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Submitting Organization		PHARMAKON RESEARCH INTL INC	
Contractor			
Document Title		INITIAL SUBMISSION: ACUTE ORAL TOXICITY STUDY IN RATS (14 DAY) OF SAYTEX 111	
Chemical Category		SAYTEX 111	

74-0794-001097

PHARMAKON RESEARCH INTERNATIONAL, INC.

WAVERLY, PENNSYLVANIA 18471

PHONE
(717) 586-2411



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LODGE... No. 101

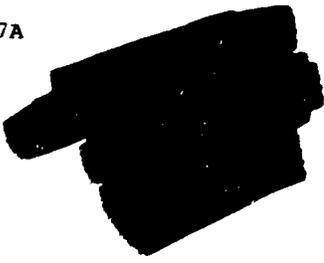


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Acute Oral Toxicity Study
in Rats (14 Day)

PH 402-ET-009-83

Saytex 111
Lot #20-1737A



Submitted to

Ethyl Corporation
Baton Rouge, Louisiana

Victor T. Mallory
Victor T. Mallory, B.S.
Study Director

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

Richard J. Matthews
Richard J. Matthews, Ph.D.
President

December 5, 1983

**Acute Oral Toxicity Study
in Rats (14 Day)**

PH 402-ET-009-83

One group of ten rats (five males and five females) were fasted for eighteen hours and orally administered Saytex 111, Lot #20-1737A, at a dose level of 5.0 gm/kg. Decreased activity was observed immediately after dosing and at one hour. None of the animals died at the 5.0 gm/kg dose level. No test article related lesions were observed in any of the animals upon terminal necropsy.

Based upon the results from the Acute Oral Toxicity Study in Rats, the estimated acute oral LD₅₀ for Saytex 111 was determined to be greater than 5 gm/kg.

Acute Oral Toxicity Study in Rats (14 Day)

PH 402-ET-009-83

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

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

Test Facility
S.O.P. No.: PH-402

Study No.: PH 402-ET-009-83

Purpose of
the Study: To determine the acute single dose oral toxicity of
the test material.

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: Joseph Zacker, Stanley Zuczek, Victor T. Mallory,
Rosemary Lynott and Dennis Margitich

Q.A.U.
Responsible
Personnel: Leslie Maas, B.S.

Dates of
Performance: November 21, 1983 through December 5, 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

Acute Oral Toxicity Study in Rats (14 Day)
PH 402-ET-009-83

the study. Q.A.U. findings derived from the 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 central files of Pharmakon Research International, Inc.

Recording:

Standard Pharmakon Notebook

Notebook Reference:

Notebook #1009, pages 91, 93

Raw Data:

Copies of notebook recordings attached.

Statistics:

Not applicable

TEST ARTICLE

Compound Description:

Saytex 111 -- light yellow powder

Lot No.:

20-1737A

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.

Acute Oral Toxicity Study in Rats (14 Day)
PH 402-ET-009-83

TEST SYSTEM

Species: Rat

Strain: Sprague Dawley

Supplier (Source): Charles River Breeding Labs, Wilmington, Massachusetts

Sex: Male and female

Weight at Initiation: 180 - 280 gm (after fasting)

No. on Study: Ten (10) (5 males and 5 females)

Method and Justification for Randomization: Selection based upon body weight

Acclimation Period: Five (5) days

System of Identification: Cages marked with an animal number and dose level.
Rats were identified by metal numbered ear 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 - maintained at a temperature of 22°C ± 3°C, and a humidity of 30 to 70%.

Housing: Rats housed in groups, according to sex, or individually in stainless steel ½" wire mesh cages. Size in accordance with the "Guide for the Care and Use of Laboratory Animals" of the Institute of Laboratory Resources, National Research Council.

Acute Oral Toxicity Study in Rats (14 Day)
PH 402-ET-009-83

Sanitization:

Waste material removed daily. Cages and feeders were sanitized every two weeks.

Food:

Wayne Lab Blox^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 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:

<u>Dose Level</u>	<u>Test Weight</u>	<u>Final Weight</u>
5.0 gm/kg	20 gm	40 ml

Dose Administration:

5.0 gm/kg

Rationale for Dose Selection:

As specified by the sponsor

Volume Administration:

10 ml/kg

Vehicle:

0.25% methylcellulose

Acute Oral Toxicity Study in Rats (14 Day)
PH 402-ET-009-83

Route of Administration:

Oral, by gavage

Rationale for Route of Administration:

Potential route of human exposure

Frequency and Duration of Administration:

Once (1)

No. of Animals Per Dose Group:

Ten (10) (5 males and 5 females)

No. and Code of Dose Group:

<u>Rat No.</u>	<u>Dose Level</u>
7131-7140	5.0 gm/kg

Length of Study:

Fourteen (14) days

Method of Study Performance:

Limit Test

In the 5.0 gm/kg limit test, one group of ten rats (5 males and 5 females) was fasted for eighteen hours and orally administered the test article at 5 gm/kg. The rats were observed immediately after dosing and at one, four and twenty-four hours and once daily for fourteen days for pharmacotoxic, CNS effects and mortality. On the fourteenth day body weights were recorded. The rats were sacrificed by CO₂ inhalation and a gross necropsy performed.

Results:

None of the animals died at the 5.0 gm/kg level. Decreased activity was observed immediately after dosing and at one hour post treatment. No test article related lesions were observed in any animal upon terminal necropsy.

Acute Oral Toxicity Study in Rats (14 Day)
PR 402-ET-009-83

Conclusions:

Based upon the results from the Acute Oral Toxicity Study in Rats, the estimated acute oral LD_{50} for Saytex 111 was determined to be greater than 5.0 gm/kg.

PHARMAKON RESEARCH INTERNATIONAL, INC.

WAVERLY, PENNSYLVANIA 18471

PHONE
(717) 586-2411

QUALITY ASSURANCE UNIT STATEMENT

This study was performed in 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 402-FT-009-83

The following inspections were performed:

Interval	Date
<u>Pre dosing Phase</u>	<u>11/21/83</u>
<u>Dosing Phase</u>	<u>11/21/83</u>
<u>Necropsy Phase</u>	<u>12/5/83</u>
<u>Reporting Phase</u>	<u>12/6/83</u>
<u> </u>	<u> </u>
<u> </u>	<u> </u>
<u> </u>	<u> </u>

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

12/6/83
Date

Hester Maas
Quality Assurance Unit

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RAW DATA
APPENDIX

ACUTE TOXICOLOGY STUDY ASSIGNMENT FORM

Title: acute oral toxicity study in rats Study No. PH 402-ET-009-83

Sponsor: ETHYL CORP.

Purpose: To evaluate the single-dose oral toxicity of the test article.

Method: Protocol 402

Date of Initiation: 11/21/83 Date of Termination: 12/5/83

Test Article SAYTEX 111

and Description: LT. yellow powder

Vehicle: 0.25% methyl cellulose

Dose Levels: 5g/ml/kg

Route of Administration: ORAL by GAVAGE

Animal P.O. #: 0919838Tox (11/17/83) 1114838Tox

Species: RAT Strain: SPRAGUE DAWLEY

Weight Range: 180-280 AFF-FASTING Food Lot #: 06163

No. of Animals on Study: 10 Sex: Male 5

Female 5

Scale #: 6 Light cycle checked: 11/21/83

Animals shave/fluorescein N/A

Ph of Test Article: _____

Compound Preparation 20gms Test Article to 40ml. Dose volume 10 ml/kg.

Dose Level: 5.0g/ml/kg Test Weight: 20gms Final Volume: 50ml. 40ml

Comments: _____

Investigator: Joseph Zipes Date 12/5/83

Study Director: Charles Malley Date 12/5/83

RMAKON RESEARCH INTERNATIONAL

Species RAT

Article Ethyl comp.

ACUTE TOXICITY

S.O.P. 402

No. 21402-ET-09-83

LD₅₀

Vehicle 0.25% Methylcellulose

Preparation: 200mg test article in 40ml

No.	SEX	DOSE:		TIME	FINAL WT. DATE OF DEATH
		WT. (gms) DAY 7	DOSE ADM.		
7131	♂	195	1.95	11:02	318
7132	♂	182	1.82		341
7133	♂	192	1.92		347
7134	♂	190	1.90		321
7135	♂	189	1.89		330
7136	♀	180	1.80		231
7137	♀	181	1.81		235
7138	♀	181	1.81		242
7139	♀	182	1.82		226
7140	♀	184	1.84	11:18	229

TOXIC SIGNS	HOURS					DAYS												
	0	1	2	4	24	2	3	4	5	6	7	8	9	10	11	12	13	14
No signs	5	5			5	5	5	5	5	5	5	5	5	5	5	5	5	5
Increased activity																		
Decreased activity	2	2																
Convulsions, clonic																		
tonic																		
Anaemia																		
Straub tail																		
Paralysis																		
Diarrhea																		
Salivation																		
Lacrimation																		
Prosis																		
Poor grooming																		
Exophthalmos																		
Chromodacryorrhea																		
Pilo-erection																		
Muscle tone: increased																		
decreased																		
Abnormal gait																		
Abnormal stance																		
Dysnoea																		
Cyanosis																		
Body drop																		
Tremors																		
Loss of righting reflex																		
Prostration																		
Others																		
Mortality (AM)	0	0				0	0	0	0	0	0	0	0	0	0	0	0	0
Mortality (PM)	0	0				0	0	0	0	0	0	0	0	0	0	0	0	0

Autopsy findings (N = None) TERMINAL NERVOUS
 7131♂-N, 7132♂-N, 7133♂-N
 7134♂-N, 7135♂-N, 7136♀-N
 7137♀-N, 7138♀-N, 7139♀-N
 7140♀-N, 7141♀-N
 0/10 DEAD AT

REMARKS:
 Technical performance: Acceptable
 Study Director: Robert J. Melling Date: 12/5/83

PHARMAKON RESEARCH INTERNATIONAL, INC.

WAVERLY, PENNSYLVANIA 18471

Protocol - 402

PHONE
(717) 586-1411

Acute Oral Toxicity Study in Rats (14 Day)

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-402

Study No.: PH 402-ET-00983

Purpose of the Study: To evaluate the single-dose oral toxicity and/or to determine the acute oral LD₅₀ 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:

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

Q.A.U. Responsible Personnel: Leslie Maas

Dates of Performance: Study will begin within one month of the receipt of the test chemical and authorized protocol.

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
Volume administration
Observed symptomatology
Observed mortality

090182

Statistics:

By the method of Litchfield and Wilcoxon,
JPET 96: 99-114 (1949).

Raw Data:

Maintained in a Standard Pharmakon Notebook

Record Retention:

All raw data and completed notebooks.

Analytical Chemistry:

Analysis and stability of the test article and test article/carrier mixture is the responsibility of the sponsor. If requested by the sponsor, Pharmakon Research International, Inc. will, through its subcontractor, conduct appropriate analytical analysis and will indicate the additional cost involved following receipt and evaluation of the appropriate analytical method. In the case where a satisfactory method is not provided, Pharmakon Research International, Inc. or its subcontractor, at additional cost to the sponsor, will develop appropriate methods.

If the sponsor elects to analyze the test article/carrier mixtures, Pharmakon Research International, Inc. will collect the sample at appropriate designated intervals during the study and transmit the samples to the sponsor for analysis.

TEST SYSTEM

Species:

Rat

Strain:

Sprague Dawley

Supplier (Source):

Charles River Breeding Laboratories, Wilmington, Massachusetts, Blue Spruce Farms, Altamont, New York or from any U.S.D.A. acceptable source.

Sex:

Male and female

Weight at Initiation:

120 - 230 grams after fasting

No. on Study:

Ten (10) per dose level (5 males and 5 females)

Method and Justification for Randomization:

Stratification by body weight

Acclimation Period:

Five (5) days

System of Identification:

Cages marked with an animal group number and dose level. Rats are 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 - every attempt will be made to maintain a temperature of 22°C ± 3°C, and a humidity of 30 to 70%.

Housing:

Rats housed in groups, according to sex, or individually in stainless steel 1/4" wire mesh cages. Size 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 sanitized every two weeks.

Food:

Wayne Lab Blox^R, ad libitum, checked daily and added or replaced as needed. Feeders are designed to reduce soiling, bridging and scattering.

Food Analysis:

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 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 agency.

Rationale for
Dose Selection:

Based on the results of a dose-range-finding study.

Dose
Administration:

As specified by the sponsor, a sufficient number of dose levels will be used to meet the criteria of the data analysis system.

Compound
Preparation:

Proper amounts of test material are ground with a pestle or tissue grinder. Vehicle is then added in

proper increments to achieve a designated dose level.
Liquids are dose as received.

Vehicle:

The formulation for the test article will be a solution and/or suspension in distilled water, 0.25% methylcellulose (if necessary, one drop 5% Tween 80) sesame oil or corn oil.

Volume Administration:

5 ml/kg increased in increments of 5 ml to a maximum of 40 ml to achieve solubility or suspendability.

Route of Administration:

Oral. by gavage

Rationale for Route of Administration:

Potential route for human exposure.

Frequency and Duration of Administration:

Once (1)

No. and Description of Rats per Dose Group:

Ten (10) (5 males and 5 females)

Length of Study:

Fourteen (14) days.

Methods of Study Performance:

The rats are fasted for eighteen hours and given the test article at 5 gm/kg by oral gavage if there are no deaths in the dose-range-finding study. Alternatively, at the sponsor's request, the 5 gm/kg dose may be given prior to the dose-range-finding study. The rats are observed immediately after dosing and at one and four hours and daily for fourteen days for overt pharmacotoxic, CNS effects and mortality. On the fourteenth day body weights are recorded. The surviving rats are sacrificed by CO₂ inhalation and a gross necropsy performed. If the test article produced death in 40% of the animals (two of a sex out of 5 males or 5 females) or more within fourteen days additional doses are given to groups of ten rats to facilitate the statistical LD₅₀ calculation. Only upon the discretion of the sponsor, higher doses will be given if no deaths are observed.

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

Body weight (initial and final)
Daily observations
Mortality
Necropsy findings

VEHICLE

Vehicle: The formulation for the test article will be a solution and/or suspension in distilled water, 0.25% methylcellulose (if necessary, one drop 5% Tween 80) sesame oil or corn oil.

Methylcellulose
Lot No.: 784262

Supplier
(Source): Fisher Scientific Company, Fair Lawn, New Jersey

Preparation: 9.463 grams/3.785 liter distilled water

Description: White granules

Special Handling
Instructions: None

Analysis of
Purity: U.S.P. According to United States Pharmacopeia No. 18. The purity is the responsibility of the manufacturer.

How Supplied: 1 lb. jar

Rationale for
Negative Control
Article: Solubility and/or suspendability of the test article.

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 Bancroft

Date

8/15/83

Study Director

John J. Malloy

AMENDMENTS



CERTIFICATE OF AUTHENTICITY

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