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INITIAL SUBMISSION: PRIMARY DERMAL IRRITATION STUDY IN RABBITS WITH SAYTEX 111		
Chemical Category		
SAYTEX 111		

FYI-0794-001099

[redacted]

PHARMAKON RESEARCH INTERNATIONAL, INC.
WAVERLY, PENNSYLVANIA 18471

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Primary Dermal Irritation Study in Rabbits

PH 420-ET-009-83

Saytex 111

Lot #20-1737-A [redacted]

Submitted to

Ethyl Corporation
Baton Rouge, Louisiana

Victor T. Mallory, B.S.
Study Director

Robert W. Naismith, Ph.D.
Director of Toxicology

Richard J. Matthews, Ph.D.
President

November 29, 1983

Primary Dermal Irritation Study in Rabbits

PN 420-ET-009-83

SUMMARY

Test article Saytex 111, Lot #20-1737-A, was applied to two intact and two abraded skin sites on each of six rabbits (three males and three females). Slight erythema and very slight edema was observed at 24 hours following application of the test article. All sites returned to normal at 72 hours after treatment and the study was terminated.

Based upon the observations made in the Primary Dermal Irritation Study in Rabbits, Saytex 111, Lot #20-1737-A, was not considered to be a dermal irritant. (Primary Irritation Index = 0.2)

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Primary Dermal Irritation Study in Rabbits

PH 420-ET-009-83

Sponsor:	Ethyl Corporation Ethyl Tower, 451 Florida Baton Rouge, Louisiana 70801
Testing Facility:	Pharmakon Research International, Inc. Waverly, Pennsylvania 18471
Test Facility S.O.P. No.:	PH-420
Study No.:	PH 420-ET-009-83
Purpose of the Study:	To evaluate the dermal irritation produced in rabbits on intact and abraded skin by the administration of the test article.
Ownership of the Study:	The sponsor owns the study. All raw data, analysis, and reports are the property of the sponsor.
Study Monitor:	Mrs. Beverly Pancamo, Ethyl Corporation
Study Director:	Victor T. Mallory, B.S., Pharmakon Research International, Inc.
Technical Performance:	Victor T. Mallory and Stanley M. Zuczek
Q.A.U. Responsible Personnel:	Leslie Maas, B.S.
Dates of Performance:	November 22, 1983 through November 25, 1983
Good Laboratory Practices Statement:	This study was conducted in compliance with the Good Laboratory Practice Regulations except if noted. There were no significant deviations from the GLP Regulations which affected the quality or integrity of the study. Q.A.U. findings derived from the

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inspection(s) during the conduct of this study and from the audit of the final report are documented and have been provided to the study director and the test facility management.

Records Maintained: All raw data, final reports, documentation and protocol will be maintained in the Pharmakon Central Files.

Recordings: Standard Pharmakon Notebook

Notebook Reference: Notebook #383, pages 66-67

Raw Data: Copies of notebook recordings attached

TEST ARTICLE

Compound Description: Saytex 111 - White powder

Lot No.: 20-1737-A

Base Factor: Not applicable

Amount Submitted: 136 grams (material and container)

Date Submitted: November 21, 1983

Special Handling Instructions: Standard precautions

Analysis of Purity: The purity of the test article is the responsibility of the sponsor.

Stability: There was no apparent change in the physical state of the test article during administration.

TEST SYSTEM

Species: Rabbit

Strain: New Zealand White

Supplier (Source): Sgarlat's Rabbitry, Harvey's Lake, Pennsylvania

0 0 0 6

Sex:	Male and female
Weight at Initiation:	2 - 3 kilograms
No. on Study:	Six (6) (three males and three females)
Method and Justification for Randomization:	Selections based upon sex, body weight and apparent good health.
Acclimation Period:	Five (5) days
System of Identification:	Cages marked with an animal group number and dose level. Rabbits were ear tagged.

HUSBANDRY

Research Facility Registration:	U.S.D.A. Registration No. 23-107 under the Animal Welfare Act 74: SC 2131 et seq.
Animal Rooms:	Separate isolation by test system Light cycle - 12 hours light, 12 hours dark Temperature/Humidity - maintained at a temperature of 20°C ± 3°C, and a humidity of 30 to 70%.
Housing:	Rabbits were housed individually in cages sized in accordance with the "Guide for the Care and Use of Laboratory Animals" of the Institute of Laboratory Resources, National Research Council.
Sanitization:	Waste material removed daily. Cages and feeders were sanitized every two weeks.
Food:	Wayne Rabbit Ration[R], ad libitum, checked daily and added or replaced as needed. Feeders are designed to reduce soiling, bridging and scattering.
Food Analysis:	There were no contaminants that were reasonably expected to be present in the dietary material known

to be capable of interfering with the purpose or conduct of the study.

Water: Availability - fresh tap water, fit for human consumption, ad libitum, using 16 ounce glass bottles with rubber stopper and stainless steel sipper tube or an automatic watering system supplied by Edstrom Industries, Inc., Waterford, Wisconsin.

Water Analysis: Conducted by the Pennsylvania Gas and Water Company and the results provided to Pharmakon Research International, Inc.

METHODS

Rationale for Test System: As required by the regulatory agencies

Compound Preparation: As received

Dose Administration: 0.5 gm/site

Rationale for Dose Selection: As required by the regulatory agencies

Vehicle: As received

Route of Administration: Test material was applied directly on the intact and abraded skin sites.

Rationale for Route of Administration: To evaluate the irritant potential of the test article on the skin.

Frequency and Duration of Administration: Administered once and remained in contact with t... skin site for twenty-four (24) hours.

No. of Animals Per Dose Group: Six (6) (three males and three females)

No. and Code of Dose Group:

Rabbit No.	Dose
4927-4932	0.5 gm/site

Length of Study: Seventy-two (72) hours

Method and Study Performance: Each of six adult albino rabbits of the New Zealand White strain, were administered the test article at four skin sites, two abraded and two intact sites. All application sites were clipped free of fur. The skin was abraded using a 21 gauge burred needle; the abrasion penetrated the stratum corneum but not the derma. Following the application of the test material, one-inch square gauze patches were applied to each of the four sites. The trunk of the animal was then wrapped with a rubber dam and an Ace bandage to retard evaporation. The test substance was kept in contact with the skin site for twenty-four (24) hours. At the end of the twenty-four (24) hour exposure period, the wrappings were removed and the skin wiped to remove any remaining material. Animals were observed for signs of erythema and edema and scored according to the Draize Scale (Table I) at 24 and 72 hours following application of the test material.

Results: Individual rabbit data on body weight and scoring of irritation may be found in Table II or in the attached copies of notebook recordings. The pH of the test article was 6.1. Slight erythema and very slight edema were observed at 24 hours following application of the test article. All sites returned to normal at 72 hours after treatment and the study was terminated.

Conclusion: Based upon the observations made in the Primary Dermal Irritation Study in Rabbits, Saytex 111, Lot #20-1737-A, was not considered to be a dermal irritant. (Primary Irritation Index = 0.2)

TABLE I

[1]Draize Evaluation of Dermal Irritation

I. Dermal Observations

Erythema and Eschar Formation (Most severely affected area graded):

No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Edema Formation (Most severely affected area graded):

No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well-defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4

II. Primary Irritation Index

Mean values (6 animals) are calculated and summed as follows:

Erythema and eschar formation
- Intact skin - 24 and 72 hours - 2 values
- Abraded skin - 24 and 72 hours - 2 values

Edema formation
- Intact skin - 24 and 72 hours - 2 values
- Abraded skin - 24 and 72 hours - 2 values

TOTAL 8 values

Sum of mean values ÷ 8 = Primary Irritation Index

[1]Draize, J. H. 1959. The Appraisal of Chemicals in Foods, Drugs and Cosmetics, pp. 36-45. Association of Food and Drug Officials of the United States, Austin, Texas.

Federal Hazardous Substances Act Regulations. 16 CFR 1500.

TABLE II
Primary Dermal Irritation Study in Rabbits

PH 420-ET-009-83

Saytex 111

Rabbit No.	Sex	Weight (kg) Initial	Weight (kg) Final	Observed Effects 24 Hours Erythema Intact	24 Hours Erythema Abraded	24 Hours Edema Intact	24 Hours Edema Abraded	72 Hours Erythema Intact	72 Hours Erythema Abraded	72 Hours Edema Intact	72 Hours Edema Abraded
4927	M	2.010	2.097	1-1	1-1	0-0	0-0	0-0	0-0	0-0	0-0
4928	M	2.116	2.011	0-1	1-1	0-0	0-0	0-0	0-0	0-0	0-0
4929	M	2.113	2.257	0-0	0-0	0-0	0-0	0-0	0-0	0-0	0-0
4930	F	2.053	1.811	0-0	0-0	0-0	0-0	0-0	0-0	0-0	0-0
4931	F	2.193	2.169	0-0	0-0	0-1	0-0	0-0	0-0	0-0	0-0
4932	F	2.190	2.162	0-0	0-1	0-0	0-1	0-0	0-0	0-0	0-0
			TOTALS	1-2	2-3	0-1	0-1	0-0	0-0	0-0	0-0
Mean Values Erythema/Edema				0.2-0.3	0.3-0.5	0.0-0.2	0.0-0.2	0.0-0.0	0.0-0.0	0.0-0.0	0.0-0.0
Total Erythema/Edema				1.3		0.4		0.0		0.0	
Primary Irritation Index (Total ÷ 8)				0.2				0.0		= 0.2	

Irritant ___

Non-Irritant X

Study Director Victor L. Mallory Date 11/29/83

ATX1

PHARMAKON RESEARCH INTERNATIONAL, INC.
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QUALITY ASSURANCE UNIT STATEMENT

This study was perfo n accordance with the Good Laboratory Practices Regulation for non-clinical laboratory studies as developed by the U. S. Food and Drug Administration, as indicated in the Federal Register, Part II of December 22, 1978; Part 58, Title 21.

Study No. PH 420-ET-009-83

The following inspections were performed:

Interval	Date
Predosing Phase	11/21/83
Dosing Phase	11/22/83
Reporting Phase	11/29/83

Results of the above inspections were submitted to the Study Director and Management during the course of the study.

11/29/83
Date

Quality Assurance Unit

RAW DATA
APPENDIX

Project No. Ph 420-ET-009-83

E Primary Dermal Irritation Study Book No. 383

Page No.

Sponsor: Ethyl Corporation

Purpose: To evaluate the dermal irritation produced in rabbits by the administration of the test article on intact and abraded skin.

Method: Refer to S.O.P. Ph 420 or protocol from Sponsor (11/10/83).

Specie: Rabbit Strain: New Zealand White

Animal P.O.#: 111583ATOX; 110983ATOX Food Lot#: 29681583

Acclimation: Five (5) days Weight: 2-3 kg

Animal Randomization: Stratification by body weight.

Animal Identification: Cage number and ear tag.

Test Article: Saytex 111 Description: white powder

Amount Submitted: 136 gms (material & container)

Receipt date: 11/21/83

Dose: 0.5 gm/site

Vehicle: Test article moistened with 0.9% saline

Route: The test material is applied directly on intact and abraded skin sites.

Scale#: 6

~~Route~~ Light cycle: checked 11/22/83 S.Z.

Length of Study: Seventy-two hours

date of initiation: 11/22/83

date of termination: 11/25/83

Ph value of test article: 6.1 - 5% by weight with distilled H_2O (insoluble)

Rabbits shaved: 11/21/83 S.Z.

To Page No.

Witnessed & Understood by me, Date 11-[illegible] Invented by Stanley M. Zuzel Date 11/25/83

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PROTOCOL -- 420

Primary Dermal Irritation Study in Rabbits

Sponsor: Ethyl Corporation
Ethyl Tower, 451 Florida
Baton Rouge, Louisiana 70801

Testing Facility: Pharmakon Research International, Inc.
Waverly, Pennsylvania 18471

Test Facility S.O.P. No.: PH-420

Study No.: PH-420-ET-00983

Purpose of the Study: To evaluate the dermal irritation produced in rabbits by the administration of the test article on intact and abraded skin.

Ownership of the Study: The sponsor owns the study. All raw data, analysis, and reports are the property of the sponsor.

Study Monitor:

Study Director: Mr. Victor Mallory, Pharmakon Research International, Inc.

Q.A.U. Responsible Personnel: Leslie Maas

Dates of Performance:

Good Laboratory Practices Statement: This study will be conducted in compliance with the Good Laboratory Practices Regulations as stated in the Federal Register, Vol. 43, No. 247, Friday, December 22, 1978.

Tentative Date of Submission of Final Report: Within one month following the completion of the study.

Records Maintained: All raw data, final reports, documentation and protocol will be maintained in the Pharmakon Central Files.
Amendments to protocol
Feed Lot Number
Body weights, initial and final
Compound preparation

pH value of each test substance
Scores for erythema and edema for each animal at 24 and 72 hours and any subsequent observation.
Primary skin irritation scores according to the technique of Draize.

Raw Data: Maintained in a Standard Pharmakon Notebook

Record Retention: All raw data and completed notebooks

TEST SYSTEM

Species: Rabbit

Strain: Albino New Zealand White strain

Supplier (Source): Marland Breeding Farms, Inc., Hewitt, New Jersey, Perfection Breeders, Inc., Douglassville, Pennsylvania or from any U.S.D.A. acceptable source.

Sex: Male or female

Weight at Initiation: 2 - 3 kilograms

No. on Study: A minimum of six (6) animals per test article

Method and Justification for Randomization: Stratification by body weight

Acclimation Period: Five (5) days

System of Identification: Cage number and ear tattoo or tag.

HUSBANDRY

Research Facility Registration: U.S.D.A. Registration No. 23-107 under the Animal Welfare Act 74: SC 2131 et seq.

Animal Rooms: Separate isolation by test system
Light cycle - 12 hours light, 12 hours dark
Temperature/Humidity - every attempt will be made to maintain a temperature of 20°C ± 3°C, and a humidity of 50 to 70%.

Housing: Rabbits are housed individually in cages sized in accordance with the "Guide for the Care and Use of Laboratory Animals" of the Institute of Laboratory Resources, National Research Council.

Sanitization: Waste material removed daily. Cages and feeders are sanitized every two weeks.

Food: Wayne Rabbit Ration[R], ad libitum, checked daily and added or replaced as needed. Feeders are designed to reduce soiling, bridging and scattering.

Food Analysis: Acute doses minimize the effect of contaminants. There are no contaminants that are reasonably expected to be present in the dietary material known to be capable of interfering with the purpose or conduct of the study.

Water: Availability - fresh tap water, fit for human consumption, ad libitum, using 16 ounce glass bottles with rubber stopper and stainless steel sipper tube or an automatic watering system supplied by Edstrom Industries, Inc., Waterford, Wisconsin.

Water Analysis: Conducted by the Pennsylvania Gas and Water Company and the results provided to Pharmakon Research International, Inc. annually.

METHODS

Rationale for Test System: As required by the regulatory agencies.

Rationale for Dose Selection: Established by the regulatory agencies.

Dose Administration: 0.5 ml of liquid test articles
0.5 grams of solid or semi-solid test articles

Compound Preparation: The proper amounts of the test material are measured according to either weight (solids) or volume (liquids). Liquids are administered as received, solids are slightly moistened with physiological saline (quantity sufficient to prepare an applicable paste).

Vehicle: Liquids: administered as received
Solids: 0.9% NaCl solution

Volume Administration: Not applicable

Route of Administration: Test material is applied directly on the intact and abraded skin sites.

Rationale for Route of Administration: Required by the regulatory agencies

Frequency and Duration of Administration:

Test article is administered once and remains in contact with the skin site for 24 hours.

No. and Description of Rabbits per Dose Group:

Six (6) (male or female)

Length of Study:

Seventy-two (72) hours or until all irritation subsides or is obviously irreversible.

Method and Study Performance:

Each of six adult albino rabbits of the New Zealand White strain, were administered the test article at four skin sites, two abraded and two intact sites. All application sites were clipped free of fur. The skin was abraded using a 21 gauge burred needle; the abrasion penetrated the stratum corneum but not the derma. Following the application of the test material, one-inch square gauze patches were applied to each of the four sites. The trunk of the animal was then wrapped with a rubber dam and an Ace bandage to retard evaporation. The test substance was kept in contact with the skin site for twenty-four (24) hours. At the end of the twenty-four (24) hour exposure period, the wrappings were removed and the skin wiped (but not washed) to remove any test substance still remaining. It may be necessary to rinse off the material if colored test substances are used.

Type and Frequency of Test, Analysis and Measurement to be Made:

Body weight (initial and final)
pH value for each soluble test substance.
Animals are observed and signs of erythema and edema are scored according to the Draize scale (Table I) at 24 and 72 hours after application of the test substance. Observation for any irritation and scoring of any irritation (according to the method of Draize) continues on a daily basis for fourteen days or until all irritation subsides or is obviously irreversible. Irritation still present after fourteen days is considered indicative of permanent damage.

Data Analysis:

The irritation is scored according to the technique of Draize, J. H. (1959), The Appraisal of Chemicals in Foods, Drugs and Cosmetics, pp. 36-45. Association of Food and Drug Officials of the United States. Austin, Texas. Scoring sample and method for the calculation of the primary irritation index is attached. (Table I).

TABLE I

[1]Draize Evaluation of Dermal Irritation

I. Dermal Observations

Erythema and Eschar Formation (Most severely affected area graded):

No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
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Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Edema Formation (Most severely affected area graded):

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II. Primary Irritation Index

Mean values (6 animals) are calculated and summed as follows:

Erythema and eschar formation
- Intact skin - 24 and 72 hours - 2 values
- Abraded skin - 24 and 72 hours - 2 values

Edema formation
- Intact skin - 24 and 72 hours - 2 values
- Abraded skin - 24 and 72 hours - 2 values

TOTAL 8 values

Sum of mean values ÷ 4 = Primary Irritation Index

[1]Draize, J. H. 1959. The Appraisal of Chemicals in Foods, Drugs and Cosmetics, pp. 36-45. Association of Food and Drug Officials of the United States, Austin, Texas.

Federal Hazardous Substances Act Regulations. 16 CFR 1500.

TEST ARTICLE

Compound:

Lot No.:

Description:

Amount Submitted:

Date Submitted:

How Supplied:

Special Handling Instructions:

Test Article/ Carrier Mixtures: Analysis for stability, uniformity and correctness of concentration is the responsibility of the sponsor.

☐ Return Test Article/Carrier Mixtures to the Sponsor

☐ Dispose of Test Article/Carrier Mixtures

Analysis of Purity/Stability: Analysis of the purity and stability of the test article is the responsibility of the sponsor.

Test Article Disposition:

☐ Test article will be disposed of 3 months following the submission of the final report.

☐ Test article to be returned upon completion of the study.

APPROVAL OF PROTOCOL

Date 11/10/83 Study Monitor Beverly Pancamo

Date 8/15/83 Study Director Victor L. Mallory

AMENDMENTS _____