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AlliedSignal Inc.  
P.O. Box 1057  
Morristown, NJ 07962-1057

**ORIGINAL**



8EHQ-95-13306

SUPP



May 1, 1995

*Contains No CBI*

Document Processing Center (7407)  
Attn: TSCA Section 8(e) Coordinator  
Office of Pollution Prevention and Toxics  
Washington, D.C. 20460-0001

**YENQ-0595-13306**

Mr. Terry R. O'Bryan

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Re: Document ID 8EHQ-0195-13306

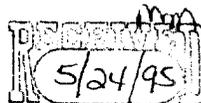
In response to your request for additional information, please find a copy of the final report, "A Dermal Corrosivity Study in Rabbits with Isooctyltrichlorosilane".

*Daniel Levine*

Daniel Levine  
Director-Product Safety & Integrity



89950000190





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

D. Levine  
Director, Product Safety and Integrity  
Allied-Signal Inc.  
Health, Safety & Environmental Sciences  
P.O. Box 1057  
Morristown, New Jersey 07692-1057

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

APR 24 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information, and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)  
Attn: TSCA Section 8(e) Coordinator  
Office of Pollution Prevention and Toxics  
U.S. Environmental Protection Agency  
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

*Terry R. O'Bryan*

Terry R. O'Bryan  
Risk Analysis Branch

Enclosure

62-111-8-1115



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### **Support Information for Confidentiality Claims**

Information submitted under specific reporting requirements of the Toxic Substances Control Act (TSCA), or in support of TSCA, is subject to the provisions of Section 14 of TSCA and to EPA's Regulations on the Confidentiality of Business Information (see 40 CFR Part 2) . You must comply with the following procedures to assert a claim of confidentiality for the information solicited in the letter attaching this statement and the substantiation questions that follow. Failure to follow these procedures fully at the time you submit the information to EPA will be interpreted by the Agency as a waiver of your claim of confidentiality.

#### **Asserting a Claim**

Information claimed as confidential must be clearly marked by boxing, circling or underlining. All pages containing such information should also be stamped "CONFIDENTIAL." Care should be taken to ensure that these markings do not obscure the submission's text.

#### **Sanitized Copy**

Two versions must be filed of any documents submitted to the US EPA containing information claimed as confidential. One copy should be complete, with the information being claimed as confidential marked in the manner described above. The other copy should have all of the information claimed as confidential excised. This version will be placed in EPA's Public Files. See 43 Federal Register, page 1113, titled, "X". Confidentiality claims, " March 16, 1978.

#### **Substantiating claims of Confidentiality**

Detailed written responses to the following questions must be provided to substantiate your confidentiality claim(s). Your responses should be as specific as possible, with examples as appropriate, and should provide substantiation arguments for all types of information (e.g., sales, or production/importation volumes, chemical identity, company identity) you claim as confidential. EPA must receive a response to these questions within twenty (20) business days of your receipt of this mailing.

#### **Substantiation Questions**

1. Is your company asserting this confidential business information (CBI) claim on its own behalf? If the answer is no, please provide company name, address and telephone number of entity asserting claim.

8. Describe the substantial harmful effects that would result to your competitive position if the CBI information is made available to the public? In your answer, explain the causal relationship between disclosure and any resulting substantial harmful effects. Consider in your answer such constraints as capital and marketing cost, specialized technical expertise, or unusual processes and your competitors' access to your customers. Address each piece of information claimed CBI separately.
9. Has the substance been patented in the U.S. or elsewhere? Is a patent for the substance currently pending?
10. Is this substance/product commercially available and if so, for how long has it been available on the commercial market?
  - a. If on the commercial market, are you competitors aware that the substance is commercially available in the U.S. ?
  - b. If not already commercially available, describe what stage of research and development (R&D) the substance is in, and estimate how soon a market will be established.
  - c. What is the substance used for and what type of product(s) does it appear in.
11. Describe whether a competitor could employ reverse engineering to identically recreate the substance?
12. Do you assert that disclosure of this information you are claiming CBI would reveal:
  - a. confidential processes used in manufacturing the substance;
  - b. if a mixture, the actual portions of the substance in the mixture; or
  - c. information unrelated to the effects of the substance on human health or the environment?

If your answer to any of the above questions is yes, explain how such information would be revealed.
13. Provide the Chemical Abstract Service Registry Number for the product, if known. Is your company applying for a CAS number now or in the near future? If you have applied for a CAS number, include a copy of the contract with CAS.



AlliedSignal Inc.  
P.O. Box 1057  
Morristown, NJ 07962-1057

**8EHQ-95-13306**

**ORIGINAL**

(A)



8EHQ-95-13306

INIT 01/06/95

**CERTIFIED MAIL  
RETURN RECEIPT REQUESTED**

November 29, 1994

U.S. Environmental Protection Agency  
Office of Pollution Prevention and Toxics  
TSCA 8(e) Coordinator  
101 M. Street, SW  
Washington, DC 20460

**Contains No CBI**

**RE: Toxic Substances Control Act - Section 8(e) Substantial Risk Report**

Dear Sir:

Preliminary, unaudited results of a dermal corrosivity test for **isooctyltrichlorosilane** (CAS # 18379-25-4), a process intermediate, indicates that it caused skin corrosion in a single rabbit after a 3-minute contact time.

This information is being added to hazard communication documents and will be communicated to plant personnel. If you have any questions regarding this communication, do not hesitate to contact me at 201-455-2733.

Sincerely,

*D. Levine*

D. Levine  
Director - Product Safety and Integrity



88950000095

95 JAN 10 1995

RECEIVED

**Date:** April 3, 1995  
**To:** E.T Asirvatham  
**From:** B.J. Dunn  
**Subject:** Summary of Final Report  
Isooctyltrichlorosilane  
TOX-071A

**A Dermal Corrosivity Study in Rabbits with Isooctyltrichlorosilane  
(478-94A), March 17, 1995  
TOX-071A-95-1 Protocol No. 94083 MA-RR-95-2184**

A Dermal Corrosivity Study in Rabbits was conducted for the purpose of evaluating the potential of Isooctyltrichlorosilane to cause corrosion of the skin.

Corrosion of the skin in a single animal was caused by application of 0.5 mL of Isooctyltrichlorosilane to a 1-inch square area of skin for an exposure period of 3 minutes. Because the skin reaction was unequivocally corrosive in the single animal, the study was terminated. The single exposed animal was humanely euthanized and no other animals were exposed to this material.

Based on the result of this study, Isooctyltrichlorosilane is a Class 8 Corrosive Material and is assigned to Packing Group I. The following is the U.S. DOT definition of a Packing Group I corrosive substance: "Substances that cause visible destruction or irreversible alterations of the skin tissue at the site of contact when tested on the intact skin of an animal for a period of not more than 3 minutes."

*BJD*

BJD - 6077

cc: D.J. Billmaier, M.D.  
R.K. Crissey  
S. O'Leary  
C.T. Mathew  
G.A. Roy - Archives\*  
Library\*  
TOX Staff  
File: TOX-071A

\*Copy of Report

**A DERMAL CORROSIVITY STUDY IN RABBITS  
WITH ISOCTYLTRICHLOROSILANE (478-94A)**

FINAL REPORT

Author

Todd N. Merriman, B.S., LATG

Study Completed on

March 17, 1995

Performing Laboratory

Springborn Laboratories, Inc. (SLS)  
Life Sciences Division  
640 North Elizabeth Street  
Spencerville, OH 45887

SLS Study No.

3167.200

AlliedSignal Protocol/Project No.

94083/TOX-071A

Submitted to

AlliedSignal Inc.  
P.O. Box 1139  
Morristown, NJ 07962-1139

Page 1 of 39

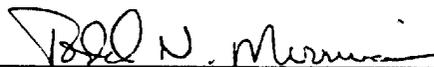
TOX Computer Entry No.  
TOX-071A-95-1 3/23/95

### COMPLIANCE STATEMENT

This study was conducted in compliance with the Good Laboratory Practice Regulations as described by the FDA (21 CFR Part 58) and the EPA (40 CFR Parts 160 and 792) with the following exceptions:

The Sponsor is responsible for any necessary evaluations related to chemical composition, purity, strength, stability and other data required by 21 CFR Part 58.105, 40 CFR Parts 160.105 and 792.105.

The in-life critical phase for this study was inadvertently not performed by the SLS Quality Assurance Unit.



\_\_\_\_\_  
Todd N. Merriman, B.S., LATG  
Study Director/Author  
Springborn Laboratories, Inc.

Date 3/17/95

**QUALITY ASSURANCE STATEMENT**

This study was inspected by the Quality Assurance Unit and reports were submitted to management and the study director in accordance with SLS's Standard Operating Procedures as follows:

<u>Phase</u>	<u>Date</u>
Data Audit	01/17/95
Draft Report Review	01/19/95
Final Report Review	03/17/95
Reports to Study Director and Management	01/19/95, 03/17/95

This study was conducted in compliance with the Good Laboratory Practice Regulations as described by the FDA (21 CFR Part 58) and the EPA (40 CFR Parts 160 and 792) except as noted on the Compliance Statement.

Christopher W. Wilson  
for Melissa R. Triplett  
Quality Assurance Auditor II

Date 3/17/95

Raymond V. Karcher  
Raymond V. Karcher, B.A., LAT  
Manager of Quality Assurance

Date 3-17-95

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### SUMMARY

The potential irritant and/or corrosive effects of Isooctyltrichlorosilane (478-94A) were evaluated on the dermal tissue of New Zealand White rabbits. One rabbit initially received three 0.5 ml doses of the test article. The doses were held in contact with the skin under a semi-occlusive binder for an exposure period of 3 minutes. Following the 3 minute exposure period, an approximate 2" x 2" section of the overlying elastic wrap was cut and the patch was removed. The remaining test article was initially wiped from the test site using dry gauze. The test site was then wiped with gauze moistened with distilled water. Due to the evidence of blanching and the smoke-like cloud reaction which was observed following residual test article removal in the one animal initially dosed, dosing was discontinued for the remaining intervals (i.e., 1 and 4 hour) and the remaining five animals. The elastic wrap and remaining patches were removed from the rabbit and the study was terminated. The animal which was dosed was humanely euthanized.

Exposure to the test article for a 3 minute exposure period produced severe blanching (whitish-green coloration of the skin site) and moderate edema on 1/1 test sites at the 3 minute scoring interval. An additional finding of a smoke-like cloud rising from the test site was also noted following residual test article removal. Due to the evidence of corrosion (severe blanching) noted at the 3 minute interval in the first animal dosed, the dosing was discontinued, the study was terminated and the dosed animal was humanely euthanized.

Under the conditions of this test, Isooctyltrichlorosilane (478-94A) was considered corrosive for the 3 minute exposure period.

## I. INTRODUCTION

This study was performed to assess the potential irritant and/or corrosive effects of Isooctyltrichlorosilane (478-94A) in New Zealand White rabbits when administered by a single dermal dose. This study is intended to provide information on the potential health hazards of the test article with respect to dermal exposure. Data from this study may serve as a basis for classification and/or labeling of the test article. This study was performed at Springborn Laboratories, Inc., 553 North Broadway, Spencerville, Ohio.

## II. MATERIALS AND METHODS

### Study Dates

Study Initiation: November 7, 1994  
Experimental Initiation: November 21, 1994  
Experimental Completion: November 21, 1994

### Protocol

The study protocol and Protocol Amendment No. 1 are presented in Appendix A.

### Test Article

Sponsor I.D.: Isooctyltrichlorosilane (478-94A)  
Lot No.: None provided  
Springborn I.D.: S94.022.3167  
Receipt Date: November 1, 1994  
Physical Description: Clear, colorless liquid  
Storage Conditions: Room temperature  
Expiration Date: None provided

The Sponsor is responsible for any necessary evaluations related to chemical composition, purity, strength, stability and other data required by 21 CFR Part 58.105, 40 CFR Parts 160.105 and 792.105.

### Test Article Preparation

The test article was administered as received from the Sponsor.

**Animals and Animal Husbandry**

Description: Adult, New Zealand White rabbits were received at SLS from Myrtle's Rabbitry, Thompson Station, TN.

Method of Identification: Upon receipt, plastic ear tags displaying unique identification numbers were used to individually identify the animals. Cage cards displaying at least the study number, animal number and sex were affixed to each cage.

Housing: The animals were housed individually in suspended stainless steel cages. All housing and care were based on the standards recommended by the Guide for the Care and Use of Laboratory Animals [1].

Environment: The animal room temperature and relative humidity were 70° F and 43%, respectively. Environmental control equipment was monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers were set to maintain a 12-hour light/12-hour dark cycle. There were ten to twelve air changes in the animal room per hour. The animal room temperature and relative humidity were recorded a minimum of once daily.

Food: Purina Certified Rabbit Chow #5322 was provided ad libitum to the animals throughout the study. The lot number and expiration date of each batch of diet used during the study were recorded. The feed was analyzed by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits, contaminants which may have been present were not expected to compromise the purpose of this study. Results of the dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These are maintained by SLS.

Water: Municipal tap water treated by reverse osmosis was available to the animals ad libitum throughout the study. The purified water was supplied by an automatic watering system. Monitoring of the drinking water for contaminants was conducted by SLS and the records are available for inspection. Within generally accepted limits, contaminants which may have been present were not expected to compromise the purpose of this study.

Quarantine: Upon receipt, animals were examined, identified with plastic ear tags and then quarantined for a minimum of five days.

Animal Selection: The animals chosen for study use were arbitrarily selected from healthy stock animals to avoid potential bias. All animals received a detailed pretest examination prior to dosing. Only healthy animals were chosen for study use.

### III. EXPERIMENTAL PROCEDURES [2]

Preliminary Procedures: On day -1, the animals chosen for use on the dermal corrosivity study had the fur removed from the dorsal area of the trunk using an animal clipper. Care was taken to avoid abrading the skin during the clipping procedure.

Dosing: On the following day (day 0), the test article was applied to a small area of intact skin on one test animal (approximately 1 inch x 1 inch) for each exposure period (one site per exposure interval) as indicated below:

Exposure Period	Concentration (%)	Amount Applied	Patch Design	No. of Animals	
				Male	Female
3 Minute	100	0.5 ml	1" x 1" square 4 ply gauze patch		
1 Hour	100	0.5 ml	1" x 1" square 4 ply gauze patch	1	0
4 Hour	100	0.5 ml	1" x 1" square 4 ply gauze patch		

For the 3 minute, 1 and 4 hour dosing procedures, the material was administered to each site under the 1" x 1" square 4 ply gauze patch. The gauze patch was held in contact with the skin at the cut edges with a non-irritating tape. Removal and ingestion of the test article was prevented by placing an elastic wrap over the trunk and test area (semi-occlusive binding). Using an indelible marker, a dot was placed on the elastic wrap over the area where each test site was located in order to facilitate removal of the patch at the appropriate exposure time interval. The elastic wrap was then further secured with adhesive tape around the trunk at the cranial and caudal ends. After dosing, a collar was placed on the animal and remained in place until removal at study termination (day 0).

Following completion of the 3 minute exposure period, an approximate 2" x 2" window was cut into the elastic wrap over the first designated test site and the gauze patch and tape removed. The corners of the test site were delineated using a marker and the residual test article was removed using dry gauze followed by wiping with gauze moistened with distilled water. Following patch removal for the exposure, the elastic wrap was taped down with nonirritating tape around the cut window in order to insure that the test site remains nonoccluded during the remainder of the study. Due to the evidence of corrosion observed (blanching) in the animal dosed, the study was terminated, the elastic wrap and remaining patches were removed from the test animal and the dosed animal was humanely euthanized following the 3 minute scoring interval.

Dermal Observations: The animal was examined for signs of erythema and edema and the responses scored after patch removal (for the 3 minute exposure period only) according to the Dermal Grading System presented in Appendix B which is based on Draize [3].

Clinical Observations: Any unusual observations and/or mortality were recorded. Mortality checks were performed twice daily, in the morning and afternoon.

Body Weights: Individual body weights were obtained for each animal prior to dosing on study day 0.

Gross Necropsy: The one animal which was dosed was euthanized (intravenous injection of sodium pentobarbital) following its 3 minute observation interval. A gross necropsy examination was not required for this animal.

### **Protocol Deviations**

The test site was initially wiped with dry gauze followed by gauze moistened with distilled water in an attempt to remove any residual test article. This occurrence was believed to have had no impact on the outcome of the study.

## **IV. ANALYSIS OF DATA [3]**

Corrosion was considered to have resulted if the substance in contact with rabbit skin had caused destruction or irreversible alteration of the tissue. Tissue destruction was considered to have occurred if there was ulceration, necrosis or severe blanching. Tissue destruction does not include merely sloughing of the epidermis, or erythema, edema or fissuring. The analyses of data was based on the one animal dosed.

## **V. MAINTENANCE OF RAW DATA AND RECORDS**

The remaining test article was returned to the Sponsor following completion of the in life phase of the study. Where necessary, the Sponsor was responsible for maintaining a retention sample of the test article. All original paper data, the final report and magnetically encoded records were transferred to the SLS archives for a period of 10 years. The Sponsor will be contacted prior to final disposition of these items

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**VI. RESULTS****Dermal Observations:**

Individual Data: Table 1

Exposure to the test article for a 3 minute exposure period produced severe blanching (whitish-green coloration of skin site) and moderate edema on 1/1 test sites at the 3 minute scoring interval. An additional finding of a smoke-like cloud rising from the test site was also noted following residual test article removal. Due to the evidence of corrosion (severe blanching) noted at the 3 minute interval in the first animal dosed, the dosing was discontinued, the study was terminated and the dosed animal was humanely euthanized.

**VII. CONCLUSION**

Under the conditions of this test, Isooctyltrichlorosilane (478-94A) was considered corrosive for the 3 minute exposure period.

Todd N. Merriman  
Todd N. Merriman, B.S., LATG  
Study Director

Date 3/17/95**VIII. REPORT REVIEW**

Deborah A. Douds  
Deborah A. Douds, M.S.  
Toxicologist

Date 3/17/95

Kimberly L. Bonnette  
Kimberly L. Bonnette, M.S., LATG  
Manager of Acute Toxicology

Date 3/17/95

IX. **REFERENCES**

1. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 86-23, 1985.
2. 49 CFR, Part 173, Sections 173.136, 173.137 and Appendix A, (USDOT, October 1, 1992).
3. Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, The Association of Food and Drug Officials of the United States, 49-51, 1959.

SLS STUDY NO.: 3167.200  
CLIENT: ALLIEDSIGNAL INC.

TABLE 1  
A DERMAL CORROSIVITY STUDY IN RABBITS  
INDIVIDUAL DERMAL IRRITATION SCORES  
(3 MINUTE EXPOSURE)

PAGE 1

Animal No./Sex Body Weight (kg)	Scoring Interval	Erythema	Edema	Comments (Key to Codes - Appendix B)
51641/M 2.248	3 Minute	4	3	BLA-4*

\*Test site appeared whitish-green in color at the time of patch removal. A smoke-like cloud rose from the test site following residual test article removal. Due to severe blanching and the additional finding noted, the study was terminated, the dosed animal was humanely euthanized and the remaining five animals were not dosed.

**APPENDIX A**

**Protocol and Amendment**

A DERMAL CORROSIVITY STUDY IN RABBITS WITH  
ISOOCTYLTRICHLOROSILANE (478-94A)

Springborn Study No. 3167.200

Springborn Laboratories, Inc. (SLS)  
Life Sciences Division  
640 North Elizabeth Street  
Spencerville, Ohio 45887

Todd N. Merriman, A.S., LATG  
Study Director

For

AlliedSignal Inc.  
P.O. Box 1139  
Morristown, NJ 07962-1139

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I. PURPOSE

To assess the potential irritant and/or corrosive effects of a test article in rabbits when administered by a single dermal dose. This study is intended to provide information on the potential health hazards of the test article with respect to dermal exposure. Data from this study may serve as a basis for classification and/or labeling of the test article.

II. SPONSOR

AlliedSignal Inc.  
P.O. Box 1139  
Morristown, NJ 07962-1139

III. SPONSOR'S REPRESENTATIVE

Mr. Brendan J. Dunn  
Phone: (201) 455-6077  
Fax: (201) 455-5405

IV. TESTING LOCATION

Springborn Laboratories, Inc.  
Life Sciences Division  
553 North Broadway  
Spencerville, OH 45887  
Phone: (419) 647-4196  
FAX: (419) 647-6458

V. SPRINGBORN PERSONNEL RESPONSIBILITIES

Todd N. Merriman, A.S., LATG  
Study Director/Toxicologist

Kimberly L. Bonnette, M.S., LATG  
Alternate Contact/Assistant Manager of Acute Toxicology

Malcolm Blair, Ph.D.  
Vice President/Director of Research

Joseph C. Siglin, M.S., DABT  
Associate Director of Toxicology

Rusty E. Rush, M.S., LAT  
Manager of Acute Toxicology and Special Studies

Deborah A. Douds, M.S.  
Toxicologist

Patricia K. Jenkins, AAS, LATG, RILAM  
Acute Toxicology Supervisor

Pamela S. Smith, ALAT  
Unit Leader

Delores P. Knippen  
Pharmacy Supervisor

Steven H. Magness, B.S., LATG  
Supervisor of Gross & Fetal Pathology

Anita M. Bosau  
Director of Quality Assurance

Raymond V. Karcher, B.A., LAT  
Quality Assurance Supervisor

VI. PROPOSED STUDY SCHEDULE

- A. Experimental Initiation: November 1994
- B. Experimental Completion: November 1994
- C. Audited Report Date: Eight weeks following experimental completion

## VII. TEST ARTICLE IDENTIFICATION

### A. Sponsor's Identification

Isooctyltrichlorosilane (478-94A)

### B. SLS Test Article Identification Number

S94.022.3167

### C. Characteristics

The Sponsor is responsible for any necessary evaluations related to chemical composition, purity, strength, stability and other data required by 21 CFR Part 58.105, 40 CFR Parts 160.105 and 792.105. Any special storage conditions for the test article will be supplied by the Sponsor.

### D. Handling Precautions

Safety data regarding the test article should be provided by the Sponsor (Material Safety Data Sheet or equivalent, if available). Technical personnel should review this information prior to handling the test article. In addition, any special handling precautions will be provided by the Sponsor/Study Director.

### E. Method of Test Article Preparation

Liquids, gels and pastes are generally administered as received from the Sponsor. Solids and powders are also generally dosed as received from the Sponsor. Solids and powders may need to be ground and sieved prior to test use in order to improve test article contact with the skin. The test article will be prepared and/or dispensed fresh on the day of dosing. The method of preparation will be documented in the raw data and presented in the final report.

## VIII. TEST SYSTEM

### A. Justification of Test System

1. The rabbit is the preferred species for primary skin irritation testing by various U.S. and International regulatory agencies.

2. The New Zealand White rabbit has been shown to be sensitive to the irritant/corrosive effects of a variety of drugs and chemicals. Therefore, this species and strain is a reasonable alternative to larger mammals for primary skin irritation testing of drugs and chemicals for human safety assessment.
3. The New Zealand White rabbit has been used extensively for skin irritation testing. Thus, data from this study may be compared and contrasted to other studies performed in New Zealand White rabbits.
4. Historical information concerning New Zealand White rabbits is available at SLS and in the published literature.
5. Healthy, outbred New Zealand White rabbits may be obtained from reliable, USDA approved and regulated suppliers.
6. The laboratory rabbit may be safely handled and manipulated by trained technical personnel.

B. Justification of Route of Exposure and Number of Animals

1. Dermal administration of the test substance was selected since this is a potential route of human exposure.
2. Since New Zealand White rabbits have no pigment and have a relatively large dorsal surface area, dermally administered substances may be accurately applied and any resulting effects easily observed.
3. The number of animals used on this study will be consistent with the guidelines published by U.S. and International regulatory agencies including DOT and IMO.

C. Description

1. Species

Rabbit

2. Strain

New Zealand White

**BEST COPY AVAILABLE**

3. Source

Myrtle's Rabbitry or another USDA approved supplier

4. Age and Body Weight Range

Adult, approximately 2.0 to 3.5 kg (prior to dosing on day 0)

5. Number and Sex

6 rabbit test (males and/or females)

D. Method of Identification

Plastic ear tags displaying unique identification numbers will be used to individually identify the animals. Cage cards displaying at least the study number, animal number, and sex will be affixed to each cage.

IX. ANIMAL HUSBANDRY AND EXPERIMENTAL DESIGNA. Animal Housing1. Housing

The animals will be housed individually in suspended stainless steel cages. All housing and care will conform to the standards recommended by the Guide for the Care and Use of Laboratory Animals [1].

2. Environment

The environmental conditions in the animal room will be controlled. The desired animal room temperature and relative humidity ranges are 61-73° F and 40-70%, respectively. Environmental control equipment will be monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers will be set to maintain a 12-hour light/12-hour dark cycle. There will be ten to twelve air changes in the animal room per hour. The animal room temperature and relative humidity will be recorded a minimum of once daily.

### 3. Food

Purina Certified Rabbit Chow #5322 will be provided ad libitum to the animals throughout the study. The lot number and expiration date of each batch of diet used during the study will be recorded. The feed is analyzed by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits, contaminants which may be present are not expected to compromise the purpose of this study. Results of the dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These will be maintained by the testing laboratory.

### 4. Water

Municipal tap water treated by reverse osmosis or deionization (back-up system) will be available ad libitum throughout the study. The purified water will be supplied by an automatic watering system. Monitoring of the drinking water for contaminants will be conducted by the testing laboratory and the records will be available for inspection. Within generally accepted limits, contaminants which may be present are not expected to compromise the purpose of this study.

### B. Quarantine

Upon receipt, the animals will be examined, identified with plastic ear tags, and then quarantined for a minimum of 5 days.

### C. Animal Selection

The animals chosen for study use will be arbitrarily selected from healthy stock animals to avoid potential bias. All animals will receive a detailed pretest observation prior to dosing. Only healthy animals will be chosen for study use. Females will be nulliparous and nonpregnant.

D. Experimental Design [2]

The Sponsor may select the following options:

- Perform a 3-minute exposure only
- Perform a 1-hour exposure only
- Perform a 4-hour exposure only
- Perform a 3-minute and a 1-hour exposure
- Perform a 1-hour and a 4-hour exposure
- Perform a 3-minute, 1-hour, and a 4-hour exposure

X. EXPERIMENTAL PROCEDURESA. Preliminary Procedures

On day -1, the animals chosen for use on the dermal corrosivity study will have the fur removed from the dorsal area of the trunk using an animal clipper. Care will be taken to avoid abrading the skin during the clipping procedure.

B. Dosing

On the following day (day 0), the test article will be applied to a small area of intact skin on each test animal (approximately 1 inch x 1 inch) for each exposure period (one site per exposure interval) as indicated below:

1. If the test article is a liquid, gel or paste, a 0.5 ml dose of the material will be administered to each site under an approximate 1 inch x 1 inch square 4 ply gauze patch. The gauze patch(es) will be held in contact with the skin at the cut edges with a non-irritating tape. Removal and ingestion of the test article will be prevented by placing an elastic wrap over the trunk and test area (semi-occlusive binding). In the event that more than one exposure interval is required, using an indelible marker, a dot will be placed on the elastic wrap over the area where each test site is located in order to facilitate removal of the patch at the appropriate exposure time interval. The elastic wrap will then be further secured with adhesive tape around the trunk at the cranial and caudal ends.

2. If the test article is a solid or a powder, 0.5 g of the test article will be applied to an approximate 1 inch x 1 inch square 4 ply gauze patch. The gauze patch will be held in contact with the skin at the cut edges with a non-irritating tape. Removal and ingestion of the test article will be prevented by placing an elastic wrap over the trunk and test area (semi-occlusive binding). In the event that more than one exposure interval is required using an indelible marker, a dot will be placed on the elastic wrap over the area where each test site is located in order to facilitate removal of the patch at the appropriate exposure time interval. The elastic wrap will then be further secured with adhesive tape around the trunk at the cranial and caudal ends. At the Sponsor's request, the test article will be moistened with 0.5 ml of distilled water and the gauze patch applied to the test site.

Following dosing, the Study Director will be notified by the technician if severe local reactions occur or if the animals exhibit overt clinical indications of pain/distress immediately postdose. If such is noted, the Sponsor will be contacted to see if the animals should be humanely euthanized. After dosing, collars will be placed on the animals and will remain in place until removal on day 3. Patch removal will be performed for each exposure period as indicated below:

- a. One exposure period study: following completion of the exposure period, the tape, elastic wrap, and gauze patch will be removed from each animal and the corners of the test site delineated using a marker. Residual test article will then be removed using gauze moistened with distilled water. If the distilled water does not sufficiently remove the test article residue, the Study Director/Sponsor may choose to use another appropriate solvent.
- b. Two exposure period study: following completion of the first exposure period, an approximate 2 inch x 2 inch window will be cut into the elastic wrap over the first test site and the gauze patch and tape removed. The corners of the test site will be delineated using a marker and the residual test article will then be removed using gauze moistened with distilled water. The elastic wrap will be taped down with nonirritating tape around the cut window in order to insure that the test site remains nonoccluded during the remainder of the study. Following completion of the second exposure period, the gauze and tape on the second exposure site and the entire elastic wrap will be removed. The corners of the test site for the

second exposure will be delineated using a marker and the residual test article removed using gauze moistened with distilled water. If the distilled water does not sufficiently remove the test article residue, the Study Director/Sponsor may choose to use another appropriate solvent. NOTE: If after the first exposure period the test sites appear to be corrosive, the Study Director will be contacted and the remaining test article periods may be terminated.

- c. Three exposure period study: Following completion of the first exposure period, an approximate 2 inch x 2 inch window will be cut into the elastic wrap over the first test site and the gauze patch and tape removed. The corners of the test site will be delineated using a marker and the residual test article will then be removed using gauze moistened with distilled water. Following patch removal for the exposure, the elastic wrap will be taped down with nonirritating tape around the cut window in order to insure that the test site remains nonoccluded during the remainder of the study. Following completion of the second exposure period, an approximate 2 inch x 2 inch window will be cut into the elastic wrap in the same manner as was performed for the first exposure site. The gauze patch and tape will be removed and the corners of the test site delineated using a marker. The residual test article will then be removed using gauze moistened with distilled water. Following patch removal for the exposure, the elastic wrap will be taped down with nonirritating tape around the cut window in order to insure that the test site remains nonoccluded during the remainder of the study. Following completion of the third exposure period, the gauze patch and tape on the third test site and the entire elastic wrap will be removed and the corners of the test site delineated using a marker. The residual test article will then be removed using gauze moistened with distilled water. If the distilled water does not sufficiently remove the test article residue, the Study Director/Sponsor may choose to use another appropriate solvent. NOTE: If after the first or second exposure period the test sites appear to be corrosive, the Study Director will be contacted and the remaining test article exposure periods may be terminated.

### C. Body Weights

Individual body weights will be obtained for each animal prior to dosing on study day 0.

D. Dermal Observations

Animals will be examined for signs of erythema and edema and the responses scored after patch removal (for each exposure period) according to the Dermal Grading System presented in Protocol Appendix A which is based on Draize [3]. Animals will be further examined for signs of erythema and edema and the responses scored at approximately 24, 48, and 72 hours after patch application. If there is no evidence of dermal irritation at the 72 hour scoring interval, the study will be terminated. If dermal irritation persists at any test site, the observation period may be extended for the affected animals (scored on days 7, 10 and 14). Animals requiring an extended observation period will remain on test (up to and including 14 days post-dose) until the irritation has resolved, permanent injury is evident, or the Study Director/Sponsor determines that additional scoring intervals are unnecessary. The dermal test sites may be reclipped as necessary to allow clear visualization of the skin.

E. Clinical Observations

Any unusual observations and/or mortality will be recorded. Mortality checks will be performed twice daily, in the morning and afternoon.

F. Unscheduled Deaths

Any animals dying or euthanized (due to a possible accidental injury) during the study period will be necropsied. Body cavities (cranial, thoracic, abdominal, and pelvic) will be observed and examined. No tissues will be retained.

G. Scheduled Euthanasia

Each surviving animal will be euthanized by an intravenous injection of sodium pentobarbital following each animals final scoring interval. A gross necropsy examination will not be required for surviving animals.

XI. DATA REPORTING

One unbound copy of the draft report will be submitted to the Sponsor. Two copies of the final report (one bound and one unbound) will be submitted to the Sponsor. The final report will include all information necessary to provide a complete and accurate description and evaluation of the experimental procedures and results.

The report will include at least the following information and data:

- Table of Contents
- Regulatory Compliance
- Summary
- Introduction
- Experimental Design and Test Procedures
- Presentation and Discussion of Results
- Conclusion
- References
- Data Tables
- Protocol and Amendments
- SLS Personnel Responsibilities

#### XII. ANALYSIS OF DATA

Each exposure period will be evaluated independently. Corrosion will be considered to have resulted if the substance in contact with rabbit skin has caused destruction or irreversible alteration of the tissue on at least two of the rabbits tested. Tissue destruction is considered to have occurred if, at any of the readings, there is ulceration or necrosis. Tissue destruction does not include merely sloughing of the epidermis, or erythema, edema or fissuring.

#### XIII. MAINTENANCE OF RAW DATA, RECORDS AND SPECIMENS

All original data, magnetically encoded records, specimens and reports from this study are the property of the Sponsor. These materials shall be available at SLS to facilitate auditing of the study during its progress and prior to acceptance of the final report. The remaining test article(s) will be returned to the Sponsor following completion of the in-life phase of the study. Where necessary, the Sponsor will be responsible for maintaining a retention sample of the test article. All original paper data, the final report, magnetically encoded records, and any specimens will be transferred to the SLS archives for a period of 10 years. The Sponsor will be contacted prior to the final disposition of these items.

#### XIV. REGULATORY COMPLIANCE

This study may be submitted to and will be performed in general compliance with DOT guidelines; the principles of the Good Laboratory Practice regulations as described by the FDA (21 CFR Part 58) and the EPA (40 CFR Parts 160 and 792). Changes may be made in this protocol prior to, during, and/or following study

completion. A protocol amendment will be prepared for such changes and will be signed by the Study Director, SLS Quality Assurance Unit and the Sponsor. The Sponsor shall be notified as soon as practical whenever an event occurs that is unexpected and may have an effect on the study.

#### XV. QUALITY ASSURANCE

The study will be inspected at least once during the in-life phase by the Springborn Laboratories, Inc., Life Sciences Division's Quality Assurance Unit to assure compliance with Good Laboratory Practice regulations, SLS's Standard Operating Procedures and for conformance with the protocol and protocol amendments. The final report will be audited prior to submission to the Sponsor to ensure that it completely and accurately describes the test procedures and results of the study.

#### XVI. USDA ANIMAL WELFARE COMPLIANCE STATEMENT

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR) and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (OPRR, NIH, 1986). Wherever possible, procedures used in this study have been designed to avoid or minimize discomfort, distress and pain to animals. All methods are described in this study protocol or in written laboratory standard operating procedures. These procedures are based on the most currently available technologies concerning proper laboratory animal use and management. This protocol has been reviewed and approved by Springborn Laboratories, Inc. Institutional Animal Care and Use Committee (IACUC) for a maximum of 12 animals.

This study is being conducted to evaluate potential irritant effects of the test article and potential reversibility of such effects. Following dosing, the Study Director will be notified by the technician if severe local reactions occur or if the animals exhibit overt clinical indications of pain/distress immediately postdose. If such is noted, the Sponsor will be contacted to see if the animals should be humanely euthanized. In the event that the Sponsor cannot be contacted, the Study Director and/or Facility Veterinarian may decide to humanely euthanize the animals. Methods of euthanasia used during this study are in conformance with the above referenced regulations and the American Veterinary Medical Association Panel on Euthanasia (JAVMA, 1993).

XVII. PROTOCOL APPROVAL

The Sponsor's signature below documents for the Study Director that there are no acceptable non-animal alternatives for this study, the study does not unnecessarily duplicate previous studies and that the study is needed for regulatory purposes and/or human safety assessment.

Todd N. Merriman Date 11/7/94  
Todd N. Merriman, A.S., LATG  
Study Director (SLS)

Raymond V. Karcher Date 11-4-94  
Raymond V. Karcher, B.A., LAT  
Quality Assurance Unit (SLS)

Patricia K. Jenkins Date 11-7-94  
Patricia K. Jenkins, A.A.S., LATG, RILAM  
IACUC Representative (SLS)

Brendan J. Dunn Date 11-11-94  
Brendan J. Dunn  
Sponsor's Representative  
(Principal Investigator)

XVIII. REFERENCES

1. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 86-23, 1985.
2. 49 CFR, Part 173, Sections 173.136, 173.137 and Appendix A, (USDOT, October 1, 1992).
3. Draize, J.H., Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, The Association of Food and Drug Officials of the United States, 49-51, 1959.

PROTOCOL APPENDIX A  
DERMAL GRADING SYSTEM

ERYTHEMA	
OBSERVATION	CODE
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 formations (injuries in depth)	4

EDEMA	
OBSERVATION	CODE
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 extends beyond the area of exposure)	4

An erythema and edema code will be assigned to each test site.

PROTOCOL APPENDIX A--(Continued)  
DERMAL GRADING SYSTEM

NOTABLE DERMAL LESIONS		
OBSERVATION	CODE	DEFINITION
Eschar - Focal/pinpoint	ES-1	Focal and/or pinpoint areas in test site.
Eschar - Mild	ES-2	>focal/pinpoint < 25% of test site.
Eschar - Moderate	ES-3	>25% < 50% of test site.
Eschar - Severe	ES-4	>50% of test site.
Blanching - Focal/pinpoint	BLA-1	Focal and/or pinpoint areas in test site.
Blanching - Mild	BLA-2	>focal/pinpoint < 25% of test site.
Blanching - Moderate	BLA-3	>25% < 50% of test site.
Blanching - Severe	BLA-4	>50% of test site.
Ulceration - Focal/pinpoint	U-1	Focal and/or pinpoint areas in test site.
Ulceration - Mild	U-2	>focal/pinpoint < 25% of test site.
Ulceration - Moderate	U-3	>25% < 50% of test site.
Ulceration - Severe	U-4	>50% of test site.

If the eschar, blanching and/or ulceration is focal and/or pinpoint, the remaining portion of the test site will be assigned the appropriate erythema and edema score (ie: 0, 1, 2, 3 or 4) and the score footnoted with the appropriate code (ie: BLA-1, ES-1 and/or U-1).

If the eschar, blanching and/or ulceration is greater than the focal and/or pinpoint, the maximum score of "4" will be assigned to the site for erythema and the score footnoted with the appropriate code (ex: BLA-2, ES-3 and/or U-4). The appropriate edema score will then be assigned to the site.

PROTOCOL APPENDIX A--(Continued)  
DERMAL GRADING SYSTEM

SECONDARY DERMAL FINDINGS		
OBSERVATION	CODE	DEFINITION
Desquamation	DES	Characterized by scaling or flaking of dermal tissue with or without denuded areas. Scab-like areas of eschar are not scored for desquamation.
Fissuring	FIS	Characterized by cracking of the skin with or without moist exudate. Fissuring should be checked prior to manipulating the test site. Scab-like areas of eschar are not scored for fissuring
Eschar Exfoliation	EXF	The process by which a scab-like or slough-like formation flakes off the test site.
Test Article Staining Test Site	TAS	Skin located at test site appears to be discolored due to the test article (note color of staining).
Ancillary Irritation on the Trunk Outside the Test Site	IT	Dermal irritation or lesions that are located outside the test site on the animals' trunk. These findings are commonly mechanically induced (ex: animal movement following wrapping, compression of the skin by the tape/binder and/or removal of the adhesive tape).

Any additional dermal findings will be noted in the raw data and in the final report.

**A DERMAL CORROSIVITY STUDY IN RABBITS  
WITH ISOCTYLTRICHLOROSILANE (478-94A)**

**PROTOCOL AMENDMENT  
NO. 1**

SLS Study No.: 3167.200  
AlliedSignal Protocol/Project No.: 94083/TOX-071A  
Test Article I.D.: Isooctyltrichlorosilane (478-94A)

Page 1 of 1

1) PART TO BE CHANGED/REVISED: TITLE PAGE

CHANGE/REVISION: Add the following:

AlliedSignal Protocol/Project No.

94083/TOX-071A

REASON FOR CHANGE/REVISION: The AlliedSignal Protocol/Project No. was inadvertently not added to the protocol.

2) PART TO BE CHANGED/REVISED: XII. ANALYSIS OF DATA

CHANGE/REVISION: Change the third sentence to read as follows: Tissue destruction is considered to have occurred if, at any of the readings, there is ulceration, necrosis or severe blanching.

REASON FOR CHANGE/REVISION: Severe blanching was listed as an added criteria for identifying tissue destruction in the ANALYSIS OF DATA section.

Todd N. Merriman  
Todd N. Merriman, A.S., LATG  
Study Director (SLS)

Date 1/19/95

Brendan J. Dunn  
Brendan J. Dunn  
Sponsor's Representative

Date 1-23-95

Raymond V. Karcher  
Raymond V. Karcher, B.A., LAT  
Quality Assurance Supervisor (SLS)

Date 1-19-95

**APPENDIX B**

**Dermal Grading System**

**DERMAL GRADING SYSTEM**

ERYTHEMA	
OBSERVATION	CODE
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 formations (injuries in depth)	4

EDEMA	
OBSERVATION	CODE
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 extends beyond the area of exposure)	4

An erythema and edema code were assigned to each test site.

**DERMAL GRADING SYSTEM**

NOTABLE DERMAL LESIONS		
OBSERVATION	CODE	DEFINITION
Eschar - Focal/pinpoint	ES-1	Focal and/or pinpoint areas in test site.
Eschar - Mild	ES-2	> focal/pinpoint < 25% of test site.
Eschar - Moderate	ES-3	> 25% < 50% of test site.
Eschar - Severe	ES-4	> 50% of test site.
Blanching - Focal/pinpoint	BLA-1	Focal and/or pinpoint areas in test site.
Blanching - Mild	BLA-2	> focal/pinpoint < 25% of test site.
Blanching - Moderate	BLA-3	> 25% < 50% of test site.
Blanching - Severe	BLA-4	> 50% of test site.
Ulceration - Focal/pinpoint	U-1	Focal and/or pinpoint areas in test site.
Ulceration - Mild	U-2	> focal/pinpoint < 25% of test site.
Ulceration - Moderate	U-3	> 25% < 50% of test site.
Ulceration - Severe	U-4	> 50% of test site.

If the eschar, blanching and/or ulceration was focal and/or pinpoint, the remaining portion of the test site was assigned the appropriate erythema and edema score (i.e., 0, 1, 2, 3 or 4) and the score footnoted with the appropriate code (i.e., BLA-1, ES-1 and/or U-1).

If the eschar, blanching and/or ulceration was greater than the focal and/or pinpoint, the maximum score of "4" was assigned to the site for erythema and the score footnoted with the appropriate code (ex: BLA-2, ES-3 and/or U-4). The appropriate edema score was then assigned to the site.

**DERMAL GRADING SYSTEM**

<b>SECONDARY DERMAL FINDINGS</b>		
<b>OBSERVATION</b>	<b>CODE</b>	<b>DEFINITION</b>
<b>Desquamation</b>	<b>DES</b>	Characterized by scaling or flaking of dermal tissue with or without denuded areas. Scab-like areas of eschar are not scored for desquamation.
<b>Fissuring</b>	<b>FIS</b>	Characterized by cracking of the skin with or without moist exudate. Fissuring should be checked prior to manipulation the test site. Scab-like areas of eschar are not scored for fissuring.
<b>Eschar Exfoliation</b>	<b>EXF</b>	The process by which a scab-like or slough-like formation flakes off the test site.
<b>Test Article Staining Test Site</b>	<b>TAS</b>	Skin located at test site appears to be discolored due to the test article (note color of staining).
<b>Ancillary Irritation on the Trunk Outside the Test Site</b>	<b>IT</b>	Dermal irritation or lesions that are located outside the test site on the animals' trunk. These finding are commonly mechanically induced (ex: animal movement following wrapping, compression of the skin by the tape/binder and/or removal of the adhesive tape).

**APPENDIX C**

**SLS Personnel Responsibilities**

**SLS PERSONNEL RESPONSIBILITIES**

Todd N. Merriman, B.S., LATG	Study Director/Toxicologist
Kimberly L. Bonnette, M.S., LATG	Alternate Contact/Manager of Acute Toxicology
Malcolm Blair, Ph.D.	Vice President/Director of Research
Joseph C. Siglin, M.S., DABT	Associate Director of Toxicology
Rusty E. Rush, M.S., LAT, DABT	Associate Director of Toxicology
Deborah A. Douds, M.S.	Toxicologist
Patricia K. Jenkins, AAS, LATG, RILAM	Acute Toxicology Supervisor
Pamela S. Smith, LAT	Unit Leader
Anita M. Bosau	Director of Regulatory Affairs
Raymond V. Karcher, B.A., LAT	Manager of Quality Assurance
Delores P. Knippen	Pharmacy Supervisor
Steven H. Magness, B.S., LATG	Gross and Fetal Pathology Supervisor