

CODING FORMS FOR SRC INDEXING

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		TSCA Section	8ECP
Submitting Organization	RHONE-POULENC INC		
Contractor	RHODIA INC		
Document Title	INITIAL SUBMISSION: PRIMARY SKIN IRRITATION WITH PRENOL IN RABBITS WITH COVER LETTER DATED 101692		
Chemical Category	PRENOL		

8(e)

# CAP

(COMPLIANCE AUDIT PROGRAM)

## TSCA CONFIDENTIAL BUSINESS INFORMATION

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NOTE: Peter provides data entry in CBITS for the 8(e) CAP Documents.

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**RHÔNE-POULENC INC.**

CN 7500, CRANBURY, NJ 08512-7500  
TELEPHONE (609) 395-8300

October 16, 1992

**CERTIFIED MAIL  
RETURN RECEIPT REQUESTED  
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8EHQ-92-11443

INIT 10/21/92



88920009724

Document Processing Center (TS-790)  
Attn: Section 8(e) Coordinator (CAP Agreement)  
Office of Toxic Substances  
Environmental Protection Agency  
401 M Street, S.W.  
Washington, D.C. 20460

RE: Report Submitted Pursuant to the TSCA Section 8(e) Compliance  
Audit Program

CAP ID NO.: 8ECAP - 0004

RP CAP REPORT NO.: RPS - 0311

Dear Sir/Madam:

On behalf of Rhône-Poulenc Inc. (RPI, CN5266, Princeton, NJ 08543-5266) and its subsidiaries, the attached report is being submitted to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program (CAP Agreement) executed by RPI and EPA (8ECAP - 0004).

The enclosed report provides information on the following chemical substance:

Chemical Identity: Prenol  
CAS Registry No.: 556-82-1  
CAS Registry Name: 2-Buten-1-ol, 3-methyl

The title of the enclosed report is:

Primary Skin Irritation Study with Prenol in Rabbits

The following is a summary of the adverse effects observed in this report.

The test material was found to be an extremely irritating, irreversible skin irritant. Tissue destruction was observed at 72 hours as evidenced by hard, black, shriveled test sites. Patches of dermal sloughing from the test sites were noted in 3 of 6 rabbits (pH = 5.7).

RPI does not claim any portion of the information in this submission to be TSCA confidential business information (TSCA CBI).

RPI has not previously submitted any TSCA Section 8(e) notices or premanufacture notification on the subject chemical substance.

In total, RPI is submitting three copies of the enclosed report and this cover letter: an original and two copies.

Further questions regarding this submission may be directed to Dr. Glenn S. Simon, Director of Toxicology at (919)549-2222 (Rhône-Poulenc, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC 27709).

Sincerely,



Charles E. Moyer, Jr., Ph.D.  
Director, Product Safety  
(609)860-3589

CEMjr/mm  
Enclosure

Contains NO CBI

Front Sheet

Study No. BCD0978  
Project No. Primary Skin Irritation  
Sponsor Chem. Division, Rhodia, Inc.  
Start Date 6-12-78  
Duration 7 days  
Finish Date 7-9-78  
Study Director J. Winbigler  
Study Personnel H. Harrison

Chemical Prenyl Alcohol (Prenol)  
Purity 99.5% pH 5.7  
Animal Rabbit  
No. ~~XX~~ F 6 adult  
Start Weight  
M  
F  
Route Dermal

Animal No.

101-106

Treatment Level

0.5 ml/test site/animal

Assays or Special Procedures

1. Shave all backs
2. Prepare two intact and 2 abraded sites
3. Evaluate skins at 24 and 72 hours

CAP ID No. 5-BL-BKH-0196  
Reviewed for Sec. 8 (e)  
Compliance Program  
On 7/1/78 By [Signature]

Special Handling

Prenol should be handled with care. Avoid skin and eye contact, in case of accidental contact, immediately wash affected areas with large volumes of water and report the incident to the study director.



RHODIA INC.  
HESS & CLARK DIVISION  
ASHLAND, OHIO 44805  
Research Department



## PROTOCOL

### TITLE

Primary Skin Irritation Study with Prenol in Rabbits

### PURPOSE

To determine if the application of Prenol on the skin of rabbits has any irritating effect according to the EPA proposed guidelines, April, 1978; sec. 162.81-5.

### LOCATION

This study will be conducted at the Rhodia, Inc., Toxicology-Pathology facility on the Hess & Clark Research Farm, Ashland, Ohio 44805.

### SPONSOR

This study is sponsored by Rhodia, Inc., Chemical Division, Monmouth Junction, New Jersey.

### ANIMALS

Six young adult female New Zealand albino rabbits will be obtained from Davidson's Mill Farm, Jamesburg, New Jersey and will weigh approximately 2 to 3 kg at the start of the study.

### HOUSING

For a 1 to 2 week acclimation and quarantine period, the rabbits will be gang housed in large wire bottom animal cages, 71 x 86 x 71 cm. Three rabbits from each shipping crate will be placed in the same cage. Feeders, waterers and cage floors will be cleaned weekly and waste pans will be flushed once or twice daily as necessary. Temperature will be maintained at  $69^{\circ} \pm 1^{\circ}$  F, humidity at 50% and room lights will be controlled automatically on a 14 hour light, 10 hour dark cycle for the quarantine and test periods.

A veterinarian will examine the rabbits with respect to their state of health and suitability as test animals.

Following the quarantine period the rabbits will be moved to the test rooms and placed in individual suspended wire bottom cages, 46 x 51 x 33 cm. Liquid litter from Pharmacal, Westport, Conn. will be used in the litter pans and changed twice weekly.



#### DIET

The rabbits will be maintained on Wayne Rabbit Ration, a nutritionally balanced standard laboratory diet, manufactured by Allied Mills, Fort Wayne, Indiana, with an analysis of 2% crude fat, 17% crude protein, 15% crude fiber and containing 0.025% sulfaquinoxaline. For 5 days after arrival Pfizer's Neo-Terramycin soluble will be added to the drinking water at 5g/gallon to prevent illness from diet change. Food and water will be available ad libitum throughout the quarantine and test periods.

#### IDENTIFICATION

After transfer from the quarantine room to the assigned test room, the rabbits will be numbered 151 through 156 by tattoo in the right ear. Each cage will bear a label stating the study number, animal number and treatment.

#### TEST SUBSTANCE

The test substance will be Prenol, an alcohol supplied by Rhodia, Inc., Chemical Division, Monmouth Junction, New Jersey and received May 24, 1978. Identifying numbers on the label are: SD4 C/6 12 ref. JRT 291-175. Prenol has a purity more than 99% and a density of 0.84. The pH is 5.7.

Warning: Handle with care, avoid skin and eye contact. In case of accidental contact, immediately wash affected areas with large volumes of water and report the incident to the study director.

#### TEST PROCEDURE

Twenty-four hours before treatment, the backs of 6 adult rabbits will be carefully clipped free of hair. The clipped area should be large enough to accommodate 4, 2.5 x 2.5 cm application sites. The application sites will be marked off on each rabbit and two of the sites, diagonal to each other, will be abraded with a firm nylon toothbrush and the other two left intact. The abrasions will be through the stratum corneum but not the dermis. 0.5 gm or 0.5 ml of the test material will be applied directly to the application sites. A 2.5 cm square gauze pad will be placed over the site. The pads will be held securely in place with adhesive tape. The entire shaved area will be covered with an impervious rubber sheet to prevent evaporation and maintain skin contact with the test material. The sheet will be secured in place with adhesive tape. Protective collars will be placed on the rabbits to prevent removal of the test material and they will be returned to their appropriate cages.



After twenty-four hours the sheets will be removed and the sites wiped (not washed) and the resulting reactions evaluated and scored at 24 and 72 hours post treatment and any subsequent period according to Draize (Table 1).

RECORDS TO BE MAINTAINED

A study record book will be maintained according to Manual #19 of the Standard Operating Procedures and will include the following records:

1. Scores for erythema eschar and edema at 24, 72 and any subsequent evaluation time.
2. Primary skin irritation score for each animal according to Draize.

DATA ANALYSIS AND FINAL REPORT

A final report will be issued and will contain the mean and range of erythema and edema scores for each time period, and the mean and range values for the primary irritation scores.

STORAGE OF DATA

All raw data generated by this study and the final report will be placed on file in the archives of Rhodia, Inc., Toxicology-Pathology facility in Ashland, Ohio.

Prepared by

  
J. C. Winbigler, B.S., M.T.  
Study Director

Approved by:

  
John G. Page, Ph.D.  
Manager, Toxicology-Pathology  
Rhodia, Inc.

Approved by:

  
E. M. Kiggins, Ph.D.  
Director of Research  
& Product Development

Table 1

Skin Reaction

Erythema and Eschar Formation:	<u>Value</u>
No erythema .....	0
Very slight erythema (barely perceptible) .....	1
Well-defined erythema .....	2
Moderate to severe erythema .....	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth) .....	4
Edema Formation:	
No edema .....	0
Very slight edema (barely perceptible) .....	1
Slight edema (edges of area well defined by definite raising) .....	2
Moderate edema (raised approximately 1 millimeter) ..	3
Severe edema (raised more than 1 millimeter and extending beyond the area of exposure) .....	4

Draize, J. H., 1959 - The Appraisal of Chemicals in Foods, Drugs, and Cosmetics, Association of Food and Drug Officials of the U.S.



OFFICE MEMORANDUM

DIVISION HESS & CLARK

To: Central File

Date: June 15, 1978

From: J. C. Winbigler

Subject: Additions to Protocol  
BCD0978

Skin reactions at 72 hrs. indicate the need for a longer observation period. One half (3) of the rabbits will be sacrificed at this time and the remainder observed for an additional 3 weeks. Skin samples will be taken for histopathological evaluation and test sites will be photographed at both the 72 hour and 25 day sacrifices.

*J. C. Winbigler*  
J. C. Winbigler  
Study Director

PRIMARY DERMAL IRRITATION STUDY WITH PRENOL IN RABBITS

Study No. BCD0978

Report No. JCW 78:30

Toxicology-Pathology Laboratory  
Rhodia Inc.  
Ashland, Ohio 44805

August 2, 1978

PRIMARY DERMAL IRRITATION STUDY WITH PRENOL IN RABBITS

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RHODIA INC.  
HESS & CLARK DIVISION  
ASHLAND, OHIO 44805  
Research Department



Author: J. C. Winbigler, B.S., M.T.  
Report No.: JCW 78:30  
Date: August 2, 1978  
Page: 1

Subject: Primary Dermal Irritation, Prenol (Prenyl Alcohol)  
Book No.: 5407 Pages 29-32, 55-57  
Study No.: BCD0978  
Dates: 6-13-78 to 7-7-78

TITLE

Primary Dermal Irritation Study with Prenol in Rabbits.

PURPOSE

To determine if Prenol has any irritating effect when applied to intact or abraded skin of rabbits according to the EPA proposed guidelines of April, 1978; sec. 162.81-5.

LOCATION

The study was conducted at the Rhodia Inc., Toxicology-Pathology facility on the Hess & Clark Research Farm in Ashland, Ohio 44805.

SPONSOR

The study was sponsored by Rhodia Inc., Chemical Division, MORMOUTH Junction, New Jersey.

SUMMARY

Prenyl Alcohol was tested for possible skin irritation according to the EPA proposed guidelines of April, 1978; sec. 162-81-5.

Prenyl Alcohol could not be evaluated for skin irritation according to the Draize method for erythema and eschar due to a gray-black discoloration of the test sites at 24 hours. No edema was noted at either the 24 or 72 hour time periods. Signs of tissue destruction were evident at 72 hours as the test sites were hard, blackened and shriveled. The patches of test skin of 3 of the rabbits were sloughed during the 3 week observation period. Regrowth of hair was not observed on the new skin that replaced the treated skin. Unhealed areas were evident in some test areas of 1 rabbit.

Prenyl Alcohol was found to be extremely irritating to skin under the conditions of this study.



## EXPERIMENTAL

### MATERIALS AND METHODS

#### ANIMALS

Six young adult female New Zealand albino rabbits were obtained from Davidson's Mill Farm, Jamesburg, New Jersey and weighed approximately 2 to 3 kg at the start of the study.

#### HOUSING

For a three week acclimation and quarantine period, the rabbits were gang housed in large wire bottom animal cages, 71 x 86 x 71 cm. Three rabbits from each shipping crate were placed in the same cage. Feeders, waterers and cage floors were cleared weekly and waste pans were flushed once or twice daily as necessary. Temperature was maintained at  $69^{\circ} \pm 1^{\circ}\text{F}$ , humidity at 50% and room lights were controlled automatically on a 14 hour light, 10 hour dark cycle for the quarantine and test periods.

A veterinarian examined the rabbits with respect to their state of health and suitability as test animals.

Following the quarantine period the rabbits were moved to the test rooms and placed in individual suspended wire bottom cages, 46 x 51 x 33 cm. Liquid litter from Pharmalac, Westport, Conn. was used in the litter pans and changed twice weekly.

#### DIET

The rabbits were maintained on Wayne Rabbit Ration, a nutritionally balanced standard laboratory diet, manufactured by Allied Mills, Fort Wayne, Indiana, with an analysis of 2% crude fat, 17% crude protein, 15% crude fiber and containing 0.025% sulfaquinoxaline. For 5 days after arrival Pfizer's Neo-Terramycin soluble was added to the drinking water at 5 g/gallon to prevent illness from diet change. Food and water were available ad libitum throughout the quarantine and test periods.

#### IDENTIFICATION

After transfer from the quarantine room to the assigned test room, the rabbits were numbered 151 through 156 by tattoo in the right ear. Each cage had a label stating the study number, animal number and treatment.

0 0 1 4



RHODIA INC.

HESS & CLARK DIVISION  
ASHLAND, OHIO 44805

Research Department



Author: J. C. Winbigler, B.S., M.T.

Report No.: JCW 78:30

Page: 3

#### TEST SUBSTANCE

The test substance was Prenol (Prenyl Alcohol) supplied by Rhodia Inc., Chemical Division, Monmouth Junction, New Jersey and received May 24, 1978. Identifying numbers on the label were: SD4 C/6 - 12 ref. JRT 291-175. The purity was 99%, density was 0.84 and the pH was 5.7.

#### TEST PROCEDURE

Twenty-four hours before treatment, the backs of 6 adult rabbits were carefully clipped free of hair. The clipped area was large enough to accommodate four 2.5 x 2.5 cm application sites. The application sites were marked off on each rabbit and two of the sites, numbers 1 and 3, were abraded with a firm nylon toothbrush and the other two left intact. The abrasions were through the stratum corneum but not the dermis. 0.5 ml of the test material was applied directly to the application sites under a 2.5 cm square gauze pad placed over each site. The pads were held securely in place with adhesive tape lined with parafilm. The entire shaved area was covered with an impervious rubberized cloth to prevent evaporation and maintain skin contact with the test material. The wrap was secured in place. Protective collars were placed on the rabbits to prevent removal of the test material and they were then returned to their appropriate cages.

After twenty-four hours the collars and sheets were removed and the sites wiped (not washed) and the resulting reactions evaluated and scored at 24 and 72 hours post treatment according to the Draize scoring system. Half of the animals were sacrificed, photographs taken and skin samples taken and half of the animals were held for an additional three week observation period, and photographs and skin samples taken.

#### RECORDS

A study record book was maintained and included skin irritation scores at the 24 and 72 hour scoring period, and 25 days for edema and discoloration.

#### STORAGE OF DATA

All raw data generated by this study and the final report are on file in the archives of Rhodia Inc., Toxicology-Pathology facility in Ashland, Ohio.



RHODIA INC.  
HESS & CLARK DIVISION  
ASHLAND, OHIO 44805  
Research Department



Author: J. C. Winbigler, B.S., M.T.  
Report No.: JCW 78:30  
Page: 4

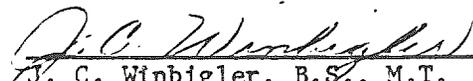
## RESULTS AND DISCUSSION

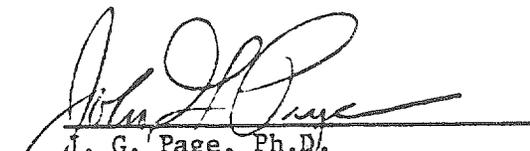
The skin evaluation scoring system according to Draize is presented in Table 1. Skin irritation reactions are shown in Table 2. Figure 1 illustrates the appearance of the test sites at 72 hours post application.

All sites were negative for edema at each of the grading periods, however, the discoloration of the skin at the test sites made accurate evaluation for erythema impossible at 24 hours. Therefore, primary skin irritation scores according to Draize could not be determined. By 48 hours post application the test sites were becoming hardened and darker in color and there was evidence of tissue destruction. At the 72 hour grading period the sites were almost black and brittle and tissue destruction was apparent. Half of the rabbits were sacrificed at this time and photographs and skin samples taken. The treated skin samples were dark red when moistened with water. The remaining 3 animals were held for an additional three weeks to determine the extent of skin repair. At one week there was no visible improvement. At 2 weeks post treatment the skin covering the test sites was sloughing. Three weeks following the 72 hour observation period one rabbit exhibited scars at the test sites, and the other two rabbits were healed. None of the three rabbits had evidence of a regrowth of hair on the new skin at the test sites. The remaining rabbits were euthanized and photographs and skin samples were taken. All tissue samples taken were submitted to Dr. Arthur Stein, Pathologist, Microscopy for Biological Research, 289 S. Allen St., Albany, N.Y.

Based on the results of this study Prenyl Alcohol is considered to be extremely irritating to the skin of albino rabbits.

Results of the pathological examination will be submitted as an addendum to this report.

  
J. C. Winbigler, B.S., M.T.  
Toxicologist

  
J. G. Page, Ph.D.  
Manager, Toxicology-Pathology  
Rhodia Inc.

  
S. E. Hastings, B.S.  
Toxicologist

  
E. M. Kiggins, Ph.D.  
Director of Research  
& Product Development

PRIMARY DERMAL IRRITATION STUDY WITH PRENOL IN RABBITS

TABLE 1

Skin Evaluation Scoring System

	<u>Value</u>
<b>Erythema and Eschar Formation:</b>	
No erythema -----	0
Very slight erythema (barely perceptible) -----	1
Well-defined erythema -----	2
Moderate to severe erythema -----	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth) -----	4
<b>Edema Formation:</b>	
No edema -----	0
Very slight edema (barely perceptible) -----	1
Slight edema (edges of area well defined by definite raising) -----	2
Moderate edema (raised approximately 1 millimeter) -----	3
Severe edema (raised more than 1 millimeter and extending beyond the area of exposure) -----	4

Draize, J. H., 1959 - The Appraisal of Chemicals in Foods, Drugs, and Cosmetics, Association of Food and Drug Officials of the U.S.



PRIMARY DERMAL IRRITATION STUDY WITH PRENOL IN RABBITS

TABLE 2

Primary Skin Irritation Reactions of Rabbits

Findings	Exposure Time (hours)	Exposure Unit (Value)						Mean Score
		151	152	153	154	155	156	
<b>Erythema and Eschar Formation</b>								
Intact Skin	24	-	-	-	-	-	-	-
	72	4	4	4	4	4	4	4
Abraded Skin	24	-	-	-	-	-	-	-
	72	4	4	4	4	4	4	4
	25 days	4	4	4	0	0	0	4
<b>Edema Formation</b>								
Intact Skin	24	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0
Abraded Skin	24	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0
	25 days	0	0	0	0	0	0	0

(-) - the gray-black discoloration at the test sites prevents accurate evaluation

PRIMARY DERMAL IRRITATION STUDY WITH PRENOL IN RABBITS

FIGURE 1

Animal #153. Test sites 72 hours after application of  
Prenyl Alcohol.



RHODIA INC.  
HESS & CLARK DIVISION  
ASHLAND, OHIO 44805  
Research Department



## PROTOCOL

### TITLE

Primary Skin Irritation Study with Prenol in Rabbits

### PURPOSE

To determine if the application of Prenol on the skin of rabbits has any irritating effect according to the EPA proposed guidelines, April, 1978; sec. 162.81-5.

### LOCATION

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Warning: Handle with care, avoid skin and eye contact. In case of accidental contact, immediately wash affected areas with large volumes of water and report the incident to the study director.

### TEST PROCEDURE

Twenty-four hours before treatment, the backs of 6 adult rabbits will be carefully clipped free of hair. The clipped area should be large enough to accommodate 4, 2.5 x 2.5 cm application sites. The application sites will be marked off on each rabbit and two of the sites, diagonal to each other, will be abraded with a firm nylon toothbrush and the other two left intact. The abrasions will be through the stratum corneum but not the dermis. 0.5 gm or 0.5 ml of the test material will be applied directly to the application sites. A 2.5 cm square gauze pad will be placed over the site. The pads will be held securely in place with adhesive tape. The entire shaved area will be covered with an impervious rubber sheet to prevent evaporation and maintain skin contact with the test material. The sheet will be secured in place with adhesive tape. Protective collars will be placed on the rabbits to prevent removal of the test material and they will be returned to their appropriate cages.



After twenty-four hours the sheets will be removed and the sites wiped (not washed) and the resulting reactions evaluated and scored at 24 and 72 hours post treatment and any subsequent period according to Draize (Table 1).

RECORDS TO BE MAINTAINED

A study record book will be maintained according to Manual #19 of the Standard Operating Procedures and will include the following records:

1. Scores for erythema eschar and edema at 24, 72 and any subsequent evaluation time.
2. Primary skin irritation score for each animal according to Draize.

DATA ANALYSIS AND FINAL REPORT

A final report will be issued and will contain the mean and range of erythema and edema scores for each time period, and the mean and range values for the primary irritation scores.

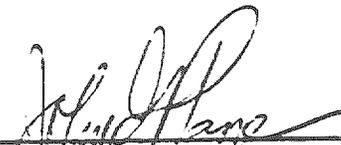
STORAGE OF DATA

All raw data generated by this study and the final report will be placed on file in the archives of Rhodia, Inc., Toxicology-Pathology facility in Ashland, Ohio.

Prepared by

  
J. C. Winbigler, B.S., M.T.  
Study Director

Approved by:

  
John G. Page, Ph.D.  
Manager, Toxicology-Pathology  
Rhodia, Inc.

Approved by:

  
E. M. Kiggins, Ph.D.  
Director of Research  
& Product Development

Table 1

Skin Reaction

Erythema and Eschar Formation:	<u>Value</u>
No erythema .....	0
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Well-defined erythema .....	2
Moderate to severe erythema .....	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth) .....	4
 Edema Formation:	
No edema .....	0
Very slight edema (barely perceptible) .....	1
Slight edema (edges of area well defined by definite raising) .....	2
Moderate edema (raised approximately 1 millimeter) ..	3
Severe edema (raised more than 1 millimeter and extending beyond the area of exposure) .....	4

Draize, J. H., 1959 - The Appraisal of Chemicals in Foods, Drugs, and Cosmetics, Association of Food and Drug Officials of the U.S.



OFFICE MEMORANDUM

DIVISION HESS & CLARK

To: Central File

Date: June 15, 1978

From: J. C. Winbigler

Subject: Additions to Protocol  
BCD0978

Skin reactions at 72 hrs. indicate the need for a longer observation period. One half (3) of the rabbits will be sacrificed at this time and the remainder observed for an additional 3 weeks. Skin samples will be taken for histopathological evaluation and test sites will be photographed at both the 72 hour and 25 day sacrifices.

*J. C. Winbigler*  
J. C. Winbigler  
Study Director

### CERTIFICATE OF AUTHENTICITY

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