

**elf atochem**

**ATO**

(B)

ELF ATOCHEM NORTH AMERICA, INC.  
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Contains No CBI

8EHQ-0894-13118

May 18, 1994

**FEDERAL EXPRESS  
RETURN RECEIPT REQUESTED**

PDCN: ~~88940000360~~  
88940000360

Document Processing Center (TS-790)  
Office of Pollution Prevention and Toxics  
Environmental Protection Agency  
401 M St. S.W.  
Washington, D.C. 20460  
Attn: Section 8(e) Coordinator



94 MAY 23 AM 10: 28

RECEIVED

Subject: TSCA Section 8(e) Submission



89940000254/0

Dear Sir/Madam:

Elf Atochem North America Inc. has received the final report from an acute dermal toxicity study in rats and is submitting it to the Environmental Protection Agency (EPA) pursuant to Toxic Substances Control Act (TSCA) Section 8(e). Preliminary results from this study were submitted to the Agency on March 1, 1994. The study provides information on Isopropylaminoethanol (mixture of CAS No. 109-56-8 and 121-93-7) and does not involve effects in humans.

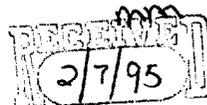
Nothing in this letter or the enclosed study report is considered confidential business information of Elf Atochem.

It is the opinion of Elf Atochem that the effects noted in this study do not necessarily support a conclusion of substantial health risk, but are being submitted in response to the EPA 8(e) reporting standards.

Elf Atochem has not previously filed any 8(e) notices or Premanufacture Notifications (PMNs) on the subject material. Further questions regarding this submission may be directed to me at (610) 337-6892.

Sincerely,

C.H. Farr, PhD, DABT  
Manager, Product Safety  
and Toxicology



Enclosure

CSRADIS copy

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3 8

STUDY TITLE

Acute Exposure Dermal Toxicity  
with Isopropylaminoethanol

AUTHOR

Victor T. Mallory, B.S., RLAT

STUDY COMPLETED ON

PERFORMING LABORATORY

Pharmakon Research International, Inc.  
Waverly, PA 18471

LABORATORY STUDY NUMBER

PH 422-ANA-002-93

SPONSOR

Elf Atochem North America, Inc.  
900 First Avenue  
King of Prussia, PA 19406

Total Number of Pages: 49

Acute Exposure Dermal Toxicity  
PH 422-ANA-002-93

COMPLIANCE STATEMENT

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

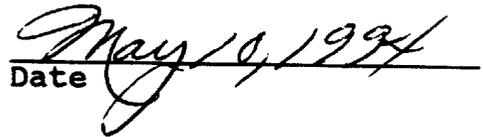
U.S. Environmental Protection Agency Good Laboratory Practice Standards Pesticide Programs (40 CFR 160).

U.S. Environmental Protection Agency Good Laboratory Practice Standards TSCA (40 CFR 792).

U.S. Food and Drug Administration Good Laboratory Practice Regulations (21 CFR 58).

OECD Guidelines for Testing Chemicals adopted by the council at its 535th meeting on May 12, 1981.

  
Study Director

  
Date

Acute Exposure Dermal Toxicity  
PH 422-ANA-002-93

APPROVAL SIGNATURE PAGE

This study was conducted in accordance with applicable Good Laboratory Practice Regulations; there were no deviations from these regulations that impacted on study conclusions.

  
Study Director

  
Date

Acute Exposure Dermal Toxicity  
PH 422-ANA-002-93

Quality Assurance Unit Statement

Study No.: PH 422-ANA-002-93

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

The Quality Assurance Unit (QAU) conducted the inspections listed below and reported the results to the study director and management on the dates indicated.

The following inspections were performed:

<u>Interval</u>	<u>Date</u>
<u>In-Life Phase</u>	October 25, 1993
<u>Gross Necropsy</u>	November 8, 1993
<u>Reporting Phase</u>	January 28, 1994; April 7, 1994; May 4, 1994

Date QAU Report Issued

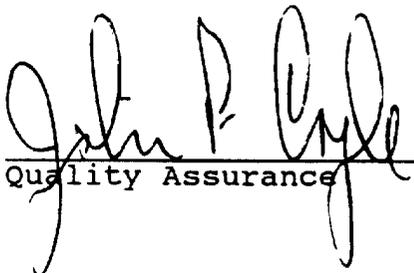
To Study Director

January 28, 1994;  
April 8, 1994;  
May 4, 1994

To Management

January 28, 1994;  
April 8, 1994;  
May 4, 1994

Date of last QAU facility inspection: March 15, 1994

  
\_\_\_\_\_  
Quality Assurance

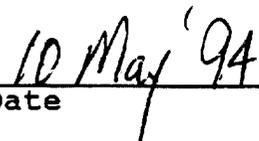
  
\_\_\_\_\_  
Date

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## Acute Exposure Dermal Toxicity

PH 422-ANA-002-93

### SUMMARY

In a Definitive LD<sub>50</sub>, three groups of ten rats (five males and five females per group) were exposed to Isopropylaminoethanol, Lot #E-06-B, at a single intact skin site for a 24-hour exposure period at dose levels of 500, 1000 and 2000 mg/kg.

Clinical signs observed at 500 mg/kg included decreased activity in one of the surviving animals. All other animals appeared normal throughout the study with the exception of necrosis, erythema, edema, fissuring and/or sloughing of the skin at the application site observed in nearly all surviving animals during the study. No clinical signs were observed in the one animal found dead at this dose level. All surviving animals were normal by Day 3. At 1000 mg/kg, clinical signs observed in all of the surviving animals included decreased activity, abnormal gait, abnormal stance along with necrosis, fissuring and sloughing of the skin at the application site. Chromodacryorrhea, tremors, flaccid body tone, dyspnea and brown nasal discharge along with erythema and edema were observed in a small percentage of the surviving animals. No clinical signs were observed in the two animals that died at 1000 mg/kg. All surviving animals were normal by Day 4. Clinical signs observed in all of the surviving animals at 2000 mg/kg included decreased activity, abnormal stance and abnormal gait along with necrosis of the skin at the application site. Fissuring and sloughing of the skin at the application site were observed in nearly all surviving animals with decreased muscle tone observed in half of the survivors and chromodacryorrhea and brown nasal discharge observed in the remaining half of the survivors. One animal died on day 1 without any clinical signs and the majority of the remaining animals dying on study exhibited clinical signs of decreased activity, abnormal gait, abnormal stance, brown nasal discharge, decreased muscle tone, diarrhea, ptosis and tremors along with necrosis of the skin at the application site. Only one animal exhibited dyspnea and prostration prior to death. All surviving animals were normal by Day 11. There was an increase in mean body weight in all surviving animals on Day 7 and at termination. One of ten animals died at 500 mg/kg. Two of ten animals died at 1000 mg/kg and six of ten animals died at 2000 mg/kg. Necropsy of the animals that died on study revealed discolored, distended and/or fluid-filled intestines and stomach and necrosis of the skin at the application site. Necrosis of the skin at the application site was observed at terminal necropsy. No other visible lesions were observed in any of the animals at terminal necropsy.

Acute Exposure Dermal Toxicity

PH 422-ANA-002-93

SUMMARY (continued)

Based upon the observations made in the Acute Exposure Dermal Toxicity Study in rats, the acute dermal LD<sub>50</sub> for Isopropylaminoethanol, Lot #E-06-B, for females and combined sexes was determined to be 1224 (799-1875) mg/kg and 1756 (1007-3064) mg/kg, respectively. The data generated for the acute dermal LD<sub>50</sub> in males did not lend itself to the statistical method employed.

Acute Exposure Dermal Toxicity

PH 422-ANA-002-93

STUDY DESCRIPTION

Sponsor: Elf Atochem North America, Inc.  
900 First Avenue  
King of Prussia, PA 19406

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

Test Facility  
S.O.P. No.: PH-422

Study No.: PH 422-ANA-002-93

Purpose of the Study: To determine the median lethal dose (LD<sub>50</sub>) of the test article using a single-dose dermal exposure and 14 day post exposure observation period.

Ownership of the Study: The Sponsor owns the study. All raw data, analyses and reports are the property of the Sponsor.

Study Monitor: Roy Bannister, Ph.D.  
Elf Atochem North America, Inc.

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

Technical Performance: Kim DiLeo, B.S., LAT, Thomas O'Neill, B.S., LAT and John Morahan, B.S., LATG

O.A.U. Responsible Personnel: Leslie J. Pinnell, M.S.  
Pharmakon Research International, Inc.

Date Protocol Signed: September 22, 1993

Dates of Technical Performance: October 25, 1993 through January 11, 1994

Good Laboratory Practice Statement: This study was conducted in compliance with the Good Laboratory Practice Regulations. There were no significant deviations from the GLP Regulations

Acute Exposure Dermal Toxicity  
PH 422-ANA-002-93

which affected the quality or integrity of the study. Q.A.U. findings derived from the inspection(s) during the conduct of this study and from the audit of the final report are documented and have been provided to the study director and the test facility management.

Records Maintained:

All raw data, final reports, documentation and the protocol will be maintained in the Pharmakon Archives.

Recordings:

Standard Pharmakon Notebook

Notebook Reference:

Notebook #1984; pages 2-96

Raw Data:

Appendix I

Statistics:

By the method of Litchfield and Wilcoxon via Pharmacologic Calculation System, Version 4.1.

TEST ARTICLE

Compound Name:

Isopropylaminoethanol

Physical Description:

Clear colorless liquid

Lot No.:

E-06-B

Specific Gravity:

0.925 g/mL

Amount Received:

492.69 grams (gross weight)

Date Received:

October 20, 1993

Special Handling Instructions:

Standard precautions including storage at room temperature.

Analysis of Purity:

The identity, purity, strength and stability of the test article were the responsibility of the Sponsor.

Acute Exposure Dermal Toxicity  
PH 422-ANA-002-93

Stability: There was no apparent change in the physical state of the test article during storage.

TEST SYSTEM

Species: Rat

Strain: Sprague Dawley

Supplier ;  
(Source): Charles River Laboratories, Inc.,  
Wilmington, Massachusetts

Purchase  
Order Nos.: 5011-092493B and 5011-122093C

Animals Received: October 7, 1993 and December 23, 1993,  
respectively

Sex: Male and female

Age at  
Initiation: 6 - 10 weeks

Weight at  
Initiation: Healthy adult animals (186-305 grams)

No. on Study: Thirty (30) (15 males and 15 females)

Method and  
Justification for  
Randomization: Test animal selection was based upon  
body weight, sex and apparent good  
health.

Acclimation  
Period: Minimum of five (5) days

System of  
Identification: Cage cards were marked with the study  
number, animal number, sex and dose  
level. Rats were ear tagged.

HUSBANDRY

Research Facility  
Registration: U.S.D.A. Registration No. 23-R-107 under  
the Animal Welfare Act 74: SC 2131 et  
seq.

Animal Rooms: Separate isolation by test system.  
Light cycle - 12 hours light, 12 hours  
dark. Every attempt was made to

Acute Exposure Dermal Toxicity  
PH 422-ANA-002-93

maintain a temperature of 18° to 26°C (64° - 79°F) and a relative humidity of 40% to 70%.

Housing:

Rats were housed individually in stainless steel  $\frac{1}{2}$ " wire mesh cages, sized in accordance with the "Guide for the Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources, National Research Council.

Sanitization:

Waste material was removed twice weekly. Cages and feeders were sanitized every two weeks.

Food:

Harlan Teklad Lab Blox®, ad libitum, checked daily and added or replaced as needed. Feeders are designed to reduce soiling, bridging and scattering.

Food Analysis:

No feed analysis was performed. There were no contaminants that were reasonably expected to be present in the dietary material known to be capable of interfering with the purpose or conduct of the study.

Water:

Fresh tap water, ad libitum.

Water Analysis:

Water is monitored for contaminants at periodic intervals according to Standard Operating Procedure PH-018. The results are maintained in the Pharmakon Archives. The quality of the water did not produce an adverse effect on the study.

METHODS

Rationale for Test System:

As per Sponsor's request.

Compound Preparation:

The test article was dosed as received using specific gravity calculations.

Dose Administration:

500, 1000 and 2000 mg/kg

Acute Exposure Dermal Toxicity  
PH 422-ANA-002-93

Rationale for  
Dose Selection:

As per Sponsor's request

Route of  
Administration:

Test material was applied directly on intact skin sites.

Rationale for  
Route of  
Administration:

The study was designed specifically for the assessment of dermal absorption and resultant toxicity.

Frequency and  
Duration of  
Administration:

Administered once and remained in contact with the skin site for twenty-four hours.

No. of Animals  
Per Dose Group:

Ten (10) (five males and five females)

No. and Code of  
Dose Groups:

<u>Rat #'s</u>	<u>Dose Level</u>
8651-8660	500 mg/kg
1901-1910	1000 mg/kg
4651-4660	2000 mg/kg

Length of Study:

Fourteen (14) days

Method of Study  
Performance:

Approximately 24 hours prior to testing, fur was clipped from the dorsal area of the trunk of the test animals. Care was taken to avoid abrading the skin which would alter its permeability. Not less than 10 percent of the body surface area was clear for the application of the test substance. The weight of the animals was taken into account when deciding on the area to be cleared and on the dimensions of the coverings used. The test substance was applied and held in contact with the skin with a porous gauze dressing (USP Type VII gauze, Kendall Company) throughout a 24-hour exposure period. The test site was covered with dental dam (The Hygiene Corporation), an elastic bandage (Medical Textiles Manufacturing, Inc.) and non-irritating tape (masking tape, Anchor Company) in a suitable manner to retain the gauze dressing and test substance and ensure that the animals could not ingest the test substance. Following the 24-hour period of

Acute Exposure Dermal Toxicity  
PH 422-ANA-002-93

exposure, the wrappings were removed. Residual test article was removed with water and gauze. Observations for pharmacotoxic signs and mortality were recorded daily through Day 14. Body weights were recorded at initiation, Day 7 and Day 14 or when found dead. All surviving rats were sacrificed on Day 14 and a gross necropsy was performed.

#### RESULTS

Summaries of animal data including individual animal clinical signs, toxic signs, mortality, body weights and gross necropsy findings may be found in Tables I-V, respectively.

Clinical signs observed at 500 mg/kg included decreased activity in one of the surviving animals. All other animals appeared normal throughout the study with the exception of necrosis, erythema, edema, fissuring and/or sloughing of the skin at the application site observed in nearly all surviving animals during the study. No clinical signs were observed in the one animal found dead at this dose level. All surviving animals were normal by Day 3. At 1000 mg/kg, clinical signs observed in all of the surviving animals included decreased activity, abnormal gait, abnormal stance along with necrosis, fissuring and sloughing of the skin at the application site.

Chromodacryorrhea, tremors, flaccid body tone, dyspnea and brown nasal discharge along with erythema and edema were observed in a small percentage of the surviving animals. No clinical signs were observed in the two animals that died at 1000 mg/kg. All surviving animals were normal by Day 4. Clinical signs observed in all of the surviving animals at 2000 mg/kg included decreased activity, abnormal stance and abnormal gait along with necrosis of the skin at the application site. Fissuring and

Acute Exposure Dermal Toxicity  
PH 422-ANA-002-93

sloughing of the skin at the application site were observed in nearly all surviving animals with decreased muscle tone observed in half of the survivors and chromodacryorrhea and brown nasal discharge observed in the remaining half of the survivors. One animal died on day 1 without any clinical signs and the majority of the remaining animals dying on study exhibited clinical signs of decreased activity, abnormal gait, abnormal stance, brown nasal discharge, decreased muscle tone, diarrhea, ptosis and tremors along with necrosis of the skin at the application site. Only one animal exhibited dyspnea and prostration prior to death. All surviving animals were normal by Day 11.

There was an increase in mean body weight in all surviving animals on Day 7 and at termination. One of ten animals died at 500 mg/kg. Two of ten animals died at 1000 mg/kg and six of ten animals died at 2000 mg/kg. Necropsy of the animals that died on study revealed discolored, distended and/or fluid-filled intestines and stomach and necrosis of the skin at the application site. Necrosis of the skin at the application site was observed at terminal necropsy. No other visible lesions were observed in any of the animals at terminal necropsy.

#### CONCLUSION

Based upon the observations made in the Acute Exposure Dermal Toxicity Study in rats, the acute dermal LD<sub>50</sub> for Isopropylaminoethanol, Lot #E-06-B, for females and combined sexes was determined to be 1224 (799-1875) mg/kg and 1756 (1007-3064) mg/kg, respectively. The data generated for the acute dermal LD<sub>50</sub> in males did not lend itself to the statistical method employed.

ACTRP/422ANA23.FIF



**TABLE I (continued)**

**PHARMAKON RESEARCH INTERNATIONAL, INC.**  
**Acute Exposure Dermal Toxicity (14 Day)**  
**Test Article: Isopropylaminoethanol**  
**Study Number: PH 422-ANA-002-93**  
**Sponsor: Elf Atochem North America, Inc.**

---

**INDIVIDUAL ANIMAL CLINICAL SIGNS**

---

**Animal Number: 8655 Male** **Dose Level: 500 mg/kg**

**Clinical Signs**

**Duration**

**Appears normal**  
**Slight erythema**  
**Necrosis**  
**Fissuring**  
**Sloughing**

**Day 1 - Day 14**  
**Day 1**  
**Day 2 - Day 14**  
**Day 4 - Day 9**  
**Day 4 - Day 14**

---



**TABLE I (continued)**

**PHARMAKON RESEARCH INTERNATIONAL, INC.**  
**Acute Exposure Dermal Toxicity (14 Day)**  
**Test Article: Isopropylaminoethanol**  
**Study Number: PH 422-ANA-002-93**  
**Sponsor: Elf Atochem North America, Inc.**

---

**INDIVIDUAL ANIMAL CLINICAL SIGNS**

---

**Animal Number: 8659 Female** **Dose Level: 500 mg/kg**

**Clinical Signs**

**Duration**

**Appears normal**

**Day 1 - Day 14**

**Fissuring**

**Day 5 - Day 9**

**Sloughing**

**Day 7 - Day 14**

**Necrosis**

**Day 1 - Day 14**

---

**Animal Number: 8660 Female**

**Dose Level: 500 mg/kg**

**Clinical Signs**

**Duration**

**Appears normal**

**Day 3 - Day 14**

**Decreased activity**

**Day 1 - Day 2**

**Necrosis**

**Day 1 - Day 14**

**Sloughing**

**Day 7 - Day 14**

---



**TABLE I (continued)**

**PHARMAKON RESEARCH INTERNATIONAL, INC.**  
**Acute Exposure Dermal Toxicity (14 Day)**  
**Test Article: Isopropylaminoethanol**  
**Study Number: PH 422-ANA-002-93**  
**Sponsor: Elf Atochem North America, Inc.**

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**INDIVIDUAL ANIMAL CLINICAL SIGNS**

---

**Animal Number: 1904 Male** **Dose Level: 1000 mg/kg**

<u>Clinical Signs</u>	<u>Duration</u>
Appears normal	Day 3 - Day 14
Decreased activity	Day 1 - Day 2
Abnormal stance	Day 1 - Day 2
Abnormal gait	Day 1 - Day 2
Chromodacryorrhea	Day 1
Necrosis	Day 1 - Day 14
Flaccid body tone	Day 1
Tremors	Day 1
Fissuring	Day 7 - Day 11
Sloughing	Day 6 - Day 14

---

**Animal Number: 1905 Male** **Dose Level: 1000 mg/kg**

<u>Clinical Signs</u>	<u>Duration</u>
Appears normal	Day 3 - Day 14
Decreased activity	Day 1
Abnormal stance	Day 1 - Day 2
Abnormal gait	Day 1 - Day 2
Necrosis	Day 1 - Day 14
Fissuring	Day 6 - Day 10
Sloughing	Day 6 - Day 14

---



TABLE I (continued)

PHARMAKON RESEARCH INTERNATIONAL, INC.  
Acute Exposure Dermal Toxicity (14 Day)  
Test Article: Isopropylaminoethanol  
Study Number: PH 422-ANA-002-93  
Sponsor: Elf Atochem North America, Inc.

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INDIVIDUAL ANIMAL CLINICAL SIGNS

---

Animal Number: 1908 Female                      Dose Level: 1000 mg/kg

<u>Clinical Signs</u>	<u>Duration</u>
Appears normal	Day 3 - Day 14
Decreased activity	Day 1 - Day 2
Abnormal stance	Day 1 - Day 2
Abnormal gait	Day 1 - Day 2
Brown nasal discharge	Day 1 - Day 2
Tremors	Day 1
Necrosis	Day 1 - Day 14
Fissuring	Day 8 - Day 14
Sloughing	Day 14
Dyspnea	Day 1

---

Animal Number: 1909 Female                      Dose Level: 1000 mg/kg

<u>Clinical Signs</u>	<u>Duration</u>
Animal died	Day 1

---

Animal Number: 1910 Female                      Dose Level: 1000 mg/kg

<u>Clinical Signs</u>	<u>Duration</u>
Animal died	Day 1

---





TABLE I (continued)

PHARMAKON RESEARCH INTERNATIONAL, INC.  
Acute Exposure Dermal Toxicity (14 Day)  
Test Article: Isopropylaminoethanol  
Study Number: PH 422-ANA-002-93  
Sponsor: Elf Atochem North America, Inc.

---

INDIVIDUAL ANIMAL CLINICAL SIGNS

---

Animal Number: 4656 Female                      Dose Level: 2000 mg/kg

<u>Clinical Signs</u>	<u>Duration</u>
Decreased activity	Day 1 - Day 4
Abnormal gait	Day 1 - Day 4
Abnormal stance	Day 1 - Day 4
Decreased muscle tone	Day 4
Ptosis	Day 4
Tremors	Day 4
Diarrhea	Day 4
Necrosis	Day 1 - Day 4
Animal died	Day 5

---

Animal Number: 4657 Female                      Dose Level: 2000 mg/kg

<u>Clinical Signs</u>	<u>Duration</u>
Decreased activity	Day 1 - Day 3
Abnormal stance	Day 1 - Day 3
Abnormal gait	Day 1 - Day 3
Decreased muscle tone	Day 3
Diarrhea	Day 3
Necrosis	Day 1 - Day 3
Tremors	Day 3
Brown nasal discharge	Day 1
Animal died	Day 4

---



**TABLE I (continued)**

**PHARMAKON RESEARCH INTERNATIONAL, INC.**  
**Acute Exposure Dermal Toxicity (14 Day)**  
**Test Article: Isopropylaminoethanol**  
**Study Number: PH 422-ANA-002-93**  
**Sponsor: Elf Atochem North America, Inc.**

---

**INDIVIDUAL ANIMAL CLINICAL SIGNS**

---

**Animal Number: 4660 Female**

**Dose Level: 2000 mg/kg**

**Clinical Signs**

**Duration**

<b>Brown nasal discharge</b>	<b>Day 1</b>
<b>Decreased activity</b>	<b>Day 1 - Day 4</b>
<b>Abnormal stance</b>	<b>Day 1 - Day 4</b>
<b>Abnormal gait</b>	<b>Day 1 - Day 4</b>
<b>Decreased muscle tone</b>	<b>Day 3 - Day 4</b>
<b>Necrosis</b>	<b>Day 1 - Day 4</b>
<b>Tremors</b>	<b>Day 4</b>
<b>Ptosis</b>	<b>Day 4</b>
<b>Diarrhea</b>	<b>Day 4</b>
<b>Animal died</b>	<b>Day 5</b>

---

**TABLE II**  
**PHARMAKON RESEARCH INTERNATIONAL, INC**  
 Acute Exposure Dermal Toxicity (14 Day)  
 Test Article: Isopropylaminoethanol  
 Study Number: PH422-ANA-002-93  
 Sponsor: Elf Atochem North America, Inc

**TOXIC SIGNS SUMMARY REPORT**

ACUTE EXPOSURE DERMAL TOXICITY  
 STUDY: 422ANA2A

MALE

DOSE (mg/kg)	OBSERVATIONS	RANGE
500	APPEARS NORMAL	DAY 1 (14:35) - DAY 14 (13:16)
	ERYTHEMA	DAY 1 (14:38) - DAY 13 (14:33)
	NECROSIS	DAY 2 (13:57) - DAY 14 (13:16)
	UNWRAP	DAY 1 (14:38) - DAY 1 (14:42)
	SLOUGHING	DAY 4 (09:08) - DAY 14 (13:16)
	FISSURING	DAY 4 (09:08) - DAY 9 (14:16)

FEMALE

DOSE (mg/kg)	OBSERVATIONS	RANGE
500	APPEARS NORMAL	DAY 1 (14:42) - DAY 14 (13:18)
	DECREASED ACTIVITY	DAY 1 (14:46) - DAY 2 (14:00)
	ERYTHEMA	DAY 1 (14:44) - DAY 8 (14:44)
	NECROSIS	DAY 1 (14:45) - DAY 14 (13:18)
	UNWRAP	DAY 1 (14:43) - DAY 1 (14:46)
	SLOUGHING	DAY 4 (09:08) - DAY 14 (13:18)
	FISSURING	DAY 5 (09:26) - DAY 12 (09:27)

TABLE II (continued)  
 PHARMAKON RESEARCH INTERNATIONAL, INC  
 Acute Exposure Dermal Toxicity (14 Day)  
 Test Article: Isopropylaminoethanol  
 Study Number: PH422-ANA-002-93  
 Sponsor: Elf Atochem North America, Inc

TOXIC SIGNS SUMMARY REPORT

ACUTE EXPOSURE DERMAL TOXICITY  
 STUDY: 422ANA2A

MALE

DOSE (mg/kg)	OBSERVATIONS	RANGE
1000	APPEARS NORMAL	DAY 3 (08:42) - DAY 14 (08:27)
	DECREASED ACTIVITY	DAY 1 (09:46) - DAY 2 (08:40)
	ABNORMAL GAIT	DAY 1 (09:46) - DAY 3 (08:43)
	ABNORMAL STANCE	DAY 1 (09:46) - DAY 3 (08:43)
	CHROMODACRYORRHEA	DAY 1 (09:52)
	TREMORS	DAY 1 (09:52)
	NECROSIS	DAY 1 (09:47) - DAY 14 (08:27)
	UNWRAP	DAY 1 (09:48)
	FLACCID BODY TONE	DAY 1 (09:52)
	SLOUGHING	DAY 6 (09:02) - DAY 14 (08:27)
	FISSURING	DAY 6 (09:05) - DAY 14 (08:26)

FEMALE

DOSE (mg/kg)	OBSERVATIONS	RANGE
1000	APPEARS NORMAL	DAY 3 (08:44) - DAY 14 (08:28)
	DECREASED ACTIVITY	DAY 1 (09:55) - DAY 2 (08:41)
	ABNORMAL GAIT	DAY 1 (09:55) - DAY 3 (08:44)
	ABNORMAL STANCE	DAY 1 (09:55) - DAY 3 (08:44)
	CHROMODACRYORRHEA	DAY 2 (08:42)
	DYSPNEA	DAY 1 (09:55)
	EDEMA	DAY 1 (09:55)
	ERYTHEMA	DAY 1 (09:55)
	TREMORS	DAY 1 (09:55)
	NECROSIS	DAY 1 (09:56) - DAY 14 (08:27)
	UNWRAP	DAY 1 (09:55)
	BROWN	
	NASAL DISCHARGE	DAY 1 (09:57) - DAY 2 (08:42)
	SLOUGHING	DAY 6 (09:06) - DAY 14 (08:28)
	FISSURING	DAY 6 (09:05) - DAY 14 (08:28)

**TABLE II (continued)**  
**PHARMAKON RESEARCH INTERNATIONAL, INC**  
 Acute Exposure Dermal Toxicity (14 DAY)  
 Test Article: Isopropylaminoethanol  
 Study Number: PH422-ANA-002-93  
 Sponsor: ELF ATOCHEM NORTH AMERICA, INC

**TOXIC SIGNS SUMMARY REPORT**

Acute Exposure Dermal Toxicity  
 STUDY: 422ANA2

MALE		
DOSE (mg/kg)	OBSERVATIONS	RANGE
-----	-----	-----
2000	APPEARS NORMAL	DAY 4 (09:31) - DAY 14 (09:02)
	DECREASED ACTIVITY	DAY 1 (09:28) - DAY 10 (11:51)
	ABNORMAL GAIT	DAY 1 (09:27) - DAY 5 (08:29)
	ABNORMAL STANCE	DAY 1 (09:27) - DAY 5 (08:29)
	CHROMODACRYORRHEA	DAY 7 (09:09) - DAY 8 (11:43)
	DIARRHEA	DAY 4 (09:30) - DAY 5 (08:29)
	DECREASED MUSCLE TONE	DAY 6 (08:46) - DAY 8 (11:43)
	UNWRAP	DAY 1 (09:26)
	NECROSIS	DAY 1 (09:26) - DAY 14 (09:02)
	BROWN NASAL DISCHARGE	DAY 1 (09:28)
	SLOUGHING	DAY 9 (08:56) - DAY 14 (09:02)
	FISSURING	DAY 10 (11:52) - DAY 14 (09:01)

FEMALE		
DOSE (mg/kg)	OBSERVATIONS	RANGE
-----	-----	-----
2000	APPEARS NORMAL	DAY 3 (11:12)
	DECREASED ACTIVITY	DAY 1 (09:30) - DAY 8 (11:43)
	ABNORMAL GAIT	DAY 1 (09:31) - DAY 8 (11:43)
	ABNORMAL STANCE	DAY 1 (09:30) - DAY 8 (11:43)
	DIARRHEA	DAY 3 (11:11) - DAY 8 (11:43)
	DECREASED MUSCLE TONE	DAY 3 (11:12) - DAY 8 (11:43)
	DYSPNEA	DAY 7 (09:13) - DAY 8 (11:43)
	PROSTRATION	DAY 6 (08:47) - DAY 8 (11:43)
	PTOSIS	DAY 4 (09:32) - DAY 8 (11:43)
	TREMORS	DAY 3 (11:12) - DAY 8 (11:43)
	UNWRAP	DAY 1 (09:30)
	NECROSIS	DAY 1 (09:30) - DAY 8 (11:43)
	BROWN NASAL DISCHARGE	DAY 1 (09:31)
	FLACCID BODY TONE	DAY 1 (09:33)

**TABLE III**  
**PHARMAKON RESEARCH INTERNATIONAL, INC**  
 Acute Exposure Dermal Toxicity (14 DAY)  
 Test Article: Isopropylaminoethanol  
 Study Number: PH422-ANA-002-93  
 Sponsor: ELF ATOCHEM NORTH AMERICA, INC

**MORTALITY SUMMARY REPORT**

Acute Exposure Dermal Toxicity  
 STUDY: 422ANA2

MALE

NUMBER OF DEATHS

-----  
 DAYS AFTER DOSING

DOSE (Mg/Kg)	NO. DEAD/ NO. DOSED	-----														
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
500	1/5		1													
1000	0/5															
2000	1/5		1													

FEMALE

NUMBER OF DEATHS

-----  
 DAYS AFTER DOSING

DOSE (Mg/Kg)	NO. DEAD/ NO. DOSED	-----														
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
500	0/5															
1000	2/5			2												
2000	5/5					1	2				2					

**TABLE IV**  
**PHARMAKON RESEARCH INTERNATIONAL, INC**  
 Acute Exposure Dermal Toxicity (14 Day)  
 Test Article: Isopropylaminoethanol  
 Study Number: PH422-ANA-002-93  
 Sponsor: Elf Atochem North America, Inc

**BODY WEIGHTS SUMMARY REPORT**

**ACUTE EXPOSURE DERMAL TOXICITY**  
**STUDY: 422ANA2A**

		BODY WT. (G)			
		MALE			
DOSE (Mg/Kg)	ANIMAL NUMBER	DAY0	DAY7	DAY14	Gain
500	8651	220	236	258	38
	8652	232	278	326	94
	8653	213	243	281	68
	8654	228	--	--	--
	8655	232	250	282	50
	MEAN	225	252	287	63
	SD	8.3	18.4	28.4	24.4
	N	5	4	4	4
	NO. DIED/NO. DOSED	1/5			

		FEMALE			
DOSE (Mg/Kg)	ANIMAL NUMBER	DAY0	DAY7	DAY14	Gain
500	8656	201	215	220	19
	8657	205	225	230	25
	8658	202	210	220	18
	8659	202	210	212	10
	8660	203	212	212	9
	MEAN	203	214	219	16
	SD	1.5	6.3	7.4	6.7
	N	5	5	5	5
	NO. DIED/NO. DOSED	0/5			

-- DATA UNAVAILABLE

**TABLE IV (continued)**  
**PHARMAKON RESEARCH INTERNATIONAL, INC**  
 Acute Exposure Dermal Toxicity (14 Day)  
 Test Article: Isopropylaminoethanol  
 Study Number: PH422-ANA-002-93  
 Sponsor: Elf Atochem North America, Inc

**BODY WEIGHTS SUMMARY REPORT**

**ACUTE EXPOSURE DERMAL TOXICITY**  
**STUDY: 422ANA2A**

		BODY WT. (G)			
		MALE			
DOSE (Mg/Kg)	ANIMAL NUMBER	DAY0	DAY7	DAY14	Gain
1000	1901	275	277	323	48
	1902	305	290	346	41
	1903	276	280	332	56
	1904	289	297	354	65
	1905	260	264	313	53
	MEAN	281	282	334	53
	SD	16.9	12.7	16.7	9.0
	N	5	5	5	5
	NO. DIED/NO. DOSED	0/5			

		FEMALE			
DOSE (Mg/Kg)	ANIMAL NUMBER	DAY0	DAY7	DAY14	Gain
1000	1906	186	197	223	37
	1907	214	217	242	28
	1908	220	237	261	41
	1909	186	--	--	--
	1910	189	--	--	--
	MEAN	199	217	242	35
	SD	16.6	20.0	19.0	6.7
	N	5	3	3	3
	NO. DIED/NO. DOSED	2/5			

-- DATA UNAVAILABLE

**TABLE IV (continued)**  
**PHARMAKON RESEARCH INTERNATIONAL, INC**  
 Acute Exposure Dermal Toxicity (14 DAY)  
 Test Article: Isopropylaminoethanol  
 Study Number: PH422-ANA-002-93  
 Sponsor: ELF ATOCHEM NORTH AMERICA, INC

**BODY WEIGHTS SUMMARY REPORT**

Acute Exposure Dermal Toxicity  
 STUDY: 422ANA2

		BODY WT. (G)			
		MALE			
DOSE (Mg/Kg)	ANIMAL NUMBER	DAY0	DAY7	DAY14	Gain
2000	4651	259	--	--	--
	4652	241	213	257	16
	4653	255	245	290	35
	4654	263	263	313	50
	4655	277	263	316	39
		MEAN	259	246	294
	SD	13.0	23.6	27.3	14.2
	N	5	4	4	4
	NO. DIED/NO. DOSED	1/5			
		FEMALE			
DOSE (Mg/Kg)	ANIMAL NUMBER	DAY0	DAY7	DAY14	Gain
2000	4656	199	--	--	--
	4657	186	--	--	--
	4658	189	141	--	--
	4659	198	185	--	--
	4660	203	--	--	--
	MEAN	195	163	--	--
	SD	7.2	31.1	--	--
	N	5	2	--	--
	NO. DIED/NO. DOSED	5/5			

-- DATA UNAVAILABLE

**TABLE V**  
**PHARMAKON RESEARCH INTERNATIONAL, INC**  
 Acute Exposure Dermal Toxicity (14 Day)  
 Test Article: Isopropylaminoethanol  
 Study Number: PH422-ANA-002-93  
 Sponsor: Elf Atochem North America, Inc

**GROSS NECROPSY SUMMARY REPORT**

ACUTE EXPOSURE DERMAL TOXICITY  
 STUDY: 422ANA2A

MALE

DOSE (mg/kg)	LOCATION	GROSS OBSERVATION	FREQUENCY	
			DECEDENTS	SURVIVORS
500	STOMACH	NORMAL	1/1	4/4
	HEART	NORMAL	1/1	4/4
	INTESTINES	NORMAL	1/1	4/4
	KIDNEYS	NORMAL	1/1	4/4
	LUNGS	NORMAL	1/1	4/4
	LIVER	NORMAL	1/1	4/4
	ADRENALS	NORMAL	1/1	4/4
	SPLEEN	NORMAL	1/1	4/4
	OTHER	NORMAL	1/1	4/4
	TREATED SITE	NECROSIS	0/1	2/4
		NORMAL	1/1	2/4

FEMALE

DOSE (mg/kg)	LOCATION	GROSS OBSERVATION	FREQUENCY	
			DECEDENTS	SURVIVORS
500	STOMACH	NORMAL	0/0	5/5
	HEART	NORMAL	0/0	5/5
	INTESTINES	NORMAL	0/0	5/5
	KIDNEYS	NORMAL	0/0	5/5
	LUNGS	NORMAL	0/0	5/5
	LIVER	NORMAL	0/0	5/5
	ADRENALS	NORMAL	0/0	5/5
	SPLEEN	NORMAL	0/0	5/5
	OTHER	NORMAL	0/0	5/5
	TREATED SITE	NECROSIS	0/0	4/5
		NORMAL	0/0	1/5

**TABLE V (continued)**  
**PHARMAKON RESEARCH INTERNATIONAL, INC**  
 Acute Exposure Dermal Toxicity (14 Day)  
 Test Article: Isopropylaminoethanol  
 Study Number: PH422-ANA-002-93  
 Sponsor: Elf Atochem North America, Inc

**GROSS NECROPSY SUMMARY REPORT**

ACUTE EXPOSURE DERMAL TOXICITY  
 STUDY: 422ANA2A

MALE

DOSE (mg/kg)	LOCATION	GROSS OBSERVATION	FREQUENCY	
			DECEDENTS	SURVIVORS
1000	STOMACH	NORMAL	0/0	5/5
	HEART	NORMAL	0/0	5/5
	INTESTINES	NORMAL	0/0	5/5
	KIDNEYS	NORMAL	0/0	5/5
	LUNGS	NORMAL	0/0	5/5
	LIVER	NORMAL	0/0	5/5
	ADRENALS	NORMAL	0/0	5/5
	SPLEEN	NORMAL	0/0	5/5
	OTHER	NORMAL	0/0	5/5
	TREATED SITE	NECROSIS	0/0	5/5

FEMALE

DOSE (mg/kg)	LOCATION	GROSS OBSERVATION	FREQUENCY	
			DECEDENTS	SURVIVORS
1000	STOMACH	NORMAL	2/2	3/3
	HEART	NORMAL	2/2	3/3
	INTESTINES	NORMAL	0/2	3/3
		DISTENDED	1/2	0/3
		FLUID FILLED RED	1/2	0/3
	KIDNEYS	NORMAL	2/2	3/3
	LUNGS	NORMAL	2/2	3/3
	LIVER	NORMAL	2/2	3/3
	ADRENALS	NORMAL	2/2	3/3
	SPLEEN	NORMAL	2/2	3/3
	OTHER	NORMAL	2/2	3/3
	TREATED SITE	NECROSIS	0/2	3/3
		NORMAL	2/2	0/3

TABLE V (continued)  
 PHARMAKON RESEARCH INTERNATIONAL, INC  
 Acute Exposure Dermal Toxicity (14 DAY)  
 Test Article: Isopropylaminoethanol  
 Study Number: PH422-ANA-002-93  
 Sponsor: ELF ATOCHEM NORTH AMERICA, INC

GROSS NECROPSY SUMMARY REPORT

Acute Exposure Dermal Toxicity  
 STUDY: 422ANA2

MALE

DOSE (mg/kg)	LOCATION	GROSS OBSERVATION	FREQUENCY	
			DECEDENTS	SURVIVORS
2000	STOMACH	DISTENDED	1/1	0/4
		NORMAL	0/1	4/4
	HEART	NORMAL	1/1	4/4
	INTESTINES	NORMAL	1/1	4/4
	KIDNEYS	NORMAL	1/1	4/4
	LUNGS	NORMAL	1/1	4/4
	LIVER	NORMAL	1/1	4/4
	ADRENALS	NORMAL	1/1	4/4
	SPLEEN	NORMAL	1/1	4/4
	OTHER	NORMAL	1/1	4/4
	TREATED SITE	NECROSIS	1/1	4/4

FEMALE

DOSE (mg/kg)	LOCATION	GROSS OBSERVATION	FREQUENCY	
			DECEDENTS	SURVIVORS
2000	STOMACH	DISTENDED	4/5	0/0
		FLUID-FILLED	2/5	0/0
		BLACK SPOTS		
		THRU-OUT	1/5	0/0
	HEART	NORMAL	5/5	0/0
	INTESTINES	DISTENDED	5/5	0/0
		FLUID-FILLED	3/5	0/0
	KIDNEYS	NORMAL	5/5	0/0
	LUNGS	NORMAL	5/5	0/0
	LIVER	NORMAL	5/5	0/0
	ADRENALS	NORMAL	5/5	0/0
	SPLEEN	NORMAL	5/5	0/0
	OTHER	NORMAL	5/5	0/0
	TREATED SITE	NECROSIS	5/5	0/0

Acute Exposure Dermal Toxicity  
PH 422-ANA-002-93

APPENDIX I  
Protocol and Documentation

# PHARMAKON USA

P.O. Box 609  
Waverly, Pennsylvania 18471-0609  
Tel: (717) 586-2411  
Fax: (717) 586-3450

Protocol - 422

## Acute Exposure Dermal Toxicity (14 Day)

Sponsor: Elf Atochem North America, Inc.  
900 First Avenue  
P.O. Box 1536  
King of Prussia, PA 19406-0018

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

Test Facility S.O.P. No.: PH-422

Study No.: To be assigned at study initiation <sup>PH422-ANA-00243</sup>

Purpose of the Study: To determine the median lethal dose (LD<sub>50</sub>), its statistical limits and slope using a single exposure up to a 24-hour period and a 14-day post-exposure observation period. If a test at a dose of at least 2000 mg/kg body weight, using the procedures described for this study, produces no compound-related mortality, then a full study using additional dose levels will not be necessary.

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

Study Monitor: Roy M. Bannister, Ph.D., Elf Atochem North America, Inc.

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

O.A.U. Responsible Personnel: Leslie J. Pinnell, M.S.

Dates of Performance: The study will begin within one month of the receipt of the test article and authorized protocol.

Protocol-422  
Acute Exposure Dermal Toxicity (14 Day)

Good Laboratory Practice Statement: Protocol 422 has been designed and will be conducted in compliance with the Good Laboratory Practice Regulations as stated in the 21 CFR Parts 58, U.S. Environmental Protection Agency as stated in the 40 CFR Part 792 and all subsequent revisions, and the Organization for Economic Co-operation and Development Guidelines for Testing Chemicals (OECD), ISBN 92-64-12221-4, adopted by the council at its 535th meeting on 12th May, 1981.

IACUC Statement: Protocol-422 has been reviewed by the Institutional Animal Care and Use Committee (IACUC) and complies with acceptable standard animal welfare and humane care.

Tentative Date of Submission of Draft Report: Within one month following the completion of the study.

Records Maintained: All raw data, final reports, documentation and protocol will be maintained in the Pharmakon Archives. Amendments to protocol  
Feed Lot Number  
Body weights, initial, weekly and final  
Compound preparation  
Observed signs  
Observed mortality

Statistics: By the method of Litchfield and Wilcoxon via the Pharmacologic Calculation System Version 4.1 or any other appropriate statistical analysis.

Raw Data: Maintained in Standard Pharmakon Notebook

Record Retention: All raw data and completed notebooks

Analytical Chemistry: Analysis and stability of the test article and test article/carrier mixture are the responsibility of the Sponsor. If requested by the Sponsor, Pharmakon Research International, Inc., its subcontractor, conduct appropriate

Protocol-422  
Acute Exposure Dermal Toxicity (14 Day)

analytical analysis and indicate the additional cost involved following receipt and evaluation of the appropriate analytical method. In the case where a satisfactory method is not provided, Pharmakon Research International, Inc., or its subcontractor, at additional cost to the Sponsor, will develop appropriate methods.

TEST SYSTEM

Species: Rat

Strain: Sprague Dawley

Supplier (Source): Charles River Laboratories, Wilmington, Massachusetts or any other U.S.D.A. acceptable source

Sex: Male and female (equal number of each sex will be used for each dose level. The females will be nulliparous and non pregnant).

Age: Young adult animals will be used. The weight variation of animals used in a test will not exceed  $\pm 20$  percent of the mean weight for each sex.

No. on Study: Ten/group (five males, five females)

Method and Justification for Randomization: Selection of rats based upon body weight, sex and apparent good health.

Acclimation Period: Minimum of five (5) days

System of Identification: Cages marked with an animal number, study number and dose level. Rats are ear tagged.  
HUSBANDRY

Research Facility Registration: U.S.D.A. Registration No. 23-R-107 under the Animal Welfare Act 74: SC 2131 et seq.

Protocol-422  
Acute Exposure Dermal Toxicity (14 Day)

Animal Rooms: Separate isolation by test system.  
Light cycle - 12 hours light, 12 hours dark. Temperature/Relative Humidity - Every attempt will be made to maintain a temperature of 16°C to 21°C and a relative humidity of 40 to 70%.

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

Sanitization: Waste material will be removed twice weekly. Cages and feeders are sanitized every two weeks.

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

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

Water: Fresh tap water, ad libitum.

Water Analysis: Water is monitored for contaminants at periodic intervals according to Standard Operating Procedure PH-018.

METHODS

Rationale for Test System: As per Sponsor's request

Dose Administration: If a test at a dose of at least 2000 mg/kg body weight, using the procedures described for this study, produces no compound-related mortality, then a full study using three dose levels will not be necessary.

Protocol-422  
Acute Exposure Dermal Toxicity (14 Day)

Control Groups: Neither a concurrent untreated nor vehicle control group is recommended except when the toxicity of the vehicle is unknown.

Compound Preparation: Liquids are administered as received. When necessary, the test substance will be dissolved or suspended in a suitable vehicle. It is recommended that whenever possible the usage of an aqueous solution be considered first, followed by consideration of a solution in oil (e.g. corn oil) and then by possible solution in other vehicles. For non-aqueous vehicles the toxic characteristics of the vehicle should be known, and if not known be determined before the test.

When testing solids, which may be pulverized if appropriate, the test substance will be moistened sufficiently with water or, where necessary, a suitable vehicle to ensure good contact with skin. When a vehicle is used, the influence of the vehicle on penetration of skin by the test substance will be taken into account.

Vehicle: Liquids: administered as received.  
Solids: 0.9% NaCl solution or alternative depending upon solubility.

Route of Administration: Test material is applied directly on intact skin sites.

Rationale for Route of Administration: The study is designed specifically for the assessment of dermal absorption and resultant toxicity.

Frequency and Duration of Administration: Test article is administered once and remains in contact with the skin site for twenty-four (24) hours.

Length of Study: Fourteen (14) days

Preparation of the Skin: Shortly before testing, fur will be clipped from the dorsal area of the trunk of the test animals. Care will be

Protocol-422  
Acute Exposure Dermal Toxicity (14 Day)

taken to avoid abrading the skin which could alter its permeability. Not less than 10 percent of the body surface area will be clear for the application of the test substance. The weight of the animal will be taken into account when deciding on the area to be cleared and on the dimensions of any covering used.

The test substance will be applied uniformly over an area which is approximately 10 percent of the total body surface area. With highly toxic substances the surface area covered may be less, but as much of the area will be covered with as thin and uniform a film as possible. The test substance will be held in contact with the skin with a porous gauze dressing and non-irritating tape throughout a 24-hour exposure period. The test site will be further covered in a suitable manner to retain the gauze dressing and test substance and ensure that the animals cannot ingest the test substance. At the end of the exposure period, residual test substance will be removed, where practicable using water or an appropriate solvent.

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

A careful clinical examination will be made at least once each day. Additional observations will be made daily with appropriate actions taken to minimize loss of animals to the study (e.g. necropsy or refrigeration of those animals found dead and isolation of weak or moribund animals). The observation period will be at least 14 days. However, the duration of observation will not be fixed rigidly. It will be determined by the toxic reactions, rate of onset and length of recovery period, and may thus be extended when considered necessary. The time at which signs of toxicity appear and disappear, their duration and the time of death are important, especially if there is a tendency for deaths to be delayed.

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Acute Exposure Dermal Toxicity (14 Day)

Cage-side observations will include, but not be limited to, changes in skin and fur, eyes and mucous membranes, respiratory, circulatory, autonomic and central nervous systems, somatomotor activity and behavior pattern. Particular attention will be directed to observations of tremors, convulsions, salivation, diarrhea, lethargy, sleep and coma. Individual weights of animals will be determined shortly before the test substance is applied. Individual weights will also be taken weekly thereafter and at death. Changes in weight will be calculated and recorded when survival exceeds one day. The time of death will be recorded as precisely as possible. At the end of the test, surviving animals will be weighed and sacrificed.

Gross Pathology:

Consideration will be given to performing a gross necropsy of all animals where indicated by the nature of the toxic effects observed. All gross pathological changes will be recorded.

Histopathology:

Microscopic examination of organs showing evidence of gross pathology in animals surviving 24 hours or more will also be considered because it may yield useful information.

Data Analysis:

Data will be summarized in tabular form, showing for each test group the number of animals at the start of the test, time of death of individual animals at different dose levels, number of animals displaying other signs of toxicity, description of toxic effects and necropsy findings.

Evaluation of Results:

The dermal LD<sub>50</sub> value will be considered in conjunction with the observed toxic effects and any necropsy findings. The LD<sub>50</sub> value is a relatively coarse measurement, useful only as a reference value for classification and labelling

Protocol-422  
Acute Exposure Dermal Toxicity (14 Day)

purposes, and expressing the possible lethal potential of the test substance following dermal exposure. An evaluation will include the relationships, if any, between the animals' exposure to the test substance and the incidence and severity of all abnormalities, including behavioral and clinical abnormalities, gross lesions, body weight changes, effects on mortality, and any other toxicological effects.

Animal Care  
Provisions:

This study will be conducted in accordance with the current guidelines for animal welfare (NIH Publication 86-23, 1985). No alternative test systems exist which have been adequately validated to permit replacement of the use of live animals in this study. The requirement for this study by the regulatory agency indicated on the signature page is predicated on the basis that animal safety data constitute an appropriate and ethical prerequisite to testing new chemical compounds in humans and that data generated will be predictive of the effects in humans. Every effort has been made to obtain the maximum amount of information while reducing to a minimum the number of animals required for this study. The use of appropriate sedatives, analgesics, anesthetics or other medical treatments to alleviate pain will not be utilized in this study, unless otherwise indicated in the protocol, due to the interference of these treatments with the scientific data being generated. The use of pharmaceuticals to alleviate pain or distress may interfere with the compound being tested, thereby invalidating the data collected which would in turn require repeat testing and increase the number of animals utilized. The study will be terminated in part or

Protocol-422  
Acute Exposure Dermal Toxicity (14 Day)

whole for humane reasons if unnecessary  
pain occurs. To the best of our  
knowledge, this study is not unnecessary  
or duplicative.

ACTPT/422ANA.RAT

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Protocol-422  
Acute Exposure Dermal Toxicity (14 Day)

APPENDIX A  
Test Article Information

I Identification:

Refer to Test Article  
Description form  
with sample

Test Article (Name or Code): ISO PROPYLAMINOETHANOL  
Lot or Sample No.: \_\_\_\_\_  
Physical Description: \_\_\_\_\_  
Purity: \_\_\_\_\_  
Expiration Date: \_\_\_\_\_  
Density/Specific Gravity: \_\_\_\_\_  
Solubility (check one): Water \_\_\_\_\_ Acetone \_\_\_\_\_  
Ethanol \_\_\_\_\_ Corn Oil \_\_\_\_\_ DMSO \_\_\_\_\_  
Other (please specify) \_\_\_\_\_  
Chemical Classification: Flammable \_\_\_\_\_ Corrosive \_\_\_\_\_  
Other \_\_\_\_\_

II Storage Information:

Material Storage (check one):  
Room Temperature \_\_\_\_\_; Refrigerator \_\_\_\_\_  
Freezer \_\_\_\_\_; Other (specify) \_\_\_\_\_

III Handling Information:

Known Hazards: \_\_\_\_\_

Precautions: Routine use of protective clothing  
includes laboratory coats, latex  
gloves, dust masks, and safety  
glasses.

Other recommended precautions \_\_\_\_\_

In Case of Emergency Related to  
this substance, contact:

C. JOHNSON of ELF Atochem / ORGANIC at 215-587-6614  
(person) (company/division) (phone number)

IV Disposition:

All materials will be returned to the Sponsor three  
months following submission of the final report to  
the Sponsor. Person and address to whom test  
articles are to be returned.

Name: MR. LIONEL MONETTE  
Address: ELF Atochem North America, Inc  
17165 West Jefferson  
RIVERVIEW MICHIGAN 48192

V Signature: [Signature] Date: 7/17/93