

elf atochem

ATO

ELF ATOCHEM NORTH AMERICA, INC.
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May 18, 1994

**FEDERAL EXPRESS
RETURN RECEIPT REQUESTED**

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

Subject: TSCA Section 8(e) Submission

Contains No CBI
PDCN: ~~XXXXXXXXXX~~
88940000359

94 MAY 23 AM 10:30
RECEIVED



Dear Sir/Madam:

Elf Atochem North America Inc. has received the final report of 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 n-Propylethanolamine (CAS No. 16369-21-4) 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

mm
2/6/95

Enclosure

STUDY TITLE

Acute Exposure Dermal Toxicity
with n-Propylethanolamine

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-004-93

SPONSOR

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

Total Number of Pages: 47

Acute Exposure Dermal Toxicity
PH 422-ANA-004-93

COMPLIANCE STATEMENT

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

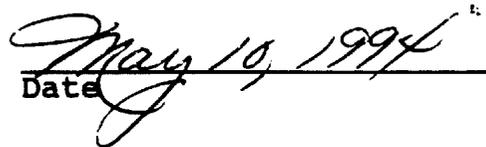
U.S. Environmental Protection Agency Good Laboratory Practice Standards Pesticide Programs (40 CFR 160).

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

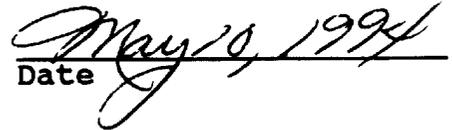

Date

Acute Exposure Dermal Toxicity
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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
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Quality Assurance Unit Statement

Study No.: PH 422-ANA-004-93

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 26, 1993; October 28, 1993
<u>Gross Necropsy</u>	November 9, 1993; November 11, 1993
<u>Reporting Phase</u>	January 31, 1994; April 7, 1994; May 4, 1994

Date QAU Report Issued

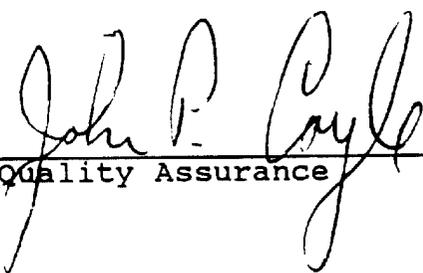
To Study Director

January 31, 1994;
April 7, 1994;
May 4, 1994

To Management

January 31, 1994;
April 7, 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-004-93

SUMMARY

In a Definitive LD₅₀, three groups of ten rats (five males and five females per group) were exposed to n-Propylethanolamine, Lot #C-19-A, at a single intact skin site for a 24-hour exposure period at dose levels of 1000, 2000 and 3200 mg/kg.

Clinical signs observed in all of the surviving animals at 1000 mg/kg included decreased activity, abnormal gait and abnormal stance along with necrosis of the skin at the application site. A few of the surviving animals exhibited flaccid body tone, dyspnea, tremors, chromodacryorrhea and brown nasal discharge. No clinical signs were observed in any of the animals dying during the study at this dose level. All surviving animals were normal by Day 7. At 2000 mg/kg clinical signs of all the surviving animals included decreased activity, abnormal gait and abnormal stance along with necrosis of the skin at the application site. Nearly all of the surviving animals exhibited a brown nasal discharge and half exhibited dyspnea. Only a few surviving animals exhibited chromodacryorrhea, decreased muscle tone, tremors and flaccid body tone. Clinical signs of the animals dying during the study included decreased activity, abnormal stance, abnormal gait, tremors, ptosis, dyspnea, chromodacryorrhea along with necrosis of the skin at the application site. All surviving animals were normal by Day 6. Half of the animals that died during the study at 3200 mg/kg did not exhibit any clinical signs. Clinical signs observed in a majority of the remaining animals dying during the study at 3200 mg/kg included decreased activity, abnormal gait, abnormal stance, ptosis and tremors along with necrosis of the skin at the application site. Only a few animals exhibited chromodacryorrhea or prostration. There was an increase in mean body weight in all surviving animals on Day 7 and at termination. Three of ten animals died at 1000 mg/kg. Two of ten animals died at 2000 mg/kg and ten of ten animals died at 3200 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.

Based upon the observations made in the Acute Exposure Dermal Toxicity Study in rats, the acute dermal LD₅₀ for n-Propylethanolamine, Lot #C-19-A, for combined sexes was determined to be 1908 mg/kg. Due to the inconsistent data generated at the 2000 mg/kg dose level, the 95% confidence

Acute Exposure Dermal Toxicity

PH 422-ANA-004-93

SUMMARY (continued)

limits were considered unacceptable. The acute dermal LD₅₀ for females was determined to be 1797 (885-3650) mg/kg. The data generated for the acute dermal LD₅₀ in males did not lend itself to the statistical method employed.

Acute Exposure Dermal Toxicity

PH 422-ANA-004-93

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-004-93

Purpose of the Study: To determine the median lethal dose (LD₅₀) 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, Sherry Yacone, ALAT, 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 26, 1993 through December 30, 1993

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 which affected the quality or integrity

Acute Exposure Dermal Toxicity
PH 422-ANA-004-93

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 188-265

Raw Data:

Appendix I

Statistics:

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

TEST ARTICLE

Compound Name:

n-Propylethanolamine

Physical Description:

Clear colorless liquid

Lot No.:

C-19-A

Specific Gravity:

0.900 g/mL

Amount Received:

470.05 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.

Stability:

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

Acute Exposure Dermal Toxicity
PH 422-ANA-004-93

TEST SYSTEM

Species: Rat

Strain: Sprague Dawley

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

Purchase Order No.: 5011-092493B, 5011-101293E and 5011-122093C

Animals Received: October 7, 1993, October 14, 1993 and
December 23, 1993, respectively

Sex: Male and female

Age at Initiation: 6 - 10 weeks

Weight at Initiation: Healthy adult animals (169-301 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
maintain a temperature of 18° to 26°C (64° - 79°F) and a relative humidity of
40% to 70%.

Acute Exposure Dermal Toxicity
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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: 1000, 2000 and 3200 mg/kg

Rationale for Dose Selection: As per Sponsor's request

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

Acute Exposure Dermal Toxicity
PH 422-ANA-004-93

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>
1921-1930	1000 mg/kg
4671-4680	2000 mg/kg
8671-8680	3200 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 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 in all of the surviving animals at 1000 mg/kg included decreased activity, abnormal gait and abnormal stance along with necrosis of the skin at the application site. A few of the surviving animals exhibited flaccid body tone, dyspnea, tremors, chromodacryorrhea and brown nasal discharge. No clinical signs were observed in any of the animals dying during the study at this dose level. All surviving animals were normal by Day 7. At 2000 mg/kg clinical signs of all the surviving animals included decreased activity, abnormal gait and abnormal stance along with necrosis of the skin at the application site. Nearly all of the surviving animals exhibited a brown nasal discharge and half exhibited dyspnea. Only a few surviving animals exhibited chromodacryorrhea, decreased muscle tone, tremors and flaccid body tone. Clinical signs of the animals dying during the study included decreased activity, abnormal stance, abnormal gait, tremors, ptosis, dyspnea, chromodacryorrhea along with necrosis of the skin at the application site. All surviving animals were normal by Day 6. Half of the animals that died during the study at 3200 mg/kg did not exhibit any clinical signs. Clinical signs observed in a majority of the remaining animals dying during the study at 3200 mg/kg included decreased activity, abnormal gait, abnormal stance, ptosis and tremors along with necrosis of the skin

Acute Exposure Dermal Toxicity
PH 422-ANA-004-93

at the application site. Only a few animals exhibited chromodacryorrhea or prostration. There was an increase in mean body weight in all surviving animals on Day 7 and at termination. Three of ten animals died at 1000 mg/kg. Two of ten animals died at 2000 mg/kg and ten of ten animals died at 3200 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 LD₅₀ for n-Propylethanolamine, Lot #C-19-A, for combined sexes was determined to be 1908 mg/kg. Due to the inconsistent data generated at the 2000 mg/kg dose level, the 95% confidence limits were considered unacceptable. The acute dermal LD₅₀ for females was determined to be 1797 (885-3650) mg/kg. The data generated for the acute dermal LD₅₀ in males did not lend itself to the statistical method employed.

TABLE I (continued)
PHARMAKON RESEARCH INTERNATIONAL, INC.
Acute Exposure Dermal Toxicity (14 Day)
Test Article: n-Propylethanolamine
Study Number: PH 422-ANA-004-93
Sponsor: Elf Atochem North America, Inc.

INDIVIDUAL ANIMAL CLINICAL SIGNS

Animal Number: 8675 Male

Dose Level: 3200 mg/kg

Clinical Signs

Duration

Decreased activity	Day 1
Abnormal stance	Day 1
Abnormal gait	Day 1
Ptosis	Day 1
Chromodacryorrhea	Day 1
Necrosis	Day 1
Animal died	Day 2

TABLE II
PHARMAKON RESEARCH INTERNATIONAL, INC
 Acute Exposure Dermal Toxicity (14 Day)
 Test Article: n-Propylethanolamine
 Study Number: PH422-ANA-004-93
 Sponsor: Elf Atochem North America, Inc

TOXIC SIGNS SUMMARY REPORT

ACUTE EXPOSURE DERMAL TOXICITY
 STUDY: 422ANA4A

MALE

DOSE (mg/kg)	OBSERVATIONS	RANGE

1000	APPEARS NORMAL	DAY 4 (08:55) - DAY 14 (08:32)
	DECREASED ACTIVITY	DAY 1 (10:22) - DAY 5 (11:48)
	ABNORMAL GAIT	DAY 1 (10:22) - DAY 2 (08:46)
	ABNORMAL STANCE	DAY 1 (10:22) - DAY 2 (08:46)
	DYSPNEA	DAY 1 (10:22) - DAY 1 (10:23)
	TREMORS	DAY 1 (10:24)
	NECROSIS	DAY 1 (10:23) - DAY 14 (08:32)
	FLACCID BODY TONE	DAY 1 (10:23) - DAY 1 (10:25)
	BROWN	
	NASAL DISCHARGE	DAY 1 (10:25) - DAY 2 (08:46)
	UNWRAP	DAY 1 (10:23) - DAY 1 (10:25)

FEMALE

DOSE (mg/kg)	OBSERVATIONS	RANGE

1000	APPEARS NORMAL	DAY 3 (08:57) - DAY 14 (08:34)
	DECREASED ACTIVITY	DAY 1 (10:27) - DAY 6 (09:17)
	ABNORMAL GAIT	DAY 1 (10:27) - DAY 2 (08:47)
	ABNORMAL STANCE	DAY 1 (10:27) - DAY 2 (08:47)
	CHROMODACRYORRHEA	DAY 1 (10:30) - DAY 2 (08:47)
	DYSPNEA	DAY 1 (10:29)
	TREMORS	DAY 1 (10:28)
	NECROSIS	DAY 1 (10:27) - DAY 14 (08:34)
	BROWN	
	NASAL DISCHARGE	DAY 1 (10:30)
	UNWRAP	DAY 1 (10:27) - DAY 1 (10:30)

TABLE II (continued)
PHARMAKON RESEARCH INTERNATIONAL, INC
 Acute Exposure Dermal Toxicity (14 Day)
 Test Article: n-Propylethanolamine
 Study Number: PH422-ANA-004-93
 Sponsor: Elf Atochem North America, Inc

TOXIC SIGNS SUMMARY REPORT

ACUTE EXPOSURE DERMAL TOXICITY
 STUDY: 422ANA4

MALE

DOSE (mg/kg)	OBSERVATIONS	RANGE
2000	APPEARS NORMAL	DAY 3 (09:40) - DAY 14 (09:00)
	DECREASED ACTIVITY	DAY 1 (09:47) - DAY 5 (08:54)
	ABNORMAL GAIT	DAY 1 (09:47) - DAY 4 (08:38)
	ABNORMAL STANCE	DAY 1 (09:47) - DAY 4 (08:38)
	CHROMODACRYORRHEA	DAY 1 (09:47) - DAY 4 (08:38)
	DECREASED MUSCLE TONE	DAY 3 (09:40) - DAY 5 (08:53)
	DYSPNEA	DAY 1 (09:47)
	TREMORS	DAY 1 (09:47)
	UNWRAP	DAY 1 (09:47) - DAY 1 (09:50)
	FLACCID BODY TONE	DAY 1 (09:50)
	BROWN NASAL DISCHARGE	DAY 1 (09:48) - DAY 3 (09:40)
	NECROSIS	DAY 1 (09:47) - DAY 14 (09:00)

FEMALE

DOSE (mg/kg)	OBSERVATIONS	RANGE
2000	APPEARS NORMAL	DAY 2 (11:23) - DAY 14 (09:02)
	DECREASED ACTIVITY	DAY 1 (09:51) - DAY 2 (11:24)
	ABNORMAL GAIT	DAY 1 (09:51) - DAY 4 (08:39)
	ABNORMAL STANCE	DAY 1 (09:51) - DAY 4 (08:39)
	CHROMODACRYORRHEA	DAY 2 (11:24)
	DYSPNEA	DAY 1 (09:54) - DAY 2 (11:24)
	PTOSIS	DAY 2 (11:24)
	TREMORS	DAY 1 (09:52)
	UNWRAP	DAY 1 (09:51)
	FLACCID BODY TONE	DAY 1 (09:52)
	BROWN NASAL DISCHARGE	DAY 1 (09:51)
	NECROSIS	DAY 1 (09:51) - DAY 14 (09:02)

TABLE II (continued)
PHARMAKON RESEARCH INTERNATIONAL, INC
 Acute Exposure Dermal Toxicity (14 Day)
 Test Article: n-Propylethanolamine
 Study Number: PH422-ANA-004-93
 Sponsor: Elf Atochem North America, Inc

TOXIC SIGNS SUMMARY REPORT

ACUTE EXPOSURE DERMAL TOXICITY
 STUDY: 422ANA4A

MALE

DOSE (mg/kg)	OBSERVATIONS	RANGE
-----	-----	-----
3200	DECREASED ACTIVITY	DAY 1 (14:57) - DAY 1 (15:01)
	ABNORMAL GAIT	DAY 1 (14:57) - DAY 1 (15:02)
	ABNORMAL STANCE	DAY 1 (14:57) - DAY 1 (15:02)
	CHROMODACRYORRHEA	DAY 1 (15:02)
	NECROSIS	DAY 1 (14:57) - DAY 1 (15:02)
	PROSTRATION	DAY 1 (14:58)
	PTOSIS	DAY 1 (14:57) - DAY 1 (15:02)
	TREMORS	DAY 1 (14:56) - DAY 1 (15:00)
	UNWRAP	DAY 1 (14:57) - DAY 1 (15:02)

FEMALE

DOSE (mg/kg)	OBSERVATIONS	RANGE
-----	-----	-----
3200	DECREASED ACTIVITY	DAY 1 (15:08)
	ABNORMAL GAIT	DAY 1 (15:08)
	ABNORMAL STANCE	DAY 1 (15:08)
	CHROMODACRYORRHEA	DAY 1 (15:08)
	NECROSIS	DAY 1 (15:08)
	PTOSIS	DAY 1 (15:08)
	TREMORS	DAY 1 (15:08)
	UNWRAP	DAY 1 (15:08)

TABLE III
PHARMAKON RESEARCH INTERNATIONAL, INC
 Acute Exposure Dermal Toxicity (14 Day)
 Test Article: n-Propylethanolamine
 Study Number: PH422-ANA-004-93
 Sponsor: Elf Atochem North America, Inc

MORTALITY SUMMARY REPORT

ACUTE EXPOSURE DERMAL TOXICITY
 STUDY: 422ANA4A

MALE

DOSE (Mg/Kg)	NO. DEAD/ NO. DOSED	NUMBER OF DEATHS														

		DAYS AFTER DOSING														
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1000	2/5			2												
2000	0/5															
3200	5/5		1	4												

FEMALE

DOSE (Mg/Kg)	NO. DEAD/ NO. DOSED	NUMBER OF DEATHS														

		DAYS AFTER DOSING														
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1000	1/5		1													
2000	2/5			1	1											
3200	5/5		4	1												

TABLE IV
PHARMAKON RESEARCH INTERNATIONAL, INC
 Acute Exposure Dermal Toxicity (14 Day)
 Test Article: n-Propylethanolamine
 Study Number: PH422-ANA-004-93
 Sponsor: Elf Atochem North America, Inc

BODY WEIGHTS SUMMARY REPORT

ACUTE EXPOSURE DERMAL TOXICITY
STUDY: 422ANA4A

BODY WT. (G)

MALE

DOSE (Mg/Kg)	ANIMAL NUMBER	-----			
		DAY0	DAY7	DAY14	Gain
1000	1921	223	--	--	--
	1922	224	--	--	--
	1923	230	254	315	85
	1924	236	262	328	92
	1925	221	250	310	89
	MEAN	227	255	318	89
	SD	6.1	6.1	9.3	3.5
	N	5	3	3	3
	NO. DIED/NO. DOSED	2/5			

FEMALE

DOSE (Mg/Kg)	ANIMAL NUMBER	-----			
		DAY0	DAY7	DAY14	Gain
1000	1926	178	--	--	--
	1927	169	189	215	46
	1928	188	208	230	42
	1929	194	208	260	66
	1930	180	187	234	54
	MEAN	182	198	235	52
	SD	9.6	11.6	18.7	10.6
	N	5	4	4	4
	NO. DIED/NO. DOSED	1/5			

-- DATA UNAVAILABLE

TABLE IV (continued)
PHARMAKON RESEARCH INTERNATIONAL, INC
 Acute Exposure Dermal Toxicity (14 Day)
 Test Article: n-Propylethanolamine
 Study Number: PH422-ANA-004-93
 Sponsor: Elf Atochem North America, Inc

BODY WEIGHTS SUMMARY REPORT

ACUTE EXPOSURE DERMAL TOXICITY
STUDY: 422ANA4

		BODY WT. (G)			
		MALE			
DOSE (Mg/Kg)	ANIMAL NUMBER	DAY0	DAY7	DAY14	Gain
2000	4671	285	293	372	87
	4672	301	305	373	72
	4673	287	275	319	32
	4674	287	309	371	84
	4675	288	295	343	55
	MEAN	290	295	356	66
	SD	6.5	13.2	24.0	22.8
	N	5	5	5	5
	NO. DIED/NO. DOSED	0/5			
		FEMALE			
DOSE (Mg/Kg)	ANIMAL NUMBER	DAY0	DAY7	DAY14	Gain
2000	4676	217	234	258	41
	4677	216	247	280	64
	4678	222	--	--	--
	4679	200	207	229	29
	4680	205	--	--	--
	MEAN	212	229	256	45
	SD	9.1	20.4	25.6	17.8
	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: n-Propylethanolamine
 Study Number: PH422-ANA-004-93
 Sponsor: Elf Atochem North America, Inc

BODY WEIGHTS SUMMARY REPORT

ACUTE EXPOSURE DERMAL TOXICITY
STUDY: 422ANA4A

BODY WT. (G)

MALE

DOSE (Mg/Kg)	ANIMAL NUMBER	-----			
		DAY0	DAY7	DAY14	Gain
3200	8671	211	--	--	--
	8672	216	--	--	--
	8673	226	--	--	--
	8674	214	--	--	--
	8675	217	--	--	--
	MEAN	217	--	--	--
	SD	5.6	--	--	--
	N	5	--	--	--
	NO. DIED/NO. DOSED	5/5			

FEMALE

DOSE (Mg/Kg)	ANIMAL NUMBER	-----			
		DAY0	DAY7	DAY14	Gain
3200	8676	200	--	--	--
	8677	193	--	--	--
	8678	207	--	--	--
	8679	199	--	--	--
	8680	205	--	--	--
	MEAN	201	--	--	--
	SD	5.5	--	--	--
	N	5	--	--	--
	NO. DIED/NO. DOSED	5/5			

-- DATA UNAVAILABLE

TABLE V
PHARMAKON RESEARCH INTERNATIONAL, INC
 Acute Exposure Dermal Toxicity (14 Day)
 Test Article: n-Propylethanolamine
 Study Number: PH422-ANA-004-93
 Sponsor: Elf Atochem North America, Inc

GROSS NECROPSY SUMMARY REPORT

ACUTE EXPOSURE DERMAL TOXICITY
 STUDY: 422ANA4A

MALE

DOSE (mg/kg)	LOCATION	GROSS OBSERVATION	FREQUENCY	
			DECEDENTS	SURVIVORS
1000	STOMACH	DISTENDED	2/2	0/3
		NORMAL	0/2	3/3
	HEART	NORMAL	2/2	3/3
		INTESTINES	NORMAL	1/2
	INTESTINES	DISTENDED	1/2	0/3
		KIDNEYS	NORMAL	2/2
	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	2/2	3/3

FEMALE

DOSE (mg/kg)	LOCATION	GROSS OBSERVATION	FREQUENCY	
			DECEDENTS	SURVIVORS
1000	STOMACH	DISTENDED	1/1	0/4
		FLUID-FILLED	1/1	0/4
		NORMAL	0/1	4/4
	HEART	NORMAL	1/1	4/4
		INTESTINES	DISTENDED	1/1
	INTESTINES	FLUID-FILLED	1/1	0/4
		NORMAL	0/1	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

TABLE V (continued)
PHARMAKON RESEARCH INTERNATIONAL, INC
 Acute Exposure Dermal Toxicity (14 Day)
 Test Article: n-Propylethanolamine
 Study Number: PH422-ANA-004-93
 Sponsor: Elf Atochem North America, Inc

GROSS NECROPSY SUMMARY REPORT

ACUTE EXPOSURE DERMAL TOXICITY
 STUDY: 422ANA4

MALE

DOSE (mg/kg)	LOCATION	GROSS OBSERVATION	FREQUENCY	
			DECEDENTS	SURVIVORS
2000	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
2000	STOMACH	NORMAL	0/2	3/3
		DISTENDED	1/2	0/3
		FLUID FILLED BLACK	1/2	0/3
	HEART	NORMAL	2/2	3/3
	INTESTINES	NORMAL	1/2	3/3
		FLUID-FILLED	1/2	0/3
		DISTENDED	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	1/2	3/3

TABLE V (continued)
 PHARMAKON RESEARCH INTERNATIONAL, INC
 Acute Exposure Dermal Toxicity (14 Day)
 Test Article: n-Propylethanolamine
 Study Number: PH422-ANA-004-93
 Sponsor: Elf Atochem North America, Inc

GROSS NECROPSY SUMMARY REPORT

ACUTE EXPOSURE DERMAL TOXICITY
 STUDY: 422ANA4A

MALE

DOSE (mg/kg)	LOCATION	GROSS OBSERVATION	FREQUENCY	
			DECEDENTS	SURVIVORS
3200	STOMACH	DISTENDED	3/5	0/0
		NORMAL	2/5	0/0
	HEART	NORMAL	5/5	0/0
		INTESTINES	DISTENDED	4/5
	FLUID-FILLED		2/5	0/0
	NORMAL	1/5	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

FEMALE

DOSE (mg/kg)	LOCATION	GROSS OBSERVATION	FREQUENCY	
			DECEDENTS	SURVIVORS
3200	STOMACH	NORMAL	5/5	0/0
		HEART	5/5	0/0
	INTESTINES	NORMAL	3/5	0/0
		FLUID-FILLED	2/5	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-004-93

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

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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
PH 422 ANA-004-3

Purpose of the Study: To determine the median lethal dose (LD₅₀), 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

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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 ± 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.

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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.

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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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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 LD₅₀ value will be considered in conjunction with the observed toxic effects and any necropsy findings. The LD₅₀ 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

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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)

Test Article
(Name or Code): n-PropylamineETHANOL

Chemical Abstract
No. or Code No.:

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

Carrier Mixtures: Analysis for stability, uniformity and correctness of concentration of the test article in the carrier is the responsibility of the Sponsor.

Return Test Article Carrier Mixtures to the Sponsor
 Dispose of Test Article Carrier Mixtures

Person to whom carrier mixtures should be sent:

Shipping Instructions:

Government Agency Submission: FDA TSCA FIFRA
 EEC OECD MHW
 _____ Other

AMENDMENTS

APPROVAL OF PROTOCOL

Date 9/17/93 Study Monitor R. Bannister
Date September 23, 1993 Study Director John P. Malley

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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): n-PROPYLAMINEETHANOL
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: SEA MSDS

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: 214 Maple North America, Inc
7165 West Jefferson
RIVERVIEW MICHIGAN 48192

V Signature: [Signature] Date: 9/17/93