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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Date: March 24, 1999

Subject: Acute toxicity data review for reregistration of Thymol,
Product trade name: **READY TO USE THYMO-CIDE**

EPA Reg. No. 34810-25
DP Barcode: D240124
Case No.: 3143

April 20, 99

From: Hari Moy Mukhoty, DVM, Ph.D
Product Reregistration Branch (PRB)
Special Review and Reregistration Division (SRRD), Mail Code: 7508C MDP

To: Steve Morrill, CRM
PRB, SRRD, Mail Code: 7508C

Applicant: Wexford Labs, Inc
325 Leffingwell Avenue
Kirkwood, Missouri 63122

FORMULATION FROM LABEL:

Active Ingredients:	% by wt.
5-Methyl-2-isopropyl-1-phenol (Thymol).....	0.051%
Inert Ingredients:.....	99.949%
Total.....	100.000%

BACKGROUND:

The Wexford Labs, Inc. has submitted data for primary eye irritation (MRID 416344-01), and primary dermal irritation (MRID 434869-06) studies to support the reregistration of their product EPA Reg. No. 34810-25. READY TO USE THYMO-CIDE is the trade name of the aforesaid product. The acute toxicity studies were conducted by the Cosmopolitan Safety Evaluation (C.S.E.), Inc. Lafayette, NJ. The primary eye and dermal irritation studies were completed in the months of July and August of 1984, respectively. The acute toxicity studies were reviewed for AD by the Dynamac Corporation of Rockville, MD, an EPA contractor. Steven L. Malish of Team 1, RASSB/Antimicrobials Branch also reviewed and accepted the data for primary eye irritation for this product and placed it in Toxicity Category IV (Secondary reviewer was Winston Dang from the same Branch). This last review was supplied in a disc by AD to PRB on March 11, 99. This does not have any date and is not available in the product jacket.

This company is citing acute oral and dermal toxicity data from product EPA Reg. No. 34810-19 to support the reregistration of their product EPA Reg. No. 34810-25. Hari Mukhoty, PRB/SRRD reviewed and accepted the data for classification of EPA Reg. No. 34810-19 (Memorandum from Hari Mukhoty, PRB/SRRD to Steve Morrill, PRB/SRRD dated March 22, 1999). EPA Reg. No. 34810-19 contains 7% thymol and 7% o-phenylphenol as A.I. whereas EPA Reg. No. 34810-25 contains only 0.051% Thymol as A.I. Therefore, bridging acute toxicity data from a concentrated product to support the reregistration of a chemically similar diluted product is acceptable. It should be indicated here that the registrant needs to clarify in the CSF (Basic Formulation CSF, dated 08-28-97 for EPA Reg. No. 34810-25) the way percent thymol (0.051%) present in the formulation was calculated from Thymoxydichloroacetic acid (0.391%).

The Wexford Labs, Inc. is also citing acute inhalation and dermal sensitization data from product EPA Reg. No. 34810-18 to reregister EPA Reg. No. 34810-25. This is acceptable because EPA Reg No. 34810-18 contains 13% Thymol as A.I. in this formulation. However, neither the studies nor the reviews were made available to the present reviewer. Hari Mukhoty, PRB/SRRD retrieved acute inhalation and dermal sensitization studies on EPA Reg. No. 34810-18 from the Agency's information services and reviewed both studies for bridging the information for reregistration of EPA Reg. No. 34810-25.

The identity of the test materials used to determine the acute toxicity for products EPA Reg. Nos. 34810-25 and 34810-18 has been adequately established through registrant's letters dated April 2, 1999. Discussion with respect to the identification of the test material used in acute toxicity testing of EPA Reg. No. 34810-19 has been provided in Hari Mukhoty's review on the same product.

RECOMMENDATION:

The acute toxicity data requiriments for the reregistration of the undermentioned product are satisfied:

The acute toxicity profile for EPA Reg. No. 34810-25 is currently:

Acute oral toxicity	IV	Acceptable
Acute dermal toxicity	III	Acceptable
Acute inhalation toxicity	IV	Acceptable
Primary eye irritation	IV	Acceptable
Primary dermal irritation	IV	Acceptable
Dermal sensitization	Non-sensitizer	Acceptable

LABELING:

ID # : 034810-00025 READY TO USE THYMO-CIDE

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENT:

Harmful if absorbed through the skin. Avoid contact with eyes, skin or clothing. Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.

STATEMENT OF PRACTICAL TREATMENT (SOPT) :

IF ON SKIN : Wash with plenty of soap and water. Get medical attention.

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit
OPPTS Number: 870.2500

OPP Guideline Number: §81-5

DP BARCODE: D240124
P.C. CODE: 080401
EPA REG. NO.: 34810-25

SUBMISSION CODE:
TOX. CHEM. NO.:

TEST MATERIAL (PURITY): Formulation 6-76-E Concentrate (% thymoxydichloroacetic acid not specified) at a 1:256 (w:v) aqueous dilution

SYNONYMS: Ready To Use Thymo-cide Germicidal Detergent

CITATION: Robbins, G. (1990) Primary dermal irritation study in rabbits (use dilution). Cosmopolitan Safety Evaluation, Inc., Lafayette, NJ. Laboratory Study Number 1118E. September 14, 1990. MRID 41634402. Unpublished.

SPONSOR: Wexford Labs, Inc., 325 Leffingwell Avenue, Kirkwood, MO.

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 41634402), three young adult albino rabbits/sex were dermally exposed to 0.5 mL of diluted (1:256, w:v) Formulation 6-76-E Concentrate (% thymoxydichloroacetic acid not specified) for 4 hours; the diluted test substance was applied to a single intact 1-in^2 site/animal. Animals were observed for dermal irritation for up to 72 hours following application, and irritation was scored by the Draize scale.

No dermal irritation was observed during the 72-hour study. In this study, **diluted (1:256, w:v) Formulation 6-76-E Concentrate is not a dermal irritant**, and is classified as **TOXICITY CATEGORY IV** for primary dermal irritation.

This study is classified **acceptable (§81-5)** and satisfies the guideline requirement for a primary dermal irritation study in the rabbit.

COMPLIANCE: Signed and dated GLP and Data Confidentiality statements were provided. A Quality Assurance statement was not included.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Formulation 6-76-E Concentrate
   Description: Yellow transparent liquid
   Lot/Batch #: 6-76-E (not further described)
   Purity: % Thymoxydichloroacetic acid not specified

pH: Not specified
CAS #: Not specified

2. Vehicle and/or positive control: None employed

3. Test animals: Species: Rabbit
Strain: Albino, not further specified
Age: Young adult
Weight: 2.0-3.5 kg (combined sexes)
Source: Not specified
Acclimation period: ≥5 Days
Diet: Agway Special Rabbit Pellets supplemented with oats, ad libitum
Water: Tap water, ad libitum
Housing: Individual
Environmental conditions: Not specified

B. STUDY DESIGN and METHODS:

1. In-life dates: August 16-19, 1983 (reviewer estimated)

2. Animal assignment and treatment: Prior to use, 0.1 g of Formulation 6-76-E Concentrate was diluted to 256 mL with tap water; the preparation was maintained on a stir plate prior to and during treatment. Fur from the dorsal trunk area of three young adult albino rabbits/sex was clipped 1 day prior to dermal administration with 0.5 mL of the diluted test material. The test substance was applied to a single intact site/animal using a 1-in^2 gauze patch. Each patch was secured with hypoallergenic tape, and the entire trunk of each animal was then wrapped with non-irritating perforated plastic sheeting secured with masking tape. Following a 4-hour exposure period, the coverings were removed and the test sites were gently wiped with clean water-moistened paper towels. Treatment site irritation was scored using the Draize scale at 30-60 minutes and 24, 48, and 72 hours following patch removal. In addition, the animals were monitored at unspecified intervals for signs of systemic toxicity.

II. RESULTS AND DISCUSSION:

A. Clinical observations: No dermal irritation was observed during the 72-hour study. The resultant Primary Irritation Index was 0.0. In this study, diluted (1:256, w:v) Formulation 6-76-E Concentrate is not a dermal irritant.

No signs of systemic toxicity were observed during the 72-hour observation period.

B. Deficiencies: The purity/composition of the test material should be provided.

DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation - Rabbit
OPPTS Number: 870.2400

OPP Guideline Number: §81-4

DP BARCODE: D240124
P.C. CODE: 080401
EPA REG. NO.: 34810-25

SUBMISSION CODE:
TOX. CHEM. NO.:

TEST MATERIAL (PURITY): Formulation 6-76-E Concentrate (% thymoxydichloroacetic acid not specified) at a 1:256 (w:v) aqueous dilution

SYNONYMS: Ready To Use Thymo-cide Germicidal Detergent

CITATION: Robbins, G. (1990) Primary eye irritancy study in rabbits (use dilution). Cosmopolitan Safety Evaluation, Inc., Lafayette, NJ. Laboratory Study Number 1118D. September 14, 1990. MRID 41634401. Unpublished.

SPONSOR: Wexford Labs, Inc., 325 Leffingwell Avenue, Kirkwood, MO.

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 41634401), 0.1 mL of diluted (1:256, w:v) Formulation 6-76-E Concentrate (% thymoxydichloroacetic acid not specified) was instilled into the conjunctival sac of one eye of six young adult albino rabbits (four male and two female). The treated eyes were not rinsed. The animals were observed for up to 72 hours following instillation, and eye irritation was scored using a modified Draize scheme.

No positive ocular irritation was observed during the 72-hour observation period. In this study, **diluted (1:256, w:v) Formulation 6-76-E Concentrate is not an ocular irritant**, and is classified as **TOXICITY CATEGORY IV** for primary eye irritation.

This study is classified **acceptable (§81-4)** and satisfies the guideline requirement for a primary eye irritation study in the rabbit.

COMPLIANCE: Signed and dated GLP and Data Confidentiality statements were provided. A Quality Assurance statement was not included.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Formulation 6-76-E Concentrate
   Description: Yellow transparent liquid
   Lot/Batch #: 6-76-E (not further described)
   Purity: % Thymoxydichloroacetic acid not specified

pH: Not specified
CAS #: Not specified

2. Vehicle and/or positive control: None employed

3. Test animals: Species: Rabbit
Strain: Albino, not further specified
Age: Young adult
Weight: 2.0-3.5 kg (combined sexes)
Source: Not specified
Acclimation period: ≥5 Days
Diet: Agway Special Rabbit Pellets supplemented with oats, ad libitum
Water: Tap water, ad libitum
Housing: Individual
Environmental conditions: Not specified

B. STUDY DESIGN and METHODS:

1. In-life dates: July 4-7, 1984 (reviewer estimated)

2. Animal assignment and treatment: Prior to use, 0.1 g of Formulation 6-76-E Concentrate was diluted to 256 mL with tap water. A 0.1-mL aliquot of the diluted material was then instilled into the conjunctival sac of one eye of six young adult albino rabbits (four male and two female). The upper and lower lids were held together for approximately 1 second before releasing to prevent loss of the material. The treated eyes were not rinsed, and the other eye of each animal served as an untreated control. Ocular irritation was scored using the Draize scale at 1, 24, 48, and 72 hours following instillation. At the 24- and 72-hour observation intervals, fluorescein dye was used to confirm the absence of corneal ulceration. In addition, the animals were monitored at unspecified intervals for signs of systemic toxicity.

II. RESULTS AND DISCUSSION:

A. Clinical observations: Slight conjunctival redness (score of 1) was observed in 1/6 treated eyes 1 hour following instillation. No other ocular irritation was noted during the 72-hour observation period. In this study, diluted (1:256, w:v) Formulation 6-76-E Concentrate is not an ocular irritant.

No signs of systemic toxicity were observed during the 72-hour observation period.

B. Deficiencies: The purity/composition of the test material should be provided.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (81-3, 870-1300)

Product Manager: Robert Brennis, 32
MRID No.: 434869-01

Reviewer: Hari Mukhoty
Study completion Date: May 31, 1994
Report No.: C3377

Testing Laboratory: Cosmopolitan Safety Evaluation, Inc. Lafayette, NJ 07848
Author: Gerald Roseenfeld

Quality Assurance (40 CFR: 160.12): Included
Test Material: READY TO USE THYMOCIDE, EPA Reg. No. 34810-25, Thymol- 0.051%, Lot/Batch No.: 777-28-B, 12-28-93, assigned C.S.E. compound number s1688-31, a yellowish liquid, pH 2.8
Exposure Type: Chamber exposure

Species: Sprauge-Dawley derived
Weight: Males: 306-329 grams Females: 240-265 grams
Age: Not specific - young adult
Source: Cosmopolitan Safety Evaluation, Inc. Laboratory bred

Summary:

1. **LC50 (mg/kg):** Combined >5.65 mg/L

2. **Toxicity Category:** IV

3. **Classification:** Acceptable

Procedure (Deviation from 81-3): None

Methods: Five male and five female healthy young adult rats (Sprague-Dawley derived) were exposed for four hours to a dynamic atmosphere (>10 changes per hour) containing a nominal concentration of 10.3 mg of the test substance per liter of air. A similar control group, which did not receive test substance was also used. The actual concentration measured gravimetrically in the breathing zone thrice during exposure was 5.46 mg/L, 6.48 mg/L and 5.01 mg/ L (mean 5.65 mg/L), which was the maximum attainable concentration of the aerodynamic particles of the preparation used. This was a limit test.

Clinical observations: There was no mortality. All rats showed evidence of irritation to the respiratory tract and had marked loses of body weight during the first two days following exposure following which normal gain resumed. Control rats appeared normal throughout the exposure period and subsequent observations. On return to their cages, the common symptoms were dorsal fur wet and matted, abdominal staining and/or perineal staining (yellow) with frequent decreased locomotor activity (3 males, 3 females) and occasional dyspnea. On day 1, 2 males and

4 females appeared normal. Two males and one female had chromorhinorrhea and yellow nasal discharge which usually persisted until day 4 or day 5. On day 6 all rats appeared normal and remained normal until study termination.

Gross Necropsy findings: Neither in the control group nor in the group exposed to the test substance were there any pathognomonic findings. All organs and tissues examined grossly, including the respiratory tract, appeared normal.

Reported mortality	(NUMBER KILLED / NUMBER TESTED)		
Exposure concentration mg/L	Males	Females	Combined
5.65	0/5	0/5	0/10

Nom conc	Grav conc	MMAD	GSD	Temp [C]	R.Humd	Air Flow
10.3 mg/L	5.65 mg/L	0.5	5.5	20	80-90%	10.0 L/m

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (81-6 / 870-2600)

Product Manager: Robert Brennis, 32
MRID No.: 434869-02

Reviewer: Hari Mukhoty
Study Completion Date: May 31, 1994
Report No.: F3377

Testing Laboratory: Cosmopolitan Safety Evaluation, Inc. Lafayette, NJ 07848
Author: Gerald Rosenfeld

Quality Assurance (40 CFR: 160.12): Included
Test Material: READY TO USE THYMO-CIDE, EPA Reg. No. 34810-25, Thymol 0.051%, Lot/Batch No.: 777-28-B, 12-28-93, compound number s1688-31, a yellowish liquid, pH 2.8
Positive Control Material: 1,4-p-phenylenediamine dihydrochloride

Species: Albino guinea pigs
Weight: 420-496 grams
Age: Not specific, young adult
Source: Camm Research Lab Animals, Wayne, NJ
Method: Buehler's Method

Summary:

1. **This Product is not a Dermal Sensitizer.**

2. **Classification:** Acceptable

Procedure (Deviation from 83-6): None

Methods and Results:

Range-finding study:

Method: A range finding test was conducted with 5 guinea pigs using 100%, 50%, 20% and 10% w/w suspension of the test material in distilled water.

Results: The concentration which caused minimal irritation was determined to be between 20% and 50%; a 30% concentration was selected for induction, and 105 was tentatively selected for challenge.

Method: Twenty-four hours before first application of the test material, and subsequently as necessary, hair was closely clipped on the right side of ten animals. A dose of 0.5 ml of the freshly prepared test solution was applied to an area of 6 cm square. The exposure was for 6 hours. This induction procedure was repeated at the same site during the next two weeks for a total of three six-hour exposures. The interval between induction exposures varied between 5 and 9 days. The animals were then left untreated for approximately 2 weeks prior to primary challenge. If a second challenge was used, animals were rested for at least one week after the primary challenge.

Results: The first induction application of 30% cause slight erythema in 6/10 animals and moderate erythema at 4/10 animals at 24 hours read; slightly more intense erythema was present at 72 hours with slight confluent erythema in 2/10 animals and moderate erythema in 8/10 animals. Consequently the concentration was reduced to 20% in second and third applications. These application were followed by moderate erythema at most sites and erythema persisted for 72 hours.

Challenge test:

Methods: Two weeks after the last induction, the animals and a naive group were challenged at a virgin site with 0.5 ml (0.5 grams of solid or a 6 cm square piece of the test substance).

Results: Challenge with substance applied as a 10% w/w preparation at the virgin sites caused slight patchy erythema at 5/10 sites and slight confluent erythema at 5/10 sites at 24 hours read; by 72 hours 3/10 sites showed no reaction and there was slight patchy erythema at 7/10 sites. Naive animals also treated with the 10% w/w concentration of the test substance at the same time as the challenge application, showed similar reactions to the challenge on induced animals.

Challenge at a 10% concentration caused a 5[+/-] + 5[1] response in induced animals and a 3[+/-] + 2[1] responses in controls, level of irritation, comparable in both groups, led to **rechallenge** at a 5% concentration.

When **rehallenged** with a 5% concentration, there was no reaction at sites and a slight patchy erythema at 4 sites at 24 hour in previously induced animals; erythema subsided within 72 hours. The naive group had no reaction in 2 and questionable slight erythema in 3, one naive animal still showed slight response at 72 hours.

Positive control study:

In contrast with the results from the rechallenged test data, guinea pigs tested with 1,4-Phenylenediamine dihydrochloride all had substantially higher scores following challenge than in the induction period and more positive scores than naive animals.

Conclusion:

As a result of this study, THYMO-CIDE was not considered a sensitizer in guinea pigs.

ACUTE TOX ONE-LINERS :

1. **PC Code:** 80401
2. **Current Date:** March 26, 1999
3. **Test Material:** READY TO USE THYMO-CIDE, EPA Reg. No. 34810-25, Thymol (0.051%), yellowish liquid, pH 2.8

Study / Species/ Lab/ Study # / Date	MRID No.	Results	Tox Cat	Core Grade
Acute inhalation toxicity/ Rat/ Cosmopolitan Safety Evaluation, Inc. / C3377/ 5-31-94	434869-01	LC50 > 5.65 mg/L	IV	A
Primary eye irritation/ Rabbit/ Cosmopolitan Safety Evaluation, Inc./ 1118D/ 7-7-84	416344-01	No eye irritation was seen at any time. No overt systemic effects.	IV	A
Primary dermal irritation/ Rabbit/ Cosmopolitan Safety Evaluation, Inc./ 1118E/ 8-19-84	416344-02	No irritation was seen at 24 or 72 hours.	IV	A
Skin sensitization/ Guinea pig/ Cosmopolitan Safety Evaluation, Inc./ F3377/ 5-13-94	434869-02	Non-sensitizer.	---------	A

Core Grade Keys: A=Acceptable, U= Unacceptable, S= Supplementary (Upgradeable)