

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

Product Manager: (21) Reviewer: Lucy D. Markarian
MRID No.: 412060-14 Report Date: 5/24/90
Testing Laboratory: Ricerca, Inc., Plainsville, Ohio Report No. 88-053
Author(s): Marta-Louise Ackerman, Steven K. Shultz, Nelson H. Wilson, James C. Killeen
Species: Rabbit, New Zealand White, Kings Wheel Rabbitry, Mount Vernon, Ohio
Age: Not specified
Sex: 3♂ + 3♀
Weight: 2300 - 2650 gm
Dosage: 0.5 ml
Test Material: Tuffcide 500, SDS-2787-0402-2101 Ricerca code T-232-1
Quality Assurance (40 CFR §160.12): included

Summary:

The Primary Irritation Index = 5.67

Toxicity Category: II

Classification: Core minimum

Procedure (Deviations From §81-5): Test material was administered to skin, covered with 2" of Dermiform Tape, animal wrapped with Vetaplastic. Collars were worn by animals for the 4 hr. exposure. Sites were wiped with wet paper towels. Evaluation was done by the Draize system.

Results:

Severe edema was the most remarkable reaction at 1 hr (5/6 a, 1/6 3). At 24 hrs all animals showed well defined moderate to marked erythema and somewhat subsided moderate to severe edema. At 48 hrs Erythema and edema appears have intensified as a whole, judged by the PI index rising from 5.3 to 6.2. At 72 hrs moderate to marked erythema and edema persisted in all animals. Irritation lasted to 11 days in 5/6 and 12 days in 2/6. Additionally desquamation, fissures and thickening of the skin were observed.

Special Comments:

In the observations at 1 hr or at any other interval, there is no indication of blanching. Therefore it is difficult to understand how a site exhibiting a marked degree of edema(3

11

could only have barely discernable erythema. It would have been most convincing if erythema had been accompanied by blanching and hiding the intensity of the redness. Furthermore the tabulated observations indicate that 3/6 sites showed Thickening of the skin on day 4, which is a result of 1/4 depth injury. The scores don't indicate this. According to the results some animals are indicated as having edema and Thickening at the same Time. It is not clear how they distinguished between The two, and how each can be evaluated simultaneously and correctly.

When calculating the Primary irritation index they have disregarded the 48 hour readings. Accordingly Their calculations are slightly lower Than what it actually is.

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

Product Manager: (21)
MRID No.: 41206[illegible]-15
Testing Laboratory: Ricerca Inc. Painesville, Ohio
Author(s): Steven K. Shultz, Nelson H. Wilson, James C. Killeen
Species: Guinea Pig, Hartley HDS:(HA) BR
Sex: 25 ♂ + 25 ♀ Weight: 314 - 370 g
Source: Sprague Dawley Inc. Indianapolis, Indiana
Test Material: Tuffcide 500, SDS 002787-0002-2101 Ricerca Code T-232-1
Positive Control Material: DNCB, product C-6396, Lot 44F-0565 (Sigma chem.)
Quality Assurance (40 CFR §160.12): included

Reviewer: Lucy D. Mastracion
Report Date: 5/24/90
Report No. 32-055

Method: Modified Buehler (closed patch repeated insult)

Summary:
1. This product is / is not a dermal sensitizer.
2. Classification: Supplimentary

Procedure (Deviation From §81-6): The main Test used fifty animals. Additional 12 animals were used for range finding Tests in groups of six with four sites of application per animal. The first range finding group was tested with 100% and v/v aqueous suspensions at 70, 50 and 30% of Tuffcide 500, and the second group was tested with 20, 15, 10, and 7% v/v aqueous suspensions. The dilutions were in deionized water.

The main Test animals were devided in 4 groups

1. Group Treated with 100% Test material for elicitation. (20. 10♂ & 10♀)
2. Group Treated with 0.3% DNCB in 80% ETOH for positive Control (10: 5♂ & 5♀)
3. Group of naive controls for Test material and DNCB used at challenge 1 only
4. Group of naive controls for Test material irritation used at challenge 2 only

Tuffcide 500, undiluted, was applied in Hilltop chambers (25mm) in 0.3 ml aliquots, and DNCB in 0.4 ml aliquots. Both were applied once a week for Three weeks, in closed patch method, for Three weeks. 14 days after the last application the first group of animals were challenged with 7% v/v suspension of Tuffcide 500 in deionized water and the Positive Control group was challenged with 0.075% DNCB in acetone. The Ten animals in group 3 were challenged with both Tuffcide 500 and DNCB. The second challenge followed in 7 days for the animals in Group

Treated with Tuffcide 500 and Group 4, the 10 naive controls for irritation. The results were evaluated according to Draize system.

Results:

According to the results of this test all the animals in Group I Tested positive for the sensitization. However review of the methods and the results finds this conclusion is open to question and the results inconclusive for the following reasons:

1- a. The irritation scores from the range finding studies indicate scores between very slight (0.5 or ±) to slight confluent or moderate patchy erythema (1) for all levels, with hardly any qualitative or quantitative gradation of response in regard to concentrations used. For example the 100% application of the test material elicited virtually the same response as the application at 50% dilution at 48 hours: 1/6(±) and 5/6(1) for both. At 30 and 15% dilutions responses were 5/6(±) and 4/6(±) 1/6(1) -respectively with 15% dilution showing slightly more irritation Than 30%. There were no true determination of the maximum non irritating dose.

b- There is no indication where the group of 12 animals used for range finding came from - According to the report 52 animals were received, 40 of those were used for the main test and Twelve were used for the range finding tests. The animals used for This purpose could have been from a different source, weight range, age, and not representative of the test colony and as such not acceptable and the results obtained not applicable to the colony of animals used for the main test.

14

2. At elicitation 100% Test material cannot be considered the minimally irritating concentration when results at 50% dilution are at the same intensity and frequency as the undiluted test material. To further support this conclusion it is pointed out that the test material was irritating enough that even though it was applied only three times one week apart, after the second elicitation caused in depth damage to the skin, the sites of application had to be moved for the third elicitation. This may also indicate early sensitization, however at that concentration it cannot be so concluded.

3. The scoring of the resulting irritation from the elicitation applications are not graded correctly or according to Beuhler as stated. Among all the sites graded only one site is graded with a numerical gradation of 3 meaning marked redness or eschar. Yet separately from the numerical grade it is recorded that eschar, Thickening of skin, and blanching were present at sites graded numerically as 2, meaning a well defined erythema. Beuhler grades eschar as 3. Thickening is hyperplasia resulting from eschar and blanching is sign of necrosis resulting from in depth injury and must be graded numerically as 3. The protocal states that the modified Beuhler method was used in application and grading, when in effect the test material was not applied according to Beuhlers (0.3ml versus 0.4 of Beuhler) nor graded as such consequently breaching the GLP regulations.

Therefore the study is graded as supplimentary

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

Product Manager: (21)
MRID No.: 412198-00
* Testing Laboratory: Huntingdon Research Centre Inc. Cambridgeshire, England
Author(s): Graham C. Jackson, Colin Harding
Species: _____
Sex : _____ Weight: _____
Source: _____
Test Material: Tuffcide 500 Ricerca Code T-232-1
Quality Assurance (40 CFR §160.12): _____

Reviewer: Lucy J. Markarian
Report Date: 5/24/90
Report No. RIC 3/89152
Ricerca Document II 5079-88-0075-Tox-001

Summary: SEE PAGE 2

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

Procedure (Deviations From §81-2): _____

Results:

Exposure Concentration (mg/L)	Reported Mortality (NUMBER KILLED/NUMBER TESTED) Males	Females	Combined

Symptomology & Gross Necropsy Findings:

* The testing was sent to Huntingdon from Ricerca Inc. of Plainsville, Ohio

The applicant has submitted Aerosolizability evaluation of Tuftcide-500 in place of an actual inhalation toxicity study to substantiate that the test material is too viscous to be able to generate sufficient amounts of aerosol even if generation is under aggravated conditions that would normally yield higher aerosol concentrations.

The study consists of two separate trials in aerosolizing undiluted Tuftcide 500.

The test chamber used was of acrilic sheets that formed a 51cm x 51cm x 38cm square bottom and a 20cm high pyramidal top section with approximate volume of 120L. The aerosol was introduced into this chamber through a centred orifice at the bottom. A supply of clean and dry air was connected to a large generator and the air flow adjusted to 30L/min with operating pressure at 50 psig. The test material was introduced with a 5 ml syringe pump to feed 0.1ml per minute. This test atmosphere was maintained for 25 minutes. Then the syringe was replaced and the flow rate adjusted to 0.2ml per minute. This was maintained for 20 minutes. Total time was 45 minutes. Flow rates higher than 0.2ml/min overloaded the pump. The second trial utilized a generator with a smaller bore and required higher operating pressure. The supply pressure was set at 15 psig/min and the flow rate at 0.1 ml/min. Flow rates in excess of this overloaded the syringe pump. This trial lasted 65 minutes.

Two air samples from the first trial and four samples from the second trial were taken for gravimetric determination of concentrations by withdrawing air samples through Wattman glass fiber filter at a sampling rate of 4 L/min. Gas volume was

measured using a wet-type gas meter.

The samples from the first trial yielded no measurable amounts of test material. The samples from the second trial yielded from 0.001 mg/L to 0.014 mg/L of test material. The nominal concentration was 6.7 mg/L. The highest measured concentration, 0.014 mg/L, was approximately 0.2% of the nominal concentration. This was attributed to the high viscosity of Tuftcide 500.

No attempt was made at particle sizing.

The conclusion put forward is that undiluted Tuftcide 500 will not yield sufficient concentrations of aerosol under conditions likely to be useful for the purpose of an inhalation study. It was further concluded by Ricerca that Tuftcide, under normal conditions of use, would not be an inhalation hazard.

It is therefore assumed that the applicant would like a waiver for the submission of inhalation toxicity support in behalf of Tuftcide 500 due to the viscosity and the unlikelyhood of the opportunity during normal use to generate an aerosol that causes inhalation toxicity.