

The BFGoodrich Company
3925 Embassy Parkway
Akron, Ohio 44333-1799

Carl A. Mattia
Vice President
Environmental Health and
Safety Management Systems



INIT 03/08/94

(A)

March 3, 1994



88940000162

Document Control Officer
Chemical Information Division
Office of Toxic Substances
Room E-108
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

OFFICE OF TOXIC SUBSTANCES
U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Re: Notice of Substantial Risk Under TSCA Section 8(e)

Dear Sir/Madam:

The B.F.Goodrich Company (BFG) submits this notice in accordance with Section 8(e) of the Toxic Substances Control Act (TSCA) and EPA's numerous interpretive statements.

We are advising the EPA of possible evidence of neurotoxicity in an acute toxicity in rats in a pre-TSCA/pre-GLP study reported March 28, 1974. Although we are making this submission to ensure compliance with the latest expressed indications of the EPA for reporting such information, BFG believes that these test results do not demonstrate a human risk from the manufacture or use of this product.

Background

Good-rite® OBTS (CAS No. 102-77-2) is an accelerator used in the manufacture of synthetic rubber. In the process of updating the MSDS for this product, BFG has identified and reviewed a pre-TSCA/pre-GLP report describing the results of acute toxicity studies in rodents. The report notes neurotoxic signs in rats following acute oral administration. However some of these signs and symptoms were observed only at doses where there was morbidity/mortality. Furthermore, because the study is pre-GLP and the laboratory is no longer in operation, the detail of reporting is limited and a full assessment of the significance of the data is not possible.

March 3, 1994
Page Two

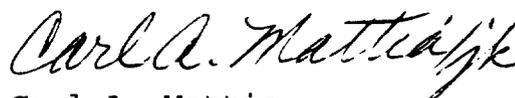
Significance/Assessment of the Data

This chemical has been manufactured for years without any evidence that it poses any significant health concerns. However, we are updating our MSDS for this product.

If you have any questions regarding this submission, please contact Dr. Robert K. Hinderer at (216) 447-5181.

Sincerely,

THE B.F.GOODRICH COMPANY



Carl A. Mattia
Vice President
Environmental, Health and Safety
Management Systems

CAM/jk

AN- 3546

Industrial **BIO-TEST** *Laboratories, Inc.*

1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

Contains No CBI

REPORT TO

B. F. GOODRICH COMPANY

ACUTE TOXICITY STUDIES WITH
FOUR SAMPLES

MARCH 28, 1974

IBT NO. 601-04729

Industrial **BIO-TEST** *Laboratories, Inc.*

1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

March 28, 1974

Mr. W. C. Betchel
Medical and Environmental Laboratories
B. F. Goodrich Company
500 South Main Street
Akron, Ohio 44318

Dear Mr. Betchel:

Re: IBT No. 601-04729 - Acute Toxicity Studies with
Four Samples

We are submitting herewith our laboratory report dated
March 28, 1974, prepared in connection with the above study.

Very truly yours,



J. C. Calandra
President

JCC:bp

REPORT TO

B. F. GOODRICH COMPANY

ACUTE TOXICITY STUDIES WITH
FOUR SAMPLES

MARCH 28, 1974

IBT NO. 601-04729

I. Introduction

Four samples identified as 3630-1-A OBTS, 3630-1-B, recrystallized OBTS, 3630-1-C OBTS, and 3630-1-D OBTS were received from B. F. Goodrich. Eye and primary skin irritation tests in albino rabbits were conducted with each sample. In addition an acute oral toxicity study in albino rats and an acute dermal toxicity study in albino rabbits were conducted with 3630-1-A OBTS.

II. Summary

The results of the acute toxicity studies are presented in Table I.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report prepared by: *Randy Knapp*
Randy Knapp, B.S.
Assistant Toxicologist
Acute Toxicity

Ronald G. Baker
Ronald G. Baker, B.S.
Assistant Toxicologist
Acute Toxicity

Report approved by: *C. W. Mastri*
C. W. Mastri, B.S.
Section Head, Acute Toxicity

M. L. Keplinger
M. L. Keplinger, Ph.D.
Manager, Toxicology

mcb

TABLE I
Summary of Results

Test Material	Acute Oral Toxicity Study - Albino Rats	Acute Dermal Toxicity Study - Albino Rabbits	Eye Irritation Test - Albino Rabbits	Primary Skin Irritation Test - Albino Rabbits
3630-1-A OBTS	Practically Non-Toxic LD ₅₀ = 12,560 mg/kg	Practically Non-Toxic LD ₅₀ > 3,000 mg/kg	Moderately Irritating (19.4/110.0)	Minimally Irritating (0.1/8.0)
3630-1-B, recrystallized OBTS	-	-	Moderately Irritating (14.7/110.0)	Minimally Irritating (0.2/8.0)
3630-1-C OBTS	-	-	Moderately Irritating (14.7/110.0)	Minimally Irritating (0.1/8.0)
3630-1-D OBTS	-	-	Moderately Irritating (34.0/110.0)	Slightly Irritating (0.8/8.0)

- = No study requested



8

III. Investigational Procedures

The detailed investigational procedures employed in these studies are presented in the appendix.

IV. Results

A. Acute Oral Toxicity Study - Albino Rats

1. Mortality and Body Weights

Individual mortality and body weight data are presented in

Table II.

TABLE II

Acute Oral Toxicity Study - Albino Rats

Mortality and Body Weight Data

Test Material: 3630-1-A OBTS
 Form Administered: 25.0% (w/v) suspension in corn oil
 Acute Oral LD₅₀: 12,560 ± 1,805 mg/kg, expressed in terms of 3630-1-A OBTS

Strain: Charles River
 IBT No.: 601-04729
 Classification: Slightly Toxic

Dose Level (mg/kg)	Animal Number and Sex	Individual Body Weights (grams)		Number Dead / Number Tested	Percent Dead
		Test Day 0	Test Day 14		
4,556	1-M	193	306	0/4	0
	2-M	209	312		
	3-F	180	224		
	4-F	183	234		
6,834	5-M	199	314	0/4	0
	6-M	205	324		
	7-F	183	228		
	8-F	186	238		
10,250	9-M	197	314	1/4	25
	10-M	189	288		
	11-F	178	(2 days)		
	12-F	183	244		
15,380	13-M	179	299	3/4	75
	14-M	186	(6-22 hours)		
	15-F	169	(6-22 hours)		
	16-F	167	(1 day)		

Note: Figures in parentheses indicate time of death.

2. Reactions

The untoward reactions exhibited by the rats following oral administration of 3630-1-A OBTS are presented in Table III.

Necropsy examination of the animals that died revealed pinpoint hemorrhages and solidified test material in the intestinal tracts. No gross pathologic alterations were noted among the animals sacrificed at the end of the 14-day observation period.

TABLE III

Acute Oral Toxicity Study - Albino Rats

Summary of Reactions

IET No.: 601-04729

Test Material: 3630-1-A OBTS

Concentration: 25.0% (w/v) suspension in corn oil

Dose Level (mg/kg)	Reaction	Time of Onset Following Dose Administration	Duration of Reaction	Time of Death Following Dose Administration
4,556	Hypoactivity	1 hour	6-22 hours	-
	Ruffed fur	1 hour	6-22 hours	-
6,834	Hypoactivity	1 hour	3 days	-
	Ruffed fur	1 hour	3 days	-
	Salivation	1 hour	6-22 hours	-
	Labored breathing	1 hour	6-22 hours	-
10,250	Hypoactivity	15 minutes	3 days	2 days
	Ruffed fur	30 minutes	3 days	
	Salivation	30 minutes	6-22 hours	
	Labored breathing	30 minutes	1 day	
	Muscular weakness	1 hour	2 days	
	Prostration	1 hour	6-22 hours	
	Diuresis	6-11 hours	1 day	

TABLE III continued

Acute Oral Toxicity Study - Albino Rats

Summary of Reactions

IBT No.: 601-04729

Test Material: 3630-1-A OBTS

Concentration: 25.0% (w/v) suspension in corn oil

Dose Level (mg/kg)	Reaction	Time of Onset Following Dose Administration	Duration of Reaction	Time of Death Following Dose Administration
15,380	Hypoactivity	15 minutes	4 days	6 hours-1 day
	Ruffed fur	30 minutes	4 days	
	Salivation	30 minutes	6-22 hours	
	Labored breathing	30 minutes	1 day	
	Muscular weakness	1 hour	3 days	
	Prostration	1 hour	1 day	
	Tremors	6-22 hours	1 day	
	Lacrimation	6-22 hours	1 day	
	Diuresis	6-22 hours	1 day	
	Diarrhea	6-22 hours	2 days	

B. Acute Dermal Toxicity Study - Albino Rabbits

1. Mortality and Body Weights

Individual mortality and body weight data are presented in

Table IV.

TABLE IV

Acute Dermal Toxicity Study - Albino Rabbits

Mortality and Body Weight Data

Test Material: 3630-1-A OBTS

IBT No.: 601-04729

Concentration: Applied as received to premoistened skin

Classification: Practically

Acute Dermal LD₅₀ > 3,000 mg/kg

Non-Toxic

Dose Level (mg/kg)	Animal Number and Sex	Individual Body Weights (kg)			Number Dead / Number Tested	Percent Dead
		Test Day Number: 0	7	14		
3,000	1-M*	2.88	2.72	3.02	0/4	0
	2-M	3.00	3.46	3.44		
	3-F*	2.50	2.68	2.90		
	4-F	2.94	3.20	3.42		

* The skin at the site of application was abraded.

2. Reactions

No untoward behavioral reactions were exhibited by any of the animals following dermal exposure to 3630-1-A OBTS.

The test material was mildly irritating to the skin of the albino rabbit. Skin changes 24 hours after application were characterized by pale red to red well-defined erythema. Slight desquamation was noted seven days after dosing; no skin reactions were observed at the end of the 14-day observation period.

Necropsy examination of all animals did not reveal any gross pathologic alteration.

C. Eye Irritation Tests - Albino Rabbits

The results of the eye irritation tests are presented in Tables V through VIII.

TABLE V continued

Eye Irritation Test - Albino Rabbits

Results

IBT No.: 601-04729

Test Material: 3630-1-A OBTS

Tissue	Rabbit Number	1			24			72			14		
		Minute	Hour	Hours	Hours	Hours	Days	Days	Days	Days	Days	Days	
Cornea (D-A)	5	0	0	0	0	0	0	0	0	0	0	0	
Iris		5	5	0	0	0	0	0	0	0	0	0	
Conjunctiva (R-S-D)		6 (2-1-0)	12 (2-1-3)	10 (2-1-2)	0	0	0	0	0	0	0	0	
Total		11	17	10	0	0	0	0	0	0	0	0	
Cornea (D-A)	6	0	0	5 (1-1)	0	0	0	0	0	0	0	0	
Iris		5	5	5	0	0	0	0	0	0	0	0	
Conjunctiva (R-S-D)		6 (2-1-0)	12 (2-1-3)	10 (2-1-2)	0	0	0	0	0	0	0	0	
Total		11	17	20	0	0	0	0	0	0	0	0	
<u>Averages</u>													
Cornea		0.0	0.0	5.8	2.5	1.7	0.8						
Iris		5.0	5.0	3.3	0.0	0.0	0.0						
Conjunctiva		7.0	11.7	10.3	0.7	0.0	0.0						
Total		12.0	16.7	19.4	3.2	1.7	0.8						

Conjunctiva:
 R = Redness
 S = Swelling
 D = Discharge
 Conjunctival Score = (R+S+D) x 2
 Maximum Score = 20

Cornea:
 D = Density
 A = Area
 Corneal Score = D x A x 5
 Maximum Score = 80

Iris:
 Iris Score = Value x 5
 Maximum Score = 10

V = Vascularization

TABLE VI continued
 Eye Irritation Test - Albino Rabbits

Results

IBT No.: 601-04729

Test Material: 3630-1-B, recrystallized OBTS

Tissue	Rabbit Number	1		24		72		7		14	
		Minute	Hour	Hours	Hours	Hours	Days	Days	Days	Days	
Cornea (D-A)	5	0	0	5 (1-1)	0	0	0	0	0	0	0
Iris		5	0	0	0	0	0	0	0	0	0
Conjunctiva (R-S-D)		8 (2-1-1)	8 (2-1-1)	8 (2-1-1)	0	0	0	0	0	0	0
Total		13	8	13	0	0	0	0	0	0	0
Cornea (D-A)	6	0	0	0	0	0	0	0	0	0	0
Iris		5	5	0	0	0	0	0	0	0	0
Conjunctiva (R-S-D)		8 (2-1-1)	10 (2-1-2)	6 (1-1-1)	0	0	0	0	0	0	0
Total		13	15	6	0	0	0	0	0	0	0
<u>Averages</u>											
Cornea		0.0	0.0	5.0	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Iris		5.0	2.5	1.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Conjunctiva		8.7	11.0	8.0	1.0	1.0	0.0	0.0	0.0	0.0	0.0
Total		13.7	13.5	14.7	1.8	1.8	0.8	0.8	0.8	0.8	0.8

Cornea:
 D = Density
 A = Area
 Corneal Score = D x A x 5
 Maximum Score = 80
Iris:
 Iris Score = Value x 5
 Maximum Score = 10
Conjunctiva:
 R = Redness
 S = Swelling
 D = Discharge
 Conjunctival Score = (R+S+D) x 2
 Maximum Score = 20
 V = Vascularization

TABLE VII

Eye Irritation Test - Albino Rabbits

Results

Test Material: 3630-1-C OBTS
 Form Administered: 100 mg, Undiluted
 Special Instructions: Unwashed Eyes

IBT No.: 601-04729
 Descriptive Rating: Moderately Irritating
 (14.7/110.0)

Tissue	Rabbit Number	1		24		72		7		14	
		Minute	Hour	Hours	Hours	Hours	Days	Days	Days	Days	
Rabbit 1	1	0	0	15 (1-3)	10 (1-2)	5 (1-1), V	0	0	0	0	0
	iris	5	5	5	0	0	0	0	0	0	0
	Conjunctiva (R-S-D)	8 (2-1-1)	12 (2-2-2)	12 (2-1-3)	4 (1-1-0)	0	0	0	0	0	0
Total		13	17	32	14	5	0	0	0	0	0
Rabbit 2	2	0	0	5 (1-1)	5 (1-1)	5 (1-1), V	0	0	0	0	0
	iris	5	5	5	0	0	0	0	0	0	0
	Conjunctiva (R-S-D)	8 (2-1-1)	10 (2-1-2)	12 (2-1-3)	0	0	0	0	0	0	0
Total		13	15	22	5	5	0	0	0	0	0
Rabbit 3	3	0	0	5 (1-1)	0	0	0	0	0	0	0
	iris	5	5	5	0	0	0	0	0	0	0
	Conjunctiva (R-S-D)	8 (2-1-1)	12 (2-1-3)	6 (2-1-0)	4 (1-1-0)	0	0	0	0	0	0
Total		13	17	16	4	0	0	0	0	0	0
Rabbit 4	4	0	0	0	0	0	0	0	0	0	0
	iris	5	5	0	0	0	0	0	0	0	0
	Conjunctiva (R-S-D)	8 (2-1-1)	6 (2-1-0)	6 (2-1-0)	0	0	0	0	0	0	0
Total		13	11	6	0	0	0	0	0	0	0

TABLE VII continued

Eye Irritation Test - Albino Rabbits

Results

IBT No.: 601-04729

Test Material: 3630-1-C OBTS

Tissue	Rabbit Number	1		24		72		14	
		Minute	Hour	Hours	Hours	Days	Days	Days	Days
Cornea (D-A)	5	0	0	0	0	0	0	0	0
Iris		5	5	0	0	0	0	0	0
Conjunctiva (R-S-D)		8 (2-1-1)	8 (2-1-1)	6 (2-1-0)	0	0	0	0	0
Total		13	13	6	0	0	0	0	0
Cornea (D-A)	6	0	0	0	0	0	0	0	0
Iris		0	0	0	0	0	0	0	0
Conjunctiva (R-S-D)		8 (2-1-1)	10 (2-1-2)	6 (2-1-0)	4 (1-1-0)	0	0	0	0
Total		8	10	6	4	0	0	0	0
<u>Averages</u>									
Cornea		0.0	0.0	4.2	2.5	1.7	0.0	0.0	0.0
Iris		4.2	4.2	2.5	0.0	0.0	0.0	0.0	0.0
Conjunctiva		8.0	9.7	8.0	2.0	0.0	0.0	0.0	0.0
Total		12.2	13.9	14.7	4.5	1.7	0.0	0.0	0.0

Cornea:
 D = Density
 A = Area
 Corneal Score = D x A x 5
 Maximum Score = 80

Iris:
 Iris Score = Value x 5
 Maximum Score = 10

Conjunctiva:
 R = Redness
 S = Swelling
 D = Discharge
 Conjunctival Score = (R+S+D) x 2
 Maximum Score = 20

V = Vascularization

TABLE VIII continued

Eye Irritation Test - Albino Rabbits

Results

Test Material: 3630-1-D OBTS
 Form Administered: 100 mg, Undiluted
 Special Instructions: Unwashed Eyes

IBT No.: 601-04729
 Descriptive Rating: Moderately Irritating
 (34.0/110.0)

Issue	Rabbit Number	1		1 Hour	24 Hours		72 Hours	7 Days		14 Days	
		Minute	Hour		Hours	Hours		Days	Days		
Cornea (D-A) Iris	1	0	0	20 (2-2)	20 (2-2)	20 (2-2)	10 (1-2), V	10 (1-2), V	10 (1-2), V	0	0
		0	0	0	0	0	0	0	0	0	0
		10 (2-1-2)	14 (2-2-3)	12 (2-1-3)	4 (1-1-0)	0	0	0	0	0	0
Total		10	14	32	24	24	10	10	10	0	0
Cornea (D-A) Iris	2	0	0	5 (1-1)	5 (1-1)	5 (1-1)	5 (1-1), V	5 (1-1), V	5 (1-1), V	0	0
		5	5	5	0	0	0	0	0	0	0
		10 (2-1-2)	14 (2-2-3)	14 (2-2-3)	0	0	0	0	0	0	0
Total		15	19	24	24	5	5	5	5	0	0
Cornea (D-A) Iris	3	0	0	20 (2-2)	20 (2-2)	20 (2-2)	10 (1-2), V	10 (1-2), V	10 (1-2), V	10 (1-2), V	0
		0	5	5	0	0	0	0	0	0	0
		8 (2-1-1)	14 (2-2-3)	12 (2-1-3)	6 (2-1-0)	0	0	0	0	0	0
Total		8	19	37	26	26	10	10	10	0	0
Cornea (D-A) Iris	4	0	0	20 (2-2)	20 (2-2)	20 (2-2)	10 (1-2), V	10 (1-2), V	10 (1-2), V	10 (1-2), V	0
		0	5	5	0	0	0	0	0	0	0
		8 (2-1-1)	14 (2-2-3)	12 (2-1-3)	4 (1-1-0)	0	0	0	0	0	0
Total		8	19	37	24	24	10	10	10	0	0

TABLE VIII continued
Eye Irritation Test - Albino Rabbits

Results

IBT No.: 601-04729

Test Material: 3630-1-D OBTS

Issue	Rabbit Number	1				72	Days	14
		Minute	Hour	Hours	Hours			
Cornea (D-A)	5	0	0	20 (2-2)	5 (1-1)	5 (1-1), V	0	
Iris		0	5	5	0	0	0	
Conjunctiva (R-S-D)		8 (2-1-1)	14 (2-2-3)	12 (2-1-3)	4 (1-1-0)	0	0	
Total		8	19	37	9	5	0	
Cornea (D-A)	6	0	0	20 (2-2)	5 (1-1)	5 (1-1), V	5 (1-1), V	
Iris		0	5	5	0	0	0	
Conjunctiva (R-S-D)		8 (2-1-1)	14 (2-2-3)	12 (2-1-3)	4 (1-1-0)	0	0	
Total		8	19	37	9	5	5	
<u>Averages</u>								
Cornea		0.0	0.0	17.5	12.5	7.5	5.8	
Iris		0.8	4.2	4.2	0.0	0.0	0.0	
Conjunctiva		8.7	14.0	12.3	3.7	0.0	0.0	
Total		9.5	18.2	34.0	16.2	7.5	5.8	

Cornea:
D = Density
A = Area
Corneal Score = D x A x 5
Maximum Score = 80

Iris:
Iris Score = Value x 5
Maximum Score = 10

Conjunctiva:
R = Redness
S = Swelling
D = Discharge
Conjunctival Score = (R+S+D) x 2
Maximum Score = 20

V = Vascularization

D. Primary Skin Irritation Tests - Albino Rabbits

The results of the primary skin irritation tests are presented in
Tables IX through XII.

TABLE X

Primary Skin Irritation Test - Albino Rabbits

Results

Test Material: 3630-1-B, recrystallized OBTS IBT No.: 601-04729
 Form Administered: 0.5 g. Undiluted Descriptive Rating: Minimally Irritating
 (0.2/8.0)

Animal Number	Irritation Scores for Abraded Skin Sites At:				Irritation Scores for Intact Skin Sites At:			
	24 Hours		72 Hours		24 Hours		72 Hours	
	Er.	Ed.	Er.	Ed.	Er.	Ed.	Er.	Ed.
1	0	0	0	0	0	0	0	0
2	1	0	0	0	0	0	0	0
3	1	0	0	0	0	0	0	0
4	1	0	0	0	0	0	0	0
5	1	0	0	0	0	0	0	0
6	1	0	0	0	0	0	0	0
Mean	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Subtotal	0.8				0.0			
Primary Irritation Score = 0.2								

Key: Er. = Erythema
 Ed. = Edema

TABLE XI

Primary Skin Irritation Test - Albino Rabbits

Results

Test Material: 3630-1-C OBTS
Form Administered: 0.5 g, Undiluted

IBT No.: 601-04729
Descriptive Rating: Minimally Irritating
(0.1/8.0)

Animal Number	Irritation Scores for Abraded Skin Sites At:				Irritation Scores for Intact Skin Sites At:			
	24 Hours		72 Hours		24 Hours		72 Hours	
	Er.	Ed.	Er.	Ed.	Er.	Ed.	Er.	Ed.
1	1	0	0	0	1	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
5	1	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0
Mean	0.3	0.0	0.0	0.0	0.2	0.0	0.0	0.0

Subtotal

0.3

0.2

Primary Irritation Score = 0.1

Key: Er. = Erythema
Ed. = Edema

TABLE XII

Primary Skin Irritation Test - Albino Rabbits

Results

Test Material: 3630-1-D OBTS
Form Administered: 0.5 g, Undiluted

IBT No.: 601-04729
Descriptive Rating: Slightly Irritating
(0.8/8.0)

Animal Number	Irritation Scores for Abraded Skin Sites At:				Irritation Scores for Intact Skin Sites At:			
	24 Hours		72 Hours		24 Hours		72 Hours	
	Er.	Ed.	Er.	Ed.	Er.	Ed.	Er.	Ed.
1	2	0	0	0	1	0	0	0
2	2	0	0	0	1	0	0	0
3	2	0	0	0	2	0	0	0
4	1	0	0	0	1	0	0	0
5	2	0	0	0	1	0	0	0
6	2	0	0	0	1	0	0	0
Mean	1.8	0.0	0.0	0.0	1.2	0.0	0.0	0.0
Subtotal	1.8				1.2			

Primary Irritation Score = 0.8

Key: Er. = Erythema
Ed. = Edema

V. Appendix

The detailed investigational procedures employed in these studies are presented in the following pages.

ACUTE ORAL TOXICITY STUDY - ALBINO RATS

Young albino rats derived from Sprague-Dawley stock were used as test animals. All animals were kept under observation for five days prior to experimental use, during which period they were checked for general health and suitability as test animals. The animals were housed in stock cages and were permitted a standard laboratory diet plus water ad libitum, except during the 16-hour period immediately prior to oral intubation when food was withheld.

Initial screening was conducted in order to determine the general level of toxicity of the test material. Selected groups of albino rats were administered the test material at several dose levels. All doses were administered directly into the stomachs of the rats using a hypodermic syringe equipped with a ball-tipped intubating needle.

After oral administration of the test material, the rats were housed individually in suspended, wire-mesh cages and observed for the following 14 days. Initial and final body weights, mortalities, and reactions were recorded. A necropsy examination was conducted on all animals.

At the end of the observation period, the acute oral median lethal dose (LD₅₀) of the test material was calculated, if possible, using the techniques of Weil*, Thompson**, and Thompson and Weil***. The test material was then assigned a classification in accordance with Harold C. Hodge****. The classification system is presented in the following Table.

- * Weil, Carrol S.: Tables for Convenient Calculation of Median-Effective Dose (LD₅₀ or ED₅₀) and Instructions in Their Use. Biometrics, Sept. 1952.
- ** Thompson, William R.: Use of Moving Averages and Interpolation to Estimate Median-Effective Dose. Bact. Rev., Nov. 1947.
- *** Thompson, William R. and Weil, Carrol S.: On the Construction of Tables for Moving Average Interpolation. Biometrics, March 1952.
- **** Hodge, Harold C., "The LD₅₀ and its value", American Perfumer and Cosmetics 80, 57 (1965).

TABLE
Acute Oral Toxicity Study - Albino Rats

Classification of Test Materials
Based on Acute Oral LD₅₀

Acute Oral LD ₅₀ (Range of Values)	Classification	Probable lethal dose for a 70 kg man in commonly used measures
Less than 5 mg/kg	Extremely toxic	a taste (less than 7 drops)
5 - 50 mg/kg	Highly toxic	between 7 drops and 1 teaspoonful
50 - 500 mg/kg	Moderately toxic	between 1 teaspoonful and 1 ounce
500 - 5,000 mg/kg	Slightly toxic	between 1 ounce and 1 pint or 1 pound
5,000 - 15,000 mg/kg	Practically non-toxic	between 1 pint and 1 quart
Greater than 15,000 mg/kg	Relatively harmless	more than 1 quart

ACUTE DERMAL TOXICITY STUDY - ALBINO RABBITS

Young adult albino rabbits of the New Zealand strain were used as test animals. All rabbits had been maintained under observation in the laboratory for at least seven days prior to testing. During the pre-test period, the animals were examined with respect to their general health and suitability as test animals. The rabbits were housed individually in suspended, wire-bottomed cages and maintained on a standard laboratory ration. Food and water were offered ad libitum.

Twenty-four hours prior to the dermal applications, the backs of the rabbits were shaved free of hair with electric clippers. The shaved area on each animal constituted about 30 percent of the total body surface area. The animals were then returned to their cages to await testing on the following day. The 24-hour waiting period allowed recovery of the stratum corneum from the disturbance which accompanied the close-clipping procedure and permitted healing of any microscopic abrasions possibly produced during the process.

The test material was applied at the highest reasonable dose level. The test site was covered by wrapping the trunk of the animal with impervious plastic sheeting which was securely taped in place. This plastic wrap insured close contact of the epidermis and test material. To prevent oral ingestion of the test material, each animal was fitted with a light-weight, flexible plastic collar which was worn throughout the observation period.

The test material remained in contact with the skin for 24 hours. At the end of this period, the plastic sheeting and all residual test material were removed. The test sites were examined for local skin reactions and the animals were returned to their cages. Observations for mortality, local skin reactions, and behavioral abnormalities were continued for a total of 14 days following the skin applications. Initial, 7 and 14-day body weights were recorded. A necropsy examination was conducted on all animals.

In the case of significant mortality following the initial study, additional experiments were conducted at lower dose levels in order to obtain data sufficient to determine the acute dermal median lethal dose (LD_{50}), if possible, using the techniques of Weil*, Thompson**, and Thompson and Weil***.

* Weil, Carrol S.: Tables for Convenient Calculation of Median-Effective Dose (LD_{50} or ED_{50}) and Instructions in Their Use. Biometrics, Sept. 1952.

** Thompson, William R.: Use of Moving Averages and Interpolation to Estimate Median-Effective Dose. Bact. Rev., Nov. 1947.

*** Thompson, William R. and Weil, Carrol S.: On the Construction of Tables for Moving Average Interpolation. Biometrics, March 1952.

TABLE

Acute Dermal Toxicity Study - Albino Rabbits

Classification of Test Materials
Based on Acute Dermal LD₅₀

Acute Dermal LD ₅₀ (Range of Values)	Classification	Probable lethal dose for a 70 kg man in commonly used measures
Less than 20 mg/kg	Extremely toxic	approximately 30 drops
20 - 200 mg/kg	Highly toxic	between 30 drops and 4 teaspoonfuls
200 - 500 mg/kg	Moderately toxic	between 4 teaspoonfuls and 1 ounce
500 - 3,000 mg/kg	Slightly toxic	between 1 ounce and 1 pint or 1 pound
3,000 - 10,000 mg/kg	Practically non-toxic	between 1 pint and 1 quart
Greater than 10,000 mg/kg	Relatively harmless	more than 1 quart

EYE IRRITATION TEST - ALBINO RABBITS

Young albino rabbits of the New Zealand strain were used to evaluate the eye irritating properties of the test material. The test method was patterned after that of Draize et al.*

The test material was instilled into the conjunctival sac of the right eye of each rabbit. The left eye of each animal served as a control. At each scoring interval the cornea, iris, and palpebral conjunctiva were examined and graded for irritation and injury according to a standard scoring system*. The maximum possible score at any one examination and scoring period is 110 points, which indicates maximal irritation and damage to all three ocular tissues. Zero score indicates no irritation. The scoring system is presented in Table A. In this scoring system, special emphasis is placed upon irritation or damage to the cornea, while less emphasis is placed upon damage to the iris and conjunctiva.

After the completion of the test, the scores were analyzed, and a descriptive eye irritation rating was assigned to the test material. The criteria used for assignment of the descriptive rating are the frequency, the extent, and the persistence of irritation or damage which occur to the three ocular tissues.

* Draize, John H., Woodard, Geoffrey, and Calvery, Herbert O., "Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes," J. Pharm. & Exp. Ther. 82, 377 (1944).

TABLE A

Eye Irritation Test - Albino Rabbits

Scale of Weighted Scores for
Grading the Severity of Ocular Lesions

Ocular Tissues	Description	Grading
Cornea	<u>Opacity (A)</u>	
	Opacity - Degree of density (area which is most dense is taken for reading).	
	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
	<u>Area of Cornea Involved (B)</u>	
	One quarter (or less) but not zero.	1
	Greater than one-quarter but less than one-half.	2
	Greater than one-half but less than three-quarters.	3
Greater than three-quarters, up to whole area.	4	
	Score equals A x B x 5	Total maximum = 80
Iris	<u>Values (A)</u>	
	Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or a combination of any thereof), iris still reacting to light (sluggish reaction is positive).	1
	No reaction to light, hemorrhage, gross destruction (any or all of these).	2
	Score equals A x 5	Total maximum = 10

TABLE A continued

Eye Irritation Test - Albino Rabbits

Scale of Weighted Scores for
Grading the Severity of Ocular Lesions

Ocular Tissues	Description	Grading	
Conjunctiva	<u>Redness (A)</u>		
	Redness (refers to palpebral conjunctiva only). Vessels definitely injected above normal.	1	
	More diffuse, deeper crimson red, individual vessels not easily discernible.	2	
	Diffuse beefy red.	3	
	<u>Chemosis (B)</u>		
	Any swelling above normal (includes nictitating membrane).	1	
	Obvious swelling with partial eversion of the lids.	2	
	Swelling with lids about half-closed.	3	
	Swelling with lids about half-closed to completely closed.	4	
	<u>Discharge (C)</u>		
	Any amount different from normal (does not include small amount observed in inner canthus of normal animals).	1	
	Discharge with moistening of the lids and hairs just adjacent to the lids.	2	
	Discharge with moistening of the lids and hairs and considerable area around eye.	3	
	Score (A + B + C) x 2		Total maximum = 20

Note: The maximum total score is the sum of all scores obtained from the cornea, iris, and conjunctiva.

The rating is obtained by selecting the maximum mean irritation score at one, 24, or 72 hours after instillation. If the rate of dissipation of injury does not meet the requirements defined for the descriptive rating appropriate for a particular numerical score, the descriptive rating is raised by one or more levels. The rating system is presented in Table B.

TABLE B

Eye Irritation Test - Albino Rabbits

Classification of Test Materials
Based on Eye Irritation Properties

Rating	Range	Definition
Non-Irritating	0.0 - 0.5	To maintain this rating, all scores at the 24-hour reading must be zero; otherwise, increase rating one level.
Practically Non-Irritating	Greater than 0.5 - 2.5	To maintain this rating, all scores at the 24-hour reading must be zero; otherwise increase rating one level.
Minimally Irritating	Greater than 2.5 - 15.0	To maintain this rating, all scores at the 72-hour reading must be zero; otherwise, increase rating one level.
Mildly Irritating	Greater than 15.0 - 25.0	To maintain this rating, all scores at the 7-day reading must be zero; otherwise, increase rating one level.
Moderately Irritating	Greater than 25.0 - 50.0	To maintain this rating, scores at 7 days must be less than or equal to 10 for 60% or more of the animals. Also, mean 7-day score must be less than or equal to 20. If 7-day mean score is less than or equal to 20 but less than 60% of animals show scores less than 10, then no animal among those showing scores greater than 10 can exceed a score of 30 if rating is to be maintained; otherwise, increase rating one level.
Severely Irritating	Greater than 50.0 - 80.0	To maintain this rating, scores at 7 days must be less than or equal to 30 for 60% or more of the animals. Also, mean 7-day score must be less than or equal to 40. If 7-day mean score is less than or equal to 40 but less than 60% of the animals show scores less than or equal to 30, then no animal among those showing scores greater than 30 can exceed a score of 60 if rating is to be maintained; otherwise, increase rating one level.
Extremely Irritating	Greater than 80.0 - 110.0	

PRIMARY SKIN IRRITATION TEST - ALBINO RABBITS

Young albino rabbits of the New Zealand strain were used in the evaluation of the primary skin irritating properties of the test material.

The test procedure was modeled after that of Draize et al.*

Prior to the application of the test material, the hair was clipped from the back and flanks of each rabbit. Two test sites located lateral to the midline of the back approximately ten centimeters apart were selected. One of the two sites was abraded by making four epidermal incisions, two perpendicular to the other two, while the other test site remained intact.

The test material was applied to each of the test sites on each rabbit and occluded with gauze patches which were secured with masking tape. The trunk of each animal was then wrapped with impervious plastic sheeting. The wrap held the patches in position and retarded evaporation of the test material during the 24-hour exposure period.

At the end of 24 hours, the plastic wrappings, patches, and all residual test material were removed. The intact and abraded test sites were examined and scored separately for erythema and edema on a graded scale of 0 to 4. After 72 hours, the sites were again examined and scored.

* Draize, John H., Woodard, Geoffrey, and Calvery, Herbert O., "Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes," J. Pharm. & Exp. Ther. 82, 377 (1944).

In evaluating the average irritation present, the mean scores for erythema and edema of the intact test sites after 24 and 72 hours were added. Similarly, the mean scores for erythema and edema of the abraded test sites after 24 and 72 hours were added. These two values were totaled and divided by four to obtain the mean primary irritation score. The scoring criteria for erythema and edema are shown in the following Table.

The following grading system was used to arrive at a descriptive primary skin irritation rating:

<u>Mean Primary Irritation Score</u> <u>(Range of Values)</u>	<u>Descriptive Rating</u>
0	Non-Irritating
0.1 - 0.5	Minimally Irritating
0.6 - 1.5	Slightly Irritating
1.6 - 3.0	Mildly Irritating
3.1 - 5.0	Moderately Irritating
5.1 - 6.5	Severely Irritating
6.6 - 8.0	Extremely Irritating

TABLE
 Primary Skin Irritation Test - Albino Rabbits
 Scoring Criteria for Skin Reactions

Reactions	Description	Score
Erythema	Barely perceptible (Edges of area not defined)	1
	Pale red in color and area definable	2
	Definite red in color and area well defined	3
	Beet or crimson red in color	4
Edema	Barely perceptible (Edges of area not defined)	1
	Area definable but not raised more than 1 mm	2
	Area well defined and raised approximately 1 mm	3
	Area raised more than 1 mm	4
Injury In Depth	Escharosis, Necrosis	8
	Maximum Primary Irritation Score =	8