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Submitting Organization	PHARMAKON LABORATORIES		
Contractor			
Document Title	INITIAL SUBMISSION: ASSAY OF COMEDOGENICITY IN THE RABBIT EAR WITH SAYTEX 102; AND ATTACHED SAYTEX 102 TECHNICAL BULLETIN		
Chemical Category	SAYTEX 102		

741-0794-001095

PHARMAKON LABORATORIES
WAVERLY, PENNSYLVANIA 15471

PHONE
(717) 506-2411

Contains No CBI

Assay of Comedogenicity in the Rabbit Ear

PH 425-ET-001-81

Saytex 102
Lot# 4-1478J



INIT 07/21/94



84948888188

Submitted to

Ethyl Corporation
Baton Rouge, Louisiana

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

Richard J. Matthews
Richard J. Matthews, Ph.D.
Director of Research

September 21, 1981

PHARMAKON LABORATORIES

WAVERLY, PENNSYLVANIA 15471

Assay of Comedogenicity in the Rabbit Ear

PHONE
(717) 886-2411

PH 425-ET-001-01

Saytex 102

Lot# 4-1478J

SUMMARY

Saytex 102, Lot# 4-1478J, was inuncted in the right ear of each of four rabbits (two males and two females) at concentrations of 100%, 10%, 1% and 0.1%. The test article was administered once daily, five times per week for four weeks. Observations were recorded prior to the initial dose and at 7, 14, 21 and 28 days after dosing. No positive scores were recorded at Day 7, 14 or 21. On Day 28, one rabbit exhibited a slight response at the 10% concentration. Observations during the study included: slight erythema, epidermal sloughing and scaling. Terminal necropsy revealed a small yellow-white nodule on the right renal capsule in one rabbit. No visible lesions were seen in any of the remaining rabbits at any dose level.

Based upon the results from the Assay of Comedogenicity in the Rabbit Ear, Saytex 102, Lot# 4-1478J, is not considered to be a comedolytic agent.

Assay of Comedogenicity in the Rabbit Ear
PH 425-ET-001-81
Saytex 202, Lot# 4-1478J

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

Test Facility: Pharmakon Laboratories
Waverly, Pennsylvania 18471

Test Facility
S.O.P. No.: PH-425

Study No.: PH 425-ET-001-81

Purpose of
the Study: To determine if a chemical is capable of producing
comedones in the external ear canal of the rabbit
following topical application.

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

Study Monitor: Dr. Theodore J. Benya, Ethyl Corporation

Study Director: Dr. Robert W. Naismith, Pharmakon Laboratories

Technical
Performance: Victor Mallory, Patricia Carey, Andrew Krueger and
Rosemary Lynott

O.A.U.
Responsible
Personnel: Leslie Maas

Dates of
Performance: July 13, 1981 through September 7, 1981

Good Laboratory
Practices
Statement: This study was conducted in compliance with the Good
Laboratory Practices 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
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 to the
test facility management.

Records
Maintained:

All raw data, final reports, documentation and protocol will be maintained in the central files of Pharmakon Laboratories.

Recordings:

Standard Pharmakon Notebook

Notebook
Reference:

Notebook 296, pages 10-17, 44-47

Raw Data:

Copies of notebook recordings attached.

TEST ARTICLE

Compound
Description:

Saytex 102 - off-white powder

Lot No.:

4-1478J

Base Factor:

Not applicable

Amount Submitted:

2 bottles

Date Submitted:

June 25, 1981

Special Handling
Instructions:

Standard precautions

Analysis of
Purity:

The purity of the test article is the responsibility of the sponsor.

Stability:

There were no apparent changes in the physical state of the test article during administration.

TEST SYSTEM

Species:

Rabbit

Strain:

Albino New Zealand White

Supplier
(Source):

Perfection Breeders, Inc.
Douglassville, Pennsylvania

Sex:

Male and female

Weight at
Initiation:

2 - 3 kilograms

No. on Study:

Sixteen (16)

Method and
Justification of
Randomization:

Selection based upon body weight.

Acclimation
Period:

Seven (7) days

System of
Identification:

Cages marked with an animal group number and dose level. Rabbits are ear tagged.

HUSBANDRY

Research Facility
Registration:

U.S.D.A. Registration No. 23-45 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 was made to maintain a temperature of $20^{\circ}\text{C} \pm 3^{\circ}\text{C}$ and 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 was removed daily. Cages and feeders were sanitized every two weeks.

Food:

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

Food Analysis:

Acute doses minimize the effect of the contaminants. There were 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. All bottles, sipper tubes, and stoppers are sanitized three times weekly.

Water Analysis:

Conducted by Pennsylvania Gas and Water Company and the results provided to Pharmakon Laboratories annually.

METHODS

Rationale for Test System:

The rabbit has historically been used for the assessment of chloracne potential.

Compound Preparation:

100% - as received moistened with Chloroform
10% - 100 mg suspended in 0.9 ml Chloroform
1% - 100 mg suspended in 9.9 ml Chloroform
0.1% - 10 mg suspended in 9.9 ml Chloroform

Dose Administration:

0.1 ml/day

Rationale for Dose Selection:

Based on a preliminary dose-range-finding assay.

Vehicle:

Chloroform

Route of Administration:

The test article was applied to one external ear canal of each rabbit.

Rationale for Route of Administration:

The study was designed specifically for the assessment of chloracne potential.

Frequency and Duration of Administration:

Once (1)/day (five times/week for four (4) weeks)

No. of Animals per Dose Group:

Four (4) (two males and two females)

No. and Code of Dose Group:

<u>Rabbit #</u>	<u>Dose</u>
251-254	100%
255-258	10%
259-262	0.1%
297-300	1.0%

Length of Study:

Twenty-eight (28) days.

Method of Study
Performance:

The test article was innoculated to one ear canal of four groups of four rabbits (two (2) males and two (2) females/group). The test article was applied Monday through Friday for four weeks. The contralateral ear served as a control. The test article was applied at dose levels predetermined in a preliminary dose irritation study. The high dose was 10% (the maximum non-irritating dose) and the intermediate and low doses were 1% and 0.1%. The test article was inserted on the tip of a 1 ml pipette deep into the ear canal and rubbed gently over the ventral aspect, well short of the tympanic membrane. Observations were made prior to the administration of the test article and at 7, 14, 21 and 28 days. Scoring of the individual ears was made according to Table I. A post mortem gross necropsy was performed on all animals on Day 28.

Results:

Individual rabbit data on body weights and scoring of comedogenicity may be found in the attached copies of notebook recordings. No positive scores were recorded at Day 7, 14 or 21. On Day 28, one rabbit exhibited a slight response at the 10% concentration. Observations during the study included: slight erythema, epidermal sloughing and scaling. Terminal necropsy revealed a small yellow-white nodule on the right renal capsule

0

in one rabbit. No visible lesions were seen in any of the remaining rabbits at any dose level.

Conclusion:

Based upon the results from the Assay of Comedogenicity in the Rabbit Ear, Saytex 102, Lot# 4-1478J, is not considered to be comedolytic agent.

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TABLE I

Evaluation of Comedogenicity

Four point scale

- 0 = none
- 1 = slight
- 2 = moderate
- 3 = severe

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2/19

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TITLE ASSAY of Comedogenicity in the Rabbit Ear

Page No. _____

Purpose: To determine if a chemical is capable of producing comedones in the external ear canal of the rabbit following topical application.

S.O.P. No.: PH-425

Sponsor: _____

DATE of Initiation: ~~7-20-81~~ ^{PMC} 7-13-81; 8/

TEST ARTICLE

DATE of Completion: 8-10-81; 9/7/81

Lot No.: #4-1478J

Description: off-white powder

Compound Receipt: 6-25-81

AMOUNT SUBMITTED: 2 bottles

Species: RABBIT

Strain: Albino New Zealand White

Sex: Male and Female

WEIGHT: 2-3 Kilograms

Animal P.O. #: 062481 A TOX and

No. Animals per GROUP: Four (4) : 2 Males and 2 Females

FASTING: Not Applicable

Animal Randomization: Sex and body weight

Animal Identification: ear tag and cage tag,

Dose Levels: 100%, 10%, 0.1% and 1%

VEHICLE: Chloroform

Volume: 0.1 ml/day

Route of Administration: topical application in external ear canal of each rabbit

LENGTH of STUDY: 28 DAYS

FOOD Lot #: P.O. 5151

PENNSYLVANIA SCALE # 6

calibrated week of 13 July 1981 and 10 Aug

Mettler #: _____

calibrated week of 13 July 1981 and 10 August 1981

LIGHT CYCLE checked on 7-13-81 12 h. light - 12 h d - PMC

COMPOUND PREPARATION:

100% solution: TEST ARTICLE as received moistened with chloroform to form a paste, 100 mg/Animal.

10% solution: 100 mg compound suspended in 0.9 ml chloroform

0.1% solution: 10 mg compound suspended in 9.9 ml chloroform
PMC

CONTROL EAR (L) : 0.1 ml Chloroform as received.

1% solution: 100 mg compound suspended in 9.9 ml chloroform
PMC

Robert Nammitt 9/17/81

To Page No. _____

Witnessed & Understood by me,
V. Malloy

Date
9/7/81

Invented by
Patricia M. Carey
Received by: Patricia M. Carey

Date
9-7-81

ASSAY OF COMEDOGENICITY IN THE RABBIT EAR

BOOK No. 296

Form No. 22

Body Weights in Grams

Dose Level: 100%

Rabbit No.	Initial 7-13-81	DAY 7 7-20-81	DAY 14 7/27/81	DAY 21 8/3/81	DAY 28 Final 8/10/81
251 ♂	2029	2099	2125	2107	2070
252 ♂	2294	2482	2503	2619	2758
253 ♀	2195	2359	2535	2509	2708
254 ♀	2128	2396	2535	2573	2591
	PMC	PMC	PMC	PMC	PMC

Dose Level: 10%

Rabbit No.	Initial 7-13-81	DAY 7 7-20-81	DAY 14 7/27/81	DAY 21 8/3/81	DAY 28 Final 8/10/81
255 ♂	2364	2570	2741	2774	2954
256 ♂	2466	2613	2516	2657	2833
257 ♀	2611	2859	3018	3126	3309
258 ♀	2235	2240	2313	2428	2644
	PMC	PMC	PMC	PMC	PMC

Dose Level: 0.1%

Rabbit No.	Initial 7-13-81	DAY 7 7-20-81	DAY 14 7/27/81	DAY 21 8/3/81	DAY 28 Final 8/10/81
259 ♂	2572	2745	2721	2875	2823
260 ♂	2392	2633	2494	2613	2773
261 ♀	2148	2408	2617	2613	2808
262 ♀	2046	2012	1953	2015	2203
	PMC	PMC	PMC	PMC	PMC

Evaluation of Comedogenicity

⊙ EAR = Test Article

⊙ EAR = Control

Rabbit #	Initial		DAY 7		Day 14		Day 21		DAY 28		Scale:
	(R)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	
251 ♂	0	0	0	0	0	0	0	0	0	0	0 = NONE 1 = SLIGHT 2 = MODERATE 3 = SEVERE
252 ♂	0	0	0	0	0	0	0	0	0	0	
253 ♀	0	0	0	0	0	0	0	0	0	0	
254 ♀	0	0	0	0	0	0	0	0	0	0	
255 ♂	0	0	0	0	0	0	0	0	0	0	
256 ♂	0	0	0	0	0	0	0	0	0	0	
257 ♀	0	0	0	0	0	0	0	0	1	0	
258 ♀	0	0	0	0	0	0	0	0	0	0	
259 ♂	0	0	0	0	0	0	0	0	0	0	
260 ♂	0	0	0	0	0	0	0	0	0	0	
261 ♀	0	0	0	0	0	0	0	0	0	0	
262 ♀	0	0	0	0	0	0	0	0	0	0	

Robert W. [Signature]
9/7/81
To Page No. 11

Witnessed & Understood by me.

V. Malloy

Date

9/7/81

Invented by

Patricia M. Carson

Date

9/7/81

Researched by

Patricia M. Carson

ASSAY of COMEDOGENICITY in the RABBIT EAR

Project No. **#425-ET-001-81**
 Book No. **236**

Page No. **1**

Test Article:

Rabbit #	Dose	Volume (ml)	Time	Date
251 ♂	100%	0.1	2:53	7/5/81
252 ♂	100%	0.1		
253 ♀	100%	0.1		
254 ♀	100%	0.1		
255 ♂	10%	0.1	2:43	
256 ♂	10%	0.1		
257 ♀	10%	0.1		
258 ♀	10%	0.1		
259 ♂	0.1%	0.1	2:48	
260 ♂	0.1%	0.1		
261 ♀	0.1%	0.1		
262 ♀	0.1%	0.1	2:54	

7-15-81 PMC

7-13-81 Temp: 29°C Relative Humidity: 82%
 7-14-81 Temp: 29°C Relative Humidity: 62%
 7-15-81 Temp: 27°C Relative Humidity: 58%
 7-16-81 Temp: 28°C Relative Humidity: 77%
 7-17-81 Temp: 27°C Relative Humidity: 80%
 Observations: 7/13/81: no signs. PMC.
 7/14/81: no signs. PMC.
 7-15-81: no signs. PMC.
 7-16-81: #251: slight redness @ ear;
 #252, 260, 262: epidermal sloughing
 @ ear; #253, 255 through 259, and
 #261: epidermal sloughing @ + @ ear.
 #254: epidermal sloughing @ ear.

Rabbit #	Dose	Volume (ml)	Time	Date
251	100%	0.1	2:17	7/14/81
252	100%	0.1		
253	100%	0.1		
254	100%	0.1		
255	10%	0.1	2:23	
256	10%	0.1		
257	10%	0.1		
258	10%	0.1		
259	0.1%	0.1	2:27	
260	0.1%	0.1		
261	0.1%	0.1		
262	0.1%	0.1	2:30	

7-14-81 PMC

Rabbit #	Dose	Volume (ml)	Time	Date
251	100%	0.1	1:53	7/17/81
252	100%	0.1		
253	100%	0.1		
254	100%	0.1		
255	10%	0.1	2:00	
256	10%	0.1		
257	10%	0.1		
258	10%	0.1		
259	0.1%	0.1	2:06	
260	0.1%	0.1		
261	0.1%	0.1		
262	0.1%	0.1	2:11	

7-17-81 PMC

Rabbit #	Dose	Volume (ml)	Time	Date
251	100%	0.1	2:15	7/13/81
252	100%	0.1		
253	100%	0.1		
254	100%	0.1		
255	10%	0.1	2:20	
256	10%	0.1		
257	10%	0.1		
258	10%	0.1		
259	0.1%	0.1	2:25	
260	0.1%	0.1		
261	0.1%	0.1		
262	0.1%	0.1	2:30	

7-13-81 PMC

Rabbit #	Dose	Volume (ml)	Time	Date
251	100%	0.1	2:40	7/16/81
252	100%	0.1		
253	100%	0.1		
254	100%	0.1		
255	10%	0.1	2:45	
256	10%	0.1		
257	10%	0.1		
258	10%	0.1		
259	0.1%	0.1	2:50	
260	0.1%	0.1		
261	0.1%	0.1		
262	0.1%	0.1	2:55	

7-16-81 PMC

To Page No. **1**

Witnessed & Understood by me
V. Mallow

Date
 9/7/81

Invented by
 Patricia H. Casey
 Rec'd by
 Patricia H. Casey

Date
 9-7-81

Assay of Camodocanin in the Rabbit Ear

Project No. PH 45-21-001-31
Book No. 296

TEST RESULTS:

Rabbit #	Dose	Volume (ml)	Time	Date
251 ♂	100%	0.1	2:45	7/26/81
252 ♂	100%	0.1		
253 ♀	100%	0.1		
254 ♀	100%	0.1		
255 ♂	10%	0.1	2:50	
256 ♂	10%	0.1		
257 ♀	10%	0.1		
258 ♀	10%	0.1		
259 ♂	0.1%	0.1	2:55	
260 ♂	0.1%	0.1		
261 ♀	0.1%	0.1		
262 ♀	0.1%	0.1	3:00	

Rabbit #	Dose	Volume (ml)	Time	Date
251 ♂	100%	0.1	2:55	7/21/81
252 ♂	100%	0.1		
253 ♀	100%	0.1		
254 ♀	100%	0.1		
255 ♂	10%	0.1	2:40	
256 ♂	10%	0.1		
257 ♀	10%	0.1		
258 ♀	10%	0.1		
259 ♂	0.1%	0.1	2:45	
260 ♂	0.1%	0.1		
261 ♀	0.1%	0.1		
262 ♀	0.1%	0.1	2:50	

Rabbit #	Dose	Volume (ml)	Time	Date
251 ♂	100%	0.1	2:45	7/21/81
252 ♂	100%	0.1		
253 ♀	100%	0.1		
254 ♀	100%	0.1		
255 ♂	10%	0.1	2:50	
256 ♂	10%	0.1		
257 ♀	10%	0.1		
258 ♀	10%	0.1		
259 ♂	0.1%	0.1	2:55	
260 ♂	0.1%	0.1		
261 ♀	0.1%	0.1		
262 ♀	0.1%	0.1	3:00	

X				
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Rabbit #	Dose	Volume (ml)	Time	Date
251	100%	0.1	2:20	7/21/81
252	100%	0.1		
253	100%	0.1		
254	100%	0.1		
255	10%	0.1	2:25	
256	10%	0.1		
257	10%	0.1		
258	10%	0.1		
259	0.1%	0.1	2:30	
260	0.1%	0.1		
261	0.1%	0.1		
262	0.1%	0.1	2:37	

Rabbit #	Dose	Volume (ml)	Time	Date
251	100%	0.1	2:15	7/21/81
252	100%	0.1		
253	100%	0.1		
254	100%	0.1		
255	10%	0.1	2:25	
256	10%	0.1		
257	10%	0.1		
258	10%	0.1		
259	0.1%	0.1	2:30	
260	0.1%	0.1		
261	0.1%	0.1		
262	0.1%	0.1	2:35	

To Page No. 14

Witnessed & Understood by me.

H. Malloy

Date

9/7/81

Prepared by

Patience N. Casey

Recorded by

Patience N. Casey

Date

9-7-81

AMM - CANNIBALISM IN THE RABBIT EAR

TEST ARTICLE

Refid	Date	Time	Inc	Notes
2510	10/7/0	01 01	2:15	950
2520	10/7/0	01 01		
2530	10/7/0	01 01		
2540	10/7/0	01 01	2:50	
2550	10/7/0	01 01	8:35	
2560	10/7/0	01 01		
2570	10/7/0	01 01		
2580	10/7/0	01 01	8:05	
2590	01/20/1	01 01	3:05	
2600	01/20/1	01 01		
2610	01/20/1	01 01		
2620	01/20/1	01 01	3:10	

Refid	Date	Time	Inc	Notes
2510	10/7/0	01 01	2:30	8/4/81
2520	10/7/0	01 01		
2530	10/7/0	01 01		
2540	10/7/0	01 01		
2550	10/7/0	01 01	2:35	
2560	10/7/0	01 01		
2570	10/7/0	01 01		
2580	10/7/0	01 01		
2590	01/20/1	01 01	2:40	
2600	01/20/1	01 01		
2610	01/20/1	01 01		
2620	01/20/1	01 01	2:45	

Refid	Date	Time	Inc	Notes
2510	10/7/0	01 01	1:45	9/3/81
2520	10/7/0	01 01		
2530	10/7/0	01 01		
2540	10/7/0	01 01		
2550	10/7/0	01 01	1:55	
2560	10/7/0	01 01		
2570	10/7/0	01 01		
2580	10/7/0	01 01		
2590	01/20/1	01 01	2:05	
2600	01/20/1	01 01		
2610	01/20/1	01 01		
2620	01/20/1	01 01	2:15	

Refid	Date	Time	Inc	Notes
2510	10/7/0	01 01	2:15	8/7/81
2520	10/7/0	01 01		
2530	10/7/0	01 01		
2540	10/7/0	01 01		
2550	10/7/0	01 01	2:20	
2560	10/7/0	01 01		
2570	10/7/0	01 01		
2580	10/7/0	01 01		
2590	01/20/1	01 01	2:25	
2600	01/20/1	01 01		
2610	01/20/1	01 01		
2620	01/20/1	01 01	2:50	

Refid	Date	Time	Inc	Notes
2510	10/7/0	01 01	2:50	8/6/81
2520	10/7/0	01 01		
2530	10/7/0	01 01		
2540	10/7/0	01 01		
2550	10/7/0	01 01	2:55	
2560	10/7/0	01 01		
2570	10/7/0	01 01		
2580	10/7/0	01 01		
2590	01/20/1	01 01	3:00	
2600	01/20/1	01 01		
2610	01/20/1	01 01		
2620	01/20/1	01 01	3:05	

To Page No. **16**

Witnessed & Understood by me. **T. J. Maloney** Date **9/7/81**

Initiated by **Patricia M. Cully** Date **9-7-81**

Approved by **H. M. ...**

Page No. 15

- Observations: 7-17-81: Rabbits #252, 253, 255 through 261: epidermal sloughing @ and @ external ear canals; #251, #254 epidermal sloughing @ ear; #262 epidermal sloughing @ ear. PMC.
- 7-20-81: Temp: 24°C Relative Humidity: 74% All animals exhibit scaling in both @ + @ external ear canals at the site of vehicle and/or compound application. PMC
- 7-21-81: Temp: 22°C Relative Humidity: 82% All animals exhibit scaling in both @ and @ external ear canals at application site. PMC
- 7-22-81: Temp: 22°C Relative Humidity: 86% All animals exhibit slight scaling in both ear canals at application site. AK
- 7-23-81: Temp: 21°C Relative Humidity: 82% All animals show slight scaling in both ear canals, #259 has moderate erythema AK
- 7-24-81: Temp: 22°C Relative Humidity: 73% All animals exhibit scaling in both external ear canals; #259 moderate erythema both ears. AK
- 7-27-81: Temp: 23°C Relative Humidity: 82% All animals exhibit slight to moderate scaling in both external ear canals PMC. Animal #259 moderate erythema both ears; Rabbit #260 diarrhea;
- 7-28-81: Temp: 23°C Relative Humidity: 84% All animals exhibit slight scaling both external ear canals; #256, 260 diarrhea; #259 moderate erythema both ear canals. PMC
- 7-29-81: Temp: 23°C Relative Humidity: 69% #259 moderate erythema both external canals at application site; #260 diarrhea; All animals exhibit slight scaling in both external canals. Cage Change. PMC
- 7-30-81: Temp: 23°C Relative Humidity: 65% #258 slight erythema @ canal; #259 slight erythema @ canal; #260 diarrhea; all animals exhibit slight scaling both external ear canals. PMC
- 7-31-81: Temp: 23°C Relative Humidity: 73% #260 diarrhea; all animals exhibit very slight scaling both external canals. PMC
- 8-3-81: Temp: 22°C Relative Humidity: 86% #251 slight erythema @ canal; slight scaling @ ear canal: #251, 252, 253, 254, 255, 256, 257, 259, 260, 262, slight scaling @ ear canal: #253, 254, 256, 257, 258, 259, 261, 262. PMC.
- 8-4-81: Temp: 23°C Relative Humidity: 78% All animals exhibit slight scaling of both external ear canals. PMC.
- 8-5-81: Temp: 22°C Relative Humidity: 72% All animals exhibit slight scaling both external ear canals. PMC

To Page No. 17

read & Understood by me.

J. Mallowy

Date

9/2/81

Inventor

Patricia M. Carey

Recorded by Patricia M. Carey

Date

9-7-81

Observations: 7-17-81 200 P.M.C.

8-6-81. Temp: 22°C Relative Humidity: 73% #258 erythema @ canal;
All animals exhibit slight to moderate scaling both external canals. P.M.C.

8-7-81. Temp: 23°C Relative Humidity: 78% #258 erythema @ ear; all animals
exhibit slight scaling both external ear canals. P.M.C.

TERMINAL Necropsy: 8-10-81

#251: No visible lesions.

#252: No visible lesions.

#253: No visible lesions.

#254: No visible lesions.

#255: No visible lesions.

#256: No visible lesions.

#257: No visible lesions.

#258: No visible lesions.

#259: No visible lesions.

#260: Tiny yellow-white, hard nodule @ ^{side of} earal ~~face~~ capsule.

#261: No visible lesions.

#262: No visible lesions. P.M.C.

To Page No. 44
18

Used & Understood by me.
T.O. Maloney

Date
9/7/81

Invented by
Patricia M. Carey
Recorded by
H. P. ...

Date
9-7-81

106
P.H.

Page No. 18

TEST ARTICLE:

Dose Level: 1%

Body Weights

Rabbit #	initial	Day 7 8/10/81	Day 14 8/17/81	Day 21 8/24/81	Day 28 9/7/81
297 ♂	2260	2080	2261	2241	2364
298 ♂	2020	2188	2341	2333	2499
299 ♀	2227	2270	2351	2447	2570
300 ♀	2055	2255	2501	2703	2560

PMC 8/10/81 8/17/81PMC 8/24/81PMC 8/31/81PMC 9/7/81PMC

EVALUATION OF COMEDOGENICITY

Rabbit #	initial		Day 7		Day 14		Day 21		Day 28	
	(R)	(L)	(R)	(L)	(R)	(L)	(R)	(L)	(R)	(L)
297 ♂	0	0	0	0	0	0	0	0	0	0
298 ♂	0	0	0	0	0	0	0	0	0	0
299 ♀	0	0	0	0	0	0	0	0	0	0
300 ♀	0	0	0	0	0	0	0	0	0	0

PMC 8/10/81 8/17/81PMC 8/24/81PMC 8/31/81PMC 9/7/81PMC

(L) = Control
(R) = Test Article
SCALE:
0 = NONE
1 = SLIGHT
2 = MODERATE
3 = SEVERE

Observations: 8/10/81: Temp: 21°C Relative Humidity: 83% No signs. PMC
8/11/81: Temp: 21°C Relative Humidity: 81% No signs. PMC
8/12/81: Temp: 21°C Relative Humidity: 81% No signs. PMC
8/13/81: Temp: 23°C Relative Humidity: 74% No signs. PMC
8/14/81: Temp: 21°C Relative Humidity: 73% No signs. R/L
8/17/81: Temp: 21°C Relative Humidity: 76%

#297, 298, 299, 300 slight scaling both external canals; #297 slight erythema both canals. PMC

8-18-81: Temp: 22°C Relative Humidity: 73%; slight scaling both external ear canals all animals. PMC

8-19-81: Temp: 22°C; Relative Humidity: 69%; slight scaling both external ear canals all animals. PMC

8-20-81: Temp: 21°C Relative Humidity: 87% All animals exhibit slight to moderate scaling in both external ear canals. PMC

8-21-81: Temp: 22°C Relative Humidity: 73%; All animals exhibit slight scaling in both external ear canals; #298 slight erythema (L) canal. PMC

8-24-81: Temp: 21°C Relative Humidity: 86%; All animals slight scaling both external ear canals. PMC. cage change

8-25-81: Temp: 21°C Relative Humidity: 76% All animals slight scaling both external ear canals. PMC

To Page No. 45

Witnessed & Understood by me.

Date

Initiated by

Date

J. D. Malloy

9/7/81

Patricia M. Carey
Revised by: M. M. ...

9-7-81

Study of Concealment in Rabbit Ears

Project No. PH425-ET-001-81

Book No. 630

Tag No.	Subid #	Sex	Dist.	W	D	Time	Date	
	297	♂	190	0.1	0.1	1:50	8/10/81	PMC
	298	♂	190	0.1	0.1		8/10/81	
	299	♀	190	0.1	0.1		8/10/81	
	300	♀	190	0.1	0.1	1:57	8/10/81	
	297	♂	190	0.1	0.1	2:30	8/11/81	PMC
	298	♂	190	0.1	0.1		8/11/81	
	299	♀	190	0.1	0.1		8/11/81	
	300	♀	190	0.1	0.1	2:35	8/11/81	
	297	♂	190	0.1	0.1	2:50	8/12/81	PMC
	298	♂	190	0.1	0.1		8/12/81	
	299	♀	190	0.1	0.1		8/12/81	
	300	♀	190	0.1	0.1	2:55	8/12/81	
	297	♂	190	0.1	0.1	2:05	8/13/81	PMC
	298	♂	190	0.1	0.1		8/13/81	
	299	♀	190	0.1	0.1		8/13/81	
	300	♀	190	0.1	0.1	2:10	8/13/81	
	297	♂	190	0.1	0.1	3:15	8/14/81	PM
	298	♂	190	0.1	0.1		8/14/81	
	299	♀	190	0.1	0.1		8/14/81	
	300	♀	190	0.1	0.1	3:20	8/14/81	
	297	♂	190	0.1	0.1	3:00	8/17/81	PMC
	298	♂	190	0.1	0.1		8/17/81	
	299	♀	190	0.1	0.1		8/17/81	
	300	♀	190	0.1	0.1	3:05	8/17/81	
	297	♂	190	0.1	0.1	2:40	8-18-81	PMC
	298	♂	190	0.1	0.1		8-18-81	
	299	♀	190	0.1	0.1		8-18-81	
	300	♀	190	0.1	0.1	2:45	8-18-81	
	297	♂	190	0.1	0.1	2:45	8-19-81	PMC
	298	♂	190	0.1	0.1		8-19-81	
	299	♀	190	0.1	0.1		8-19-81	
	300	♀	190	0.1	0.1	2:50	8-19-81	
	297	♂	190	0.1	0.1	2:10	8/20/81	PMC
	298	♂	190	0.1	0.1		8/20/81	
	299	♀	190	0.1	0.1		8/20/81	
	300	♀	190	0.1	0.1	2:15	8/20/81	

To Page No. 46

Read & Understood by me.

D. Malloy

Date

9/7/81

Invented by

Fannie M. Carey

Recorded by

H. H. ...

Date

9-7-81

Observations (continued from page 44):

8-26-81: Temp: 21°C Relative Humidity: 77% Slight scaling both external ear canals all animals P.M.C.

8-27-81: Temp: 23°C; Relative Humidity: 69% P.M.C. Slight scaling both external ear canals all ¹⁰⁰ rabbits P.M.C.

8/28/81: Temp: 22°C; Relative Humidity: 69% Slight scaling both external ear canals all animals. P.M.C.

8/31/81: Temp: 22°C; Relative Humidity: 73% Very slight scaling both external ear canals all animals. P.M.C.

9-1-81: Temp: 22°C; Relative Humidity 74% Slight scaling both external ear canals all animals. P.M.C.

9-2-81: Temp: 22°C Relative Humidity: 73% Slight scaling both external ear canals all animals. P.M.C.

9-3-81: Temp: 22°C Relative Humidity: 77% Slight scaling both external ear canals all animals. P.M.C.

9-4-81: Temp: 22°C Relative Humidity: 77% Slight scaling both external ear canals all animals. P.M.C.

9-7-81 Temp: 22°C; Relative Humidity, 69% P.M.C.

9-7-81: Terminal Necropsy:

Rabbit # 297: No visible lesions.

Rabbit # 298: No visible lesions.

Rabbit # 299: No visible lesions.

Rabbit # 300: No visible lesions P.M.C.

Study Terminated 9/7/81 P.M.C.

To Page No. _____

Read & Understood by me.

D. Malboue

Date

9/7/81

Investigated by -

Patricia M. Carey

Date

9/7/81

Recorded by -

M. P. Davis

PHARMAKON LABORATORIES
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 425-ST-001-81

The following inspections were performed:

Interval	Date
<u>Pre dosing Phase</u>	<u>7/13/81</u>
<u>Dosing Phase</u>	<u>7/13/81</u>
<u>Recruiy Phase</u>	<u>8/10/81</u>
<u>Reporting Phase</u>	<u>9/29/81</u>

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

9/29/81
Date

Leslie Mass
Quality Assurance Unit

PHARMAKON RESEARCH INTERNATIONAL, INC.
HAVERLY, PENNSYLVANIA 18471

PHONE
(717) 224-2211

Contains No CBI

Primary Eye Irritation

18)

PH 421-ET-010-86

Saytex 102
Lot # 4540-1P

Submitted to

Ethyl Corporation
Baton Rouge, Louisiana

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

March 24, 1986
Date

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

March 24, 1986
Date

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

March 24, 1986
Date

0 0 2 9

Primary Eye Irritation

PH 421-ET-010-86

**Saytex 102
Lot # 4540-1P**

SUMMARY

In order to assess the irritant and/or the corrosive effects on the eyes of rabbits, Saytex 102, Lot # 4540-1P, was instilled into the right eye of each of six rabbits. Observations were recorded at 1, 24, 48 and 72 hours after treatment. No positive ocular scores were recorded during the course of the study. The sponsor was contacted and the study was terminated after the 72 hour observation period.

Based upon the observations made in the Primary Eye Irritation Test, Saytex 102, Lot # 4540-1P, was determined not to be an eye irritant.

0025

Primary Eye Irritation

PH 421-ET-010-86

Sponsor:

**Ethyl Corporation
451 Florida
Baton Rouge, Louisiana 70801**

Test Facility:

**Pharmakon Research International, Inc.
Waverly, Pennsylvania 18471**

**Test Facility
S.O.P. No.:**

PH-421

Study No.:

PH 421-ET-010-86

**Purpose of
the Study:**

**To determine the irritant and/or corrosive effects on
eyes of rabbits.**

**Ownership of
the Study:**

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

Study Monitor:

Mr. Michael Pinkerton, Ethyl Corporation

Study Director:

**Victor T. Mallory, B.S., RLAT, Pharmakon Research
International, Inc.**

**Technical
Performance:**

**Yvonne Coccetti, LAT, Gary G. Bolus, B.A. and Susan A.
Schirick, A.S., ALAT**

**Q.A.U.
Responsible
Personnel:**

Leslie Maas, B.S.

**Dates of
Performance:**

March 12, 1986 through March 15, 1986

**Good Laboratory
Practices
Statement:**

**This study was conducted in compliance with the Good
Laboratory Practice Regulations. 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 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.

Recordings:

Standard Pharmakon Notebook

Notebook Reference:

Notebook # 1096, pages 100-101

Raw Data:

Copies of notebook recordings attached.

TEST ARTICLE

Compound Description:

Saytex 102 -- white powder

Lot No.:

4540-1P

Base Factor:

Not applicable

Amount Submitted:

1 pound

Date Submitted:

March 10, 1986

Special Handling Instructions:

Standard precautions

Analysis of Purity:

The identity, purity, strength and stability 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:

Albino New Zealand White

Supplier (Source):

Sgarlat's Rabbitry, Harvey's Lake, Pennsylvania

Sex:

Male and female

Age at Initiation: Healthy adult animals

No. in Study: Six (6)

Method and Justification of Randomisation: Selection 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 was removed three times per week. 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 Analysis:

Availability - fresh tap water, ad libitum. Water is monitored for contaminants at periodic intervals according to Standard Operating Procedure PH-018.

METHODS

Rationale for Test System:

A variety of experimental animals have been used, but it is recommended that testing will be performed using healthy adult albino rabbits.

Compound Preparation:

Dosed as received.

Rationale for Dose Selection:

According to EPA Health Effect Test Guidelines EPA 560/6-82-001.

Dose Administration:

100 mg/eye

Vehicle:

Not applicable

Route of Administration:

The test article was administered directly into the eye.

Rationale for Route of Administration:

To evaluate the irritant potential of the test article on the eye.

Frequency and Duration of Administration:

Once (1)

No. and Description of Animals Per Dose Group:

Six (6) (three males and three females)

No. and Code of Dose Group:

Rabbit No.
5891-5896

Treatment
100 mg/right eye

Length of Study:

Seventy-two (72) hours

0029

Method of Study
Performance:

Both eyes of each experimental animal provisionally selected for testing were examined within 24 hours before testing started by the same procedure used during the test examination. Animals showing eye irritation, ocular defects or pre-existing corneal injury were not used. The test substance was placed in the conjunctival sac of one eye of each animal after gently pulling the lower lid away from the eyeball. The lids were then gently held together for about one second in order to limit loss of the material. The other eye, which remained untreated, served as a control.

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

The eyes were examined at 1, 24, 48 and 72 hours after treatment. The grades of ocular reaction (Table I) were recorded at each examination.

Scoring:

An animal exhibited a positive reaction when the test substance produced one or more of the following signs: ulceration of the cornea (other than a fine stippling), opacity of the cornea (other than a slight dulling of the normal luster), inflammation of the iris (other than a slight deepening of the rugae or a light hyperemia of the circumcorneal blood vessels), or an obvious swelling in the conjunctivae (excluding the cornea and iris) with partial eversion of the eyelids and a diffuse crimson color with individual vessels not easily discernible.

Primary Eye Irritation
FN 421-ET-010-86

Grading:

Grading of irritation is according to the method of Draize, J.H. (1965), Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics - Dermal Toxicity, pg. 49-52. Association of Food and Drug Officials of the U.S., Topeka, Kansas, and Draize, J.H. (1959), Appraisal of Chemicals in Foods, Drugs and Cosmetics, pg. 36-45. Association of Food and Drug Officials of the U.S., Austin, Texas, and Draize, J.H., et. al., J. Pharm. Exp. Ther. 82: 377-390, 1944 (see Table I). Serious effects, such as pannus or blistering of the conjunctivae and other effects indicative of corrosive action shall be reported separately.

Criteria for
Classification of
a Test Article:

The test will be considered positive if four or more of the animals in the test group exhibit a positive reaction. If only one animal exhibits a positive reaction, the test shall be regarded as negative. If two or three animals exhibit a positive reaction, the study director in charge of the test may designate the substance to be an irritant unless the sponsor, at additional cost, suggests repeating the test using a different group of six animals. The second test shall be considered positive if three or more of the animals exhibit a positive reaction.

Results:

Individual rabbit data on body weights and scores of irritation may be found in the attached copies of the notebook recordings or in Table II. The pH of the

test article was unobtainable. Observations were recorded at 1, 24, 48 and 72 hours. No positive ocular scores were recorded during the course of the study. The sponsor was contacted and the study was terminated after the 72 hour observation period.

Conclusions:

Based upon the results of the Primary Eye Irritation Test, Saytex 102, Lot # 4540-1P, was determined not to be an eye irritant.

Table I
Scale for Scoring Ocular Lesions*

(1)	Cornea	
(A)	Opacity-degree of density (area most dense taken for reading)	
	No opacity0
	Scattered or diffuse area, details of iris clearly visible1*
	Easily discernible translucent areas, details of iris slightly obscured2
	Opalescent areas, no details of iris visible, size of pupil barely discernible.3
	Opaque, iris invisible4
(2)	Iris	
(A)	Values	
	Normal0
	Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reactions is positive).1*
	No reaction to light, hemorrhage, gross destruction (any or all of these)2
(3)	Conjunctivae	
(A)	Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris).	
	Vessels normal0
	Vessels definitely injected above normal1
	More diffuse, deeper crimson red, individual vessels not easily discernible.2*
	Diffuse beefy red.3
(B)	Chemosis	
	No swelling.0
	Any swelling above normal (includes nictitating membrane).1
	Obvious swelling with partial eversion of lids2*
	Swelling with lids about half closed3
	Swelling with lids about half closed to completely closed.4

* Figures indicate lowest grades considered positive under the Federal Hazardous Substances Act Regulations at 16 CFR 1500.42.

TABLE II

Primary Eye Irritation
Draize Scores

Saytex 102
Lot # 4540-1P

PH 421-ET-010-86

Rabbit No.	Sex	Observations	1 Hr.	24 Hr.	48 Hr.	72 Hr.
5891		Cornea*	0	0	0	0
		Iris	0	0	0	0
	M	Conjunctivae	0,0	0,0	0,0	0,0
5892		Cornea	0	0	0	0
		Iris	0	0	0	0
	M	Conjunctivae	0,0	0,0	0,0	0,
5893		Cornea	0	0	0	0
		Iris	0	0	0	0
	M	Conjunctivae	1,0	1,0	0,0	0,0
5894		Cornea	0	0	0	0
		Iris	0	0	0	0
	F	Conjunctivae	1,0	0,0	0,0	0,0
5895		Cornea	0	0	0	0
		Iris	0	0	0	0
	F	Conjunctivae	0,0	0,0	0,0	0,0
5896		Cornea	0	0	0	0
		Iris	0	0	0	0
	F	Conjunctivae	0,0	0,0	0,0	0,0

* Cornea = degree of opacity
Iris = degree of iritis
Conjunctivae = redness, chemosis

PHARMAKON RESEARCH INTERNATIONAL, INC.

EMERYVILLE, PENNSYLVANIA 15127

Compliance Statement

PHONE
(717) 688-3411

This study was conducted in compliance with the Principles of Good Laboratory Practice (GLP) as promulgated by the following regulatory agencies:

U.S. Food and Drug Administration, as stated in the Code of Federal Regulations, Title 21, Part 30, revised as of April 1, 1980.

U.S. Environmental Protection Agency as stated in the Federal Register, Vol. 48, No. 230, Tuesday, November 29, 1983.

Organization for Economic Co-operation and Development Guidelines for Testing Chemicals (OECD), ISBN 92-64-12221-4, adopted by the council at its 535th meeting on 12th May, 1981.

Study No.: PH 421-ET-010-86

"To the best of my knowledge, the study was conducted in accordance with applicable Good Laboratory Practice regulations; there were no deviations from these regulations that significantly impacted on study conclusions."


Study Director

March 24, 1986
Date

RAW DATA
APPENDIX

ACUTE TOXICOLOGY STUDY ASSIGNMENT FORM

Title: Primary Eye Irritation Study No. PH401-ET-010-86

Sponsor: Ethyl Corporation Baton Rouge Louisiana

Purpose: To determine the irritant and/or corrosive effects on eyes of rabbits

Method: Ref to protocol PH401

Date of Initiation: 3/12/86 Date of Termination: 3/15/86

Test Article Santex 102 lot #4540-1P Date Recd-3/10/86

and Description: white powder Amt Sub: 1 pound

Vehicle: Not applicable

Dose Levels: 100 mg/eye

Route of Administration: Test article is administered directly into the eye

Animal P.O. #: 030786 ATOX, 022586 ATOX

Species: Rabbit Strain: New Zealand White

Weight Range: Healthy adult Food Lot #: 29021286

No. of Animals on Study: Six (6) Sex: Male Three (3)

Female Three (3)

Scale #: V Light cycle checked: 3/10/86 SMS

Animals shave/fluorescein Not applicable

pH of Test Article: unobtainable

Compound Preparation as received

Dose Level: 100 mg/eye Test Weight: N/A Final Volume: N/A

_____	_____	_____

Comments: Test article was dosed as received 3/12/86 SMS

Investigator: Susan J. Schield Date 3/15/86

Study Director: Victor Malloy Date 3/15/86

Primary Eye Irritation Study
Scoring of Ocular Lesions (non-rinsed)

Sponsor: Ethyl Corporation

Study Number: PH 421-ET-010-86

Test Article: Sandtex 102

Lot Number: 4540-1P

Rabbit Number	Sex	Time of Dose	Observations								
			1 Hour After Treatment				24 Hours After Treatment				
			Cornea	Iris	R°	C°	Cornea	Iris	R°	C°	
5891	♂	10:10	0	0	0	0	0	0	0	0	0
5892	♂		0	0	0	0	0	0	0	0	0
5893	♂		0	0	1	0	0	0	0	1	0
5894	♀		0	0	1	0	0	0	0	0	0
5895	♀		0	0	0	0	0	0	0	0	0
5896	♀	10:14	0	0	0	0	0	0	0	0	0
Initials		3/12/86 JL/CSB			3/12/86	JL				3/13/86	SRS

Rabbit Number	Sex	Observations							
		48 Hours After Treatment				72 Hours After Treatment			
		Cornea	Iris	R°	C°	Cornea	Iris	R°	C°
5891	♂	0	0	0	0	0	0	0	0
5892	♂	0	0	0	0	0	0	0	0
5893	♂	0	0	0	0	0	0	0	0
5894	♀	0	0	0	0	0	0	0	0
5895	♀	0	0	0	0	0	0	0	0
5896	♀	0	0	0	0	0	0	0	0
Initials				3/14/86	SRS			3/15/86	JL

*R = Redness, C = Chemosis

Rabbit Number	Sex	Weight (kilograms)	
		Initial	Final
5891	♂	2.088	2.216
5892	♂	2.340	2.434
5893	♂	2.021	2.052
5894	♀	1.859	2.013
5895	♀	1.957	2.157
5896	♀	1.849	1.814

3/12/86 JL/CSB 3/15/86 JL

Observations and Comments:

All animals appear normal 3/15/86 SRS

John L. Malloy 3/15/86

PHARMAKON RESEARCH INTERNATIONAL, INC.

WAVERLY, PENNSYLVANIA 18471

PHONE
(717) 988-2411

Protocol - 421

Primary Eye Irritation

Sponsor: Ethyl Corporation
8000 GSRI Avenue
Baton Rouge, Louisiana 70820

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

Test Facility
S.O.P. No.: PH-421

Study No.: To be assigned at study initiation. PH 421-ET-010-86

Purpose of the Study: To determine the irritant and/or corrosive effects on eyes of rabbits.

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: Victor T. Mallory, B.S., Pharmakon Research International, Inc.

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

Dates of Performance: The study will begin within one month of the receipt of the test article 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. 48, No. 230, Tuesday, November 29, 1983.

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
Grading and scoring of irritation according to the method of Draize
Description of lesions
pH of the test article

TEST SYSTEM

Species: Rabbit

Strain: Albino New Zealand White

Supplier: Perfection Breeders, Inc., Douglasville, Pennsylvania
(Source): or from any U.S.D.A. acceptable source.

Sex: Male and female

Weight at
Initiation: Healthy adult animals

No. on Study: Six (6) 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 - Maintained at a temperature of 20°C ± 3°C and a humidity of 30 to 70%.

Housing: Rabbits will be 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 will be removed daily. Cages and feeders will be sanitized every two weeks.

Food: Wayne Rabbit Ration^R, ad libitum, or any other acceptable Lab Chow, checked daily and added or replaced as needed. Feeders are designed to reduce soiling, bridging, and scattering.

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

Primary Eye Irritation

Water Analysis:

Availability - fresh tap water, *ad libitum*. Water is monitored for contaminants at periodic intervals according to Standard Operating Procedure PH-018.

METHODS

Rationale for Test System:

A variety of experimental animals have been used, but it is recommended that testing will be performed using healthy adult albino rabbits. Commonly used laboratory strains will be used.

Rationale for Dose Selection:

According to EPA Health Effect Test Guidelines EPA 560/6-82-001.

Dose Administration:

For testing liquids, a dose of 0.1 ml is recommended. In testing solids, pastes, and particulate substances, the amount used will have a volume of 0.1 ml or a weight of not more than 100 mg (the weight will always be recorded). If the test material is solid or granular, it will be ground to a fine dust. The volume of particulates will be measured after gently compacting them (e.g. by tapping the measuring container). To test a substance contained in a pressurized aerosol container, the eye will be held open and the test substance will be administered in a single burst of about one second from a distance of 10 cm directly in front of the eye. The dose will be estimated by weighing the container before and after use. Care will be taken not to damage the eye. Pump sprays will not be used but instead the liquid will be expelled and 0.1 ml collected and instilled into the eye as described for liquids.

Compound Preparation:

The test article is administered as received.

Route of Administration:

The test article is administered directly into the eye.

Rationale for Route of Administration:

To evaluate the irritant potential of the test article on the eye.

Frequency and Duration of Administration:

Once (1)

No. and Description of Rabbits per Dose Groups:

Six (6) (three males and three females)

Length of Study:

Seventy-two (72) hours, or at least twenty-one (21) days if injury persists.

Protocol - 421
Primary Eye Irritation

Method of Study:

Both eyes of each experimental animal provisionally selected for testing will be examined within 24 hours before testing starts by the same procedure to be used during the test examination. Animals showing eye irritation, ocular defects or pre-existing corneal injury will not be used. The test substance will be placed in the conjunctival sac of one eye of each animal after gently pulling the lower lid away from the eyeball. The lids are then gently held together for about one second in order to limit loss of the material. The other eye, which remains untreated, serves as a control. If it is thought that the substance may cause extreme pain, local anesthetic will be used prior to instillation of the test substance. The type and concentration of the local anesthetic will be carefully selected to ensure that no significant differences in reaction to the test substance will result from its use. The control eye will be similarly anesthetized. The eyes of the test animals will not be washed out for 24 hours following instillation of the test substance. At 24 hours, a washout will be used if considered appropriate. The eyes will be examined at 1, 24, 48, and 72 hours. If there is no evidence of irritation at 72 hours, the study will be ended. Extended observation at additional charge to the sponsor may be necessary if there is persistent corneal involvement or other ocular irritation in order to determine the progress of the lesions and their reversibility or irreversibility. In addition to the observations of the cornea, iris and conjunctivae, any other lesions which are noted will be recorded and reported. The grades of ocular reaction using Table I will be recorded at each examination. If the cornea, iris or conjunctivae has not healed completely by the seventh day, the unhealed animals will be retained and re-examined on the 14th day and again at the 21st day, if injury persists.

Scoring:

An animal has exhibited a positive reaction if the test substance has produced at any observation one or more of the following signs: ulceration of the cornea (other than a fine stippling), opacity of the cornea (other than a slight dulling of the normal luster), inflammation of the iris (other than a slight deepening of the rugae or a light hyperemia of the circumcorneal blood vessels) or an obvious swelling in the conjunctivae (excluding the cornea and iris) with partial eversion of the eyelids and a diffuse crimson color with individual vessels not easily discernible.

Data Evaluation:

Data will be summarized in tabular form, showing for each individual animal the irritation scores at the

designated observation time; a description of the degree and nature of irritation; the presence of serious lesions and any effects other than ocular which were observed.

The ocular irritation scores will be evaluated in conjunction with the nature and reversibility or otherwise of the responses observed. The individual scores do not represent an absolute standard for the irritant properties of a material. They will be viewed as reference values and are only meaningful when supported by a full description and evaluation of the observations.

Grading:

Grading of irritation is according to the method of Draize, J. H. (1965), Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics - Dermal Toxicity, pg. 49-52. Association of Food and Drug Officials of the U.S., Topeka, Kansas, and Draize, J. H. (1959), Appraisal of Chemicals in Foods, Drugs and Cosmetics, pg. 36-45. Association of Food and Drugs Officials of the U.S., Austin, Texas, and Draize, J. H., et. al., J. Pharm. Exp. Ther. 82: 377-390, 1944 (see Table I). Serious effects, such as pannus or blistering of the conjunctivae and other effects indicative of corrosive action shall be reported separately.

Conclusions:

The test will be considered positive if four or more of the animals in the test group exhibit a positive reaction. If only one animal exhibits a positive reaction, the test shall be regarded as negative. If two or three animals exhibit a positive reaction, the study director in charge of the test may designate the substance to be an irritant unless the sponsor, at additional cost, suggests repeating the test using a different group of six animals. The second test shall be considered positive if three or more of the animals exhibit a positive reaction.

TABLE I
 Scale for Scoring Ocular Lesions*

(1)	Cornea		
(A)	Opacity-degree of density (area most dense taken for reading)		
	No opacity		0
	Scattered or diffuse area, details of iris clearly visible		1*
	Easily discernible translucent areas, details of iris slightly obscured		2
	Opalescent areas, no details of iris visible, size of pupil barely discernible		3
	Opaque, iris invisible		4
(2)	Iris		
(A)	Values		
	Normal		0
	Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reactions is positive)		1*
	No reaction to light, hemorrhage, gross destruction (any or all of these)		2
(3)	Conjunctivae		
(A)	Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)		
	Vessels normal		0
	Vessels definitely injected above normal		1
	More diffuse, deeper crimson red, individual vessels not easily discernible		2*
	Diffuse beefy red		3
(B)	Chemosis		
	No swelling		0
	Any swelling above normal (includes nictitating membrane)		1
	Obvious swelling with partial eversion of lids		2*
	Swelling with lids about half closed		3
	Swelling with lids about half closed to completely closed		4

*Figures indicate lowest grades considered positive under the Federal Hazardous Substances Act Regulations at 16 CFR 1500.42.

TEST ARTICLES

Name: Decabromodiphenyl Oxide (Saytex 102)

Chemical Abstract No. 1165-19-5

~~CC-625-10-2~~

Lot or Batch No.: 4540-1P

Description: White powder Strength: Neat Purity:

Amount Submitted: 1bs

Expiration Date: 1 year from study initiation date

Special Handling or Storage Instructions: See attached MSDS

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

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

~~Return Test Article/Carrier Mixtures to Sponsor~~

~~Dispose of Test Article/Carrier Mixtures~~

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.

AMENDMENTS Verbal authorization for initiation of study as per telephone conversation with Victor Mallory on 3/11/86. CCF will follow under separate cover.

APPROVAL OF PROTOCOL

Date 3/11/86

Study Monitor Michael N Pinkerton

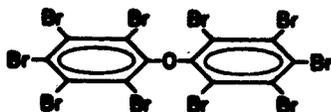
Date 3/14/86

Study Director Victor L. Mallory

Saytex[®]

FLAME RETARDANTS

SAYTEX[®] 102



SAYTEX 102, decabromodiphenyl oxide, is an aromatic bromine-containing additive flame retardant with 83% bromine. It offers these key performance features:

- low addition rate
- excellent heat stability
- low cost

SUGGESTED USES:

high impact polystyrene • thermoset and thermoplastic polyesters • non-drip polypropylene
• crosslinked polyethylene • elastomers • textile treatment

TYPICAL PROPERTIES:

Appearance	off-white free flowing powder
Bromine Content	83%
Initial weight loss by TGA	330°C (648°F)
True density by displacement	3.0 gm/cc
Solubility	insoluble in water, and common organic solvents
Average particle size	3.2 microns

SPECIFICATIONS:

Melting Point Range °C	300-310
Volatiles % @ 125°C	0.1% maximum
Iron ppm	50 maximum
Particle size avg. F.S.S. μ	5 maximum

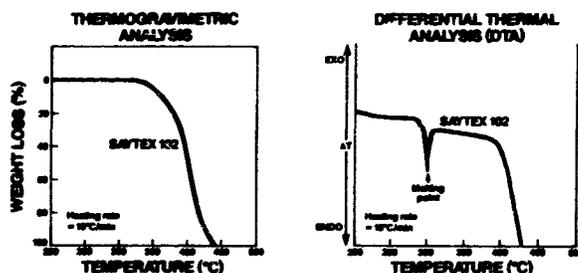
SUGGESTED FORMULATIONS:

The following are practical formulations to obtain the UL-94 test ratings as shown:

	SAYTEX 102 (wt. %)	SAYTEX 102/Sb ₂ O ₃ Ratio	UL-94* Rating
Impact polystyrene	10-13	3/1	V-0
LDPE	6	3/1	V-2
thermoplastic polyester	6-8	3/1	V-0
polypropylene talc filled	20	3/1	V-0

Note:

Special bulletins on use of Saytex 102 in various resins and elastomers are available upon request.



SAFETY AND HANDLING:

Although SAYTEX 102 is not considered hazardous within the Federal Hazardous Substances Act, basic handling precautions are recommended. Avoid prolonged or repeated skin contact. Avoid inhalation of dust or contact with eyes. Protective gloves, chemical safety goggles and approved dust respirators should be worn where there is a chance of exposure. Smoking and eating should be avoided when handling the product.

Complete material safety data and a summary of toxicological evaluations are available upon request.

*The data reported above is based upon laboratory flammability tests and should not be used to predict performance under actual fire conditions.

The facts stated and the recommendations made in this publication are based on our own research and the research of others, and are believed to be accurate. However, no guarantee of their accuracy is made because we cannot cover every possible contingency in manufacturing equipment and methods. For the same reason, the products discussed are sold without warranty, express or implied, and on the condition that purchasers shall make their own tests to determine the suitability of such products for their particular purposes. Statements concerning the possible use of our products are not intended as recommendations to use our products in the infringement of any patent.