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TSCA 8(E) SUBSTANTIAL RISK NOTICE SUPPLEMENT: Follow-up to
October 1 and December 7, 1992, 8(e) on Norpar 13 Solvent®

Dear Sir:

Enclosed is the final report of the acute dermal toxicity study in rabbits of Norpar® 12
described in my letter of December 7, 1993, T-5656.

Please contact me at 612-737-4795, if you have any questions.

Sincerely,

Georgan L. Adams
Manager, Regulatory Affairs

Enclosure

93 FEB 23 AM 8:17



8E HQ - 02 - 8582
SP002 02/23/93



89930000057

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FINAL REPORT

Ms. Janell K. Dahms
3M
Toxicology Services
Building 220-2E-02
St. Paul, MN 55144-1000

HWI Number: 21005233

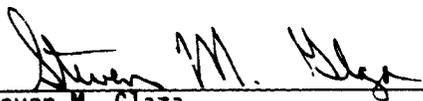
Sample: T-5656

Study Title:

Acute Dermal Toxicity Study
of T-5656 in Rabbits
(OECD Guidelines)

50 FEB 23 AM 8:17

Signed:



Steven M. Glaza
Study Director
Acute Toxicology

Date 1-29-93



0003

HMI Number: 21005233

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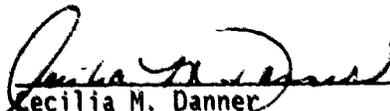
Sample: T-5656

QUALITY ASSURANCE STATEMENT

**Acute Dermal Toxicity Study of T-5656
in Rabbits (OECD Guidelines)**

The report for this study has been reviewed by the Quality Assurance Unit of Hazleton Wisconsin, Inc., in accordance with the proposed Organisation for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice. The report identifies and/or describes the authorized methods and Standard Operating Procedures followed in the conduct of the study. The Quality Assurance Unit has also conducted the following inspections of the testing facilities used in the conduct of this study and has submitted written reports of these inspections to the Study Director. Written status reports of inspections and findings are submitted to Management according to Hazleton Wisconsin, Inc., Standard Operating Procedure^c.

<u>Date of Inspection</u>	<u>Type of Inspection</u>	<u>Date Issued to Study Director</u>
01/15/93	Data Review	01/18/93
01/15/93	Report Review	01/18/93



Cecilia M. Danner
Representative, Quality Assurance Unit

Date 1/29/93

HWI Number: 21005233

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Sample: T-5656

KEY PERSONNEL

Acute Toxicology

Steven M. Glaza
Study Director
Manager

Steven R. Sorenson
Study Coordinator

Patricia Padgham
In-life Supervisor

Rose M. Bridge
Report Supervisor

Quality Assurance

Sherry R. W. Petsel
Manager

Laboratory Animal Medicine

Cindy J. Cary, DVM
Diplomate, ACLAM

Anatomical Pathology

Thomas E. Palmer, PhD
Anatomical Pathologist

Jack Serfort
Supervisor
Necropsy

Anne Mosher
Supervisor
Pathology Data

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0-0-05



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HWI Number: 21005233

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Sample: T-5656

OBJECTIVE

The objective of this study was to assess the systemic toxicity and relative skin irritancy of a test material when applied to the skin of rabbits.¹

All procedures used in this study are in compliance with the Animal Welfare Act Regulations, effective October 30, 1989. In the opinion of the Sponsor and study director, the study did not unnecessarily duplicate any previous work.

TEST MATERIAL

Identification

The test material was identified as T-5656 and described as a clear, colorless liquid.

Purity and Stability

The Sponsor assumes responsibility for purity and stability determinations (including under test conditions).

Storage and Retention

The test material was stored at room temperature. Any unused test material will be returned to the Sponsor after issuance of the final report according to Hazleton Wisconsin (HWI) Standard Operating Procedure (SOP).

Safety Precautions

The test material handling procedures were according to HWI SOPs and policies.

TEST SYSTEM

Test Animal

Adult albino rabbits of the Hra:(NZW)SPF strain were procured from Hazleton Research Products, Inc. and maintained at the Hazleton Wisconsin facility at 3802 Packers Avenue, Madison, Wisconsin. Animal husbandry and housing at HWI comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals".² The animals were individually housed in screen-bottom cages in temperature- and humidity-controlled quarters, provided access to water *ad libitum* and a measured amount of High Fiber Rabbit Chow® #5326,

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CORNING Laboratory Services Company

HMI Number: 21005233

Page 5

Sample: T-5656

Purina Mills, Inc., and held for an acclimation period of at least 7 days. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed by HMI. There were no known contaminants in the feed or water that would have interfered with or affected the results of the study.

Acclimated animals (approximately 16 to 17 weeks of age) were selected and maintained during the study in the same manner as for the acclimation period. Variations from the prescribed environmental conditions existed and were considered to have no effect on the study outcome. Five male and five female rabbits, weighing from 2,515 to 2,865 g, were used for a single dose level of 1,500 mg/kg of body weight. Animals were identified by animal number and corresponding ear tag. Approximately 24 hours before test material application, each rabbit's back was clipped free of hair with an electric clipper. The clipped area made up not less than 10% of the total body surface. The animals were clipped as needed throughout the study.

Justification for Species Selection

Historically, the New Zealand White albino rabbit has been the animal of choice because of the large amount of background information on this species.

PROCEDURES

Preparation of Test Material

The test material was administered as received. An individual dose was calculated and weighed out based upon each animal's body weight on the day of test material administration.

Treatment

The test material was applied to the intact skin on each animal's back at a dose level of 1,500 mg/kg of body weight. The area of application was covered with a 10-cm x 10-cm gauze patch secured with paper tape and overwrapped with Saran Wrap® and Elastoplast® tape to provide occlusive dressing. The test material was applied to the test site at a rate of approximately 0.40 mg/cm² in a thin and uniform layer. Collars were used to restrain the test animals during the 24-hour exposure period. Collars were reapplied to the animals on Day 1 to prevent ingestion of test material. The collars were removed on Day 2.

At the end of the 24-hour exposure period, the restraining collars and bandages were removed and the test sites were washed using tap water and disposable paper towels.

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Sample: T-5656

Reason for Route of Administration

Historically, the dermal route has been the route of choice based on the method of Draize.³

Observations

Clinical observations and mortality checks were conducted at approximately 1, 2.5, and 4 hours after test material administration. Additional clinical observations and twice a day mortality checks (morning and afternoon) were conducted daily thereafter for 14 days.

Body weights were determined before test material administration (Day 0), at Day 7, and at termination of the experimental phase (Day 14).

The initial dermal irritation reading was made approximately 30 minutes after removal of the test material according to the Draize technique (recorded as the Day 1 score). Subsequent readings of dermal irritation were made on Days 3, 7, 10, and 14.

Pathology

At termination of the experimental phase, all animals were euthanized, subjected to a gross necropsy examination, and any abnormalities were recorded. After necropsy, the animals were discarded and no tissues were saved.

Statistical Analyses

No statistical analyses were required by the protocol.

Location of Raw Data, Records, and Final Report

The raw data, records, and copy of the final report will be retained in the archives of HWI in accordance with HWI SOP.

HWI Number: 21005233

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Sample: T-5656

SUMMARY OF RESULTS

Test Animal: Albino Rabbits - Hra:(NZW)SPF
 Source: Hazleton Research Products, Inc., Kalamazoo, MI
 Date Animals Received: 10/21/92

Environmental Conditions: 66 to 75°F
 23 to 58% Relative Humidity

Experimental Start Date: 11/17/92 Experimental Termination Date: 01/29/93

Individual Body Weights

Animal Number	Body Weight (g)		
	Day 0	Day 7	Day 14

Males (1,500 mg/kg)

F43793	2,855	2,925	3,033
F43797	2,646	2,609	2,730
F43798	2,767	2,795	2,881
F43791	2,523	2,445	2,459
F43792	2,766	2,782	2,891
Mean	2,713	2,711	2,799

Females (1,500 mg/kg)

F43788	2,515	2,428	2,574
F43794	2,828	2,712	2,973
F43795	2,710	2,714	2,802
F43796	2,592	2,471	2,627
F43789	2,630	2,641	2,692
Mean	2,655	2,595	2,734

Dermal Reactions

Dermal irritation (based on the most severe score for each animal at any time point) consisted of slight to moderate erythema, slight to severe edema, slight to moderate atonia, coriaceousness, and fissuring, and slight desquamation. No other irritation was observed.



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HNI Number: 21005233

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Sample: T-5656

Individual Clinical Signs

T-5656

Animal Number	Observation	Hour			Day													
		1.0	2.5	4.0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
<u>Males (.500 mg/kg)</u>																		
F43793	Appeared normal	/	/	/	-	-	-	/	/	/	/	/	/	/	/	/	/	/
	Staggered gait	-	-	-	/	/	*	-	-	-	-	-	-	-	-	-	-	-
	Impaired use of limbs	-	-	-	/	*	-	-	-	-	-	-	-	-	-	-	-	-
	Decreased righting reflex	-	-	-	/	-	-	-	-	-	-	-	-	-	-	-	-	-
F43797	Appeared normal	/	/	/	-	-	-	-	-	/	/	/	/	/	/	/	/	/
	Staggered gait	-	-	-	/	/	*	*	*	-	-	-	-	-	-	-	-	-
	Decreased righting reflex	-	-	-	/	-	-	-	-	-	-	-	-	-	-	-	-	-
F43798	Appeared normal	/	/	/	-	-	-	/	/	/	/	/	/	/	/	/	/	/
	Staggered gait	-	-	-	/	/	*	-	-	-	-	-	-	-	-	-	-	-
	Vocalization	-	-	-	/	-	-	-	-	-	-	-	-	-	-	-	-	-
F43791	Appeared normal	/	/	/	-	-	-	-	/	/	/	/	/	/	/	/	/	/
	Staggered gait	-	-	-	/	/	/	*	-	-	-	-	-	-	-	-	-	-
	Vocalization	-	-	-	/	-	-	-	-	-	-	-	-	-	-	-	-	-
F43792	Appeared normal	/	/	/	-	-	-	-	-	-	-	-	-	-	-	-	-	/
	Staggered gait	-	-	-	/	/	/	/	/	*	*	*	*	*	*	*	*	*
	Tremors	-	-	-	/	/	/	/	/	*	*	*	*	*	*	*	*	*
	Impaired use of limbs	-	-	-	/	/	/	*	*	*	-	-	-	-	-	-	-	-

/ Condition exists.
 * Slight.

Note: Staggered gait is defined as incoordination of locomotor activity. In this study it included abnormal positioning of the feet, with the toes turned under the foot. The animals also tended to crawl in a low position as opposed to a normal hop.

The term "impaired use of limbs" as used in this study was reflective of the abnormal positioning of the front limbs. The rabbits had very limited control of the front limbs which at times were tucked underneath the body.

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HWI Number: 21005233

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Sample: T-5656

Individual Clinical Signs

T-5656

Animal Number	Observation	Hour			Day													
		1.0	2.5	4.0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Females (0.500 mg/kg)																		
F43788	Appeared normal	/	/	/	-	-	-	-	/	/	/	/	/	/	/	/	/	/
	Staggered gait	-	-	-	/	/	/	*	-	-	-	-	-	-	-	-	-	-
	Vocalization	-	-	-	/	-	-	-	-	-	-	-	-	-	-	-	-	-
	Righting reflex absent	-	-	-	/	-	-	-	-	-	-	-	-	-	-	-	-	-
F43794	Appeared normal	/	/	/	-	-	-	/	/	/	/	/	/	/	/	/	/	/
	Staggered gait	-	-	-	/	/	*	-	-	-	-	-	-	-	-	-	-	-
	Impaired use of limbs	-	-	-	/	/	*	-	-	-	-	-	-	-	-	-	-	-
	Decreased righting reflex	-	-	-	/	/	-	-	-	-	-	-	-	-	-	-	-	-
F43795	Appeared normal	/	/	/	/	-	-	/	/	/	/	/	/	/	/	/	/	/
	Staggered gait	-	-	-	-	*	*	-	-	-	-	-	-	-	-	-	-	-
F43796	Appeared normal	/	/	/	-	-	-	-	-	-	-	/	/	/	/	/	/	/
	Vocalization	-	-	-	/	-	-	-	-	-	-	-	-	-	-	-	-	-
	Staggered gait	-	-	-	-	/	/	/	*	*	*	-	-	-	-	-	-	-
F43789	Appeared normal	/	/	/	-	-	-	-	-	-	-	-	/	/	/	/	/	/
	Staggered gait	-	-	-	/	/	/	*	*	*	*	*	-	-	-	-	-	-
	Impaired use of limbs	-	-	-	/	/	/	*	-	-	-	-	-	-	-	-	-	-
	Vocalization	-	-	-	/	-	-	-	-	-	-	-	-	-	-	-	-	-

/ Condition exists.
 * Slight.

Note: Staggered gait is defined as incoordination of locomotor activity. In this study it included abnormal positioning of the feet, with the toe turned under the foot. The animals also tended to crawl in a low position as opposed to a normal hop.

The term "impaired use of limbs" as used in this study was reflective of the abnormal positioning of the front limbs. The rabbits had very limited control of the front limbs which at times were tucked underneath the body.

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HWI Number: 21005233

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Sample: T-5656

Individual Pathology Comments

Dose Level: 1,500 mg/kg of Body Weight

<u>Animal Number</u>	<u>Sex</u>	<u>Test Day</u>		<u>Necropsy Observation</u>
		<u>Died</u>	<u>Sacrificed</u>	
F43793	M	-	14	No visible lesions.
F43797	M	-	14	No visible lesions.
F43798	M	-	14	No visible lesions.
F43791	M	-	14	No visible lesions.
F43792	M	-	14	No visible lesions.
F43788	F	-	14	No visible lesions.
F43794	F	-	14	No visible lesions.
F43795	F	-	14	No visible lesions.
F43796	F	-	14	No visible lesions.
F43789	F	-	14	No visible lesions.

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HMI Number: 21005233

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Sample: T-5656

DISCUSSION

The acute dermal toxicity of T-5656 was evaluated in male and female rabbits when administered as a single topical application at a level of 1,500 mg/kg of body weight. The estimated dermal LD₅₀ for male and female rabbits was determined to be greater than 1,500 mg/kg. Clinical signs of toxicity included staggered gait, vocalization, impaired use of limbs, and decreased righting reflex. These clinical signs were most evident during the first five days of the study. There was no meaningful effect on body weight gain. The test material produced slight to severe dermal irritation. Page 11 contains a pathology report by the study pathologist.

Deviation from the Protocol

The age of the animals used for this study was approximately 16 to 17 weeks rather than approximately 14 weeks as stated in the protocol. This deviation is not considered to have had an adverse effect on the study outcome.

REFERENCES

1. "Acute Dermal Toxicity," *Organisation for Economic Cooperation and Development's Guidelines for Testing of Chemicals*, Section 402 (adopted May 12, 1981).
2. NIH Publication No. 86-23 (revised 1985).
3. Draize, J. H., "Acute Dermal Toxicity (Single Exposure)," In: *Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics - Dermal Toxicity*, Association of Food and Drug Officials of the U.S., pp. 54-56 (1975).

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HWI Number: 21005233

Page 12

Sample: T-5656

PATHOLOGY REPORT

There were 10 rabbits (five males and five females) euthanized and necropsied at the termination of the study. The dose level, day of death, and gross observations recorded for each animal are in the Individual Pathology Comments that precede this report. There were no visible lesions in any of the animals.

James B. Nold DVM PhD
 for Thomas E. Palmer, PhD
 Pathologist

1-29-93
 Date

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HWI Number: 21001933

Page 13

Sample: T-5656

APPENDIX
Raw Data/Protocol

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14

0015

PERSONNEL SIGNATURE SHEET
ACUTE TOXICOLOGY

<u>Name</u>	<u>Job Title</u>	<u>Signature</u>	<u>Initials</u>
Anthony Cass	Lab Animal Caretaker	<u>Anthony Cass</u>	AC
Cindy J. Cary, DVM	Lab Animal Veterinarian	<u>Cindy J. Cary</u>	CC
Kari Garfoot	Lab Animal Technician	<u>Kari Garfoot</u>	KG
Steven M. Glaza	Manager	<u>Steven M. Glaza</u>	SG
Ben Haley	Lab Animal Technician	<u>Ben Haley</u>	BH
Jeff Hicks	Lab Animal Technician	<u>Jeff Hicks</u>	JH
Sharen L. Howery	Research Assistant	<u>Sharen L. Howery</u>	SH
Pam Larson	Senior Clerk	<u>Pamela Larson</u>	PL
Wayne A. Madison	Supervisor	<u>Wayne A. Madison</u>	WAM
Doug McConnell	Lab Animal Technician	<u>Douglas B. McConnell</u>	DM
Eileen McConnell	Administrative Clerk	<u>Eileen McConnell</u>	EM
Henry Mikula	Lab Animal Caretaker	<u>Henry Mikula</u>	HM
Albert Oleson	Lab Animal Caretaker	<u>Albert Oleson</u>	AO
Patricia Padgham	Supervisor	<u>Patricia Padgham</u>	TP
John Seitz	Lab Animal Caretaker	<u>John Seitz</u>	JS
Steven R. Sorenson	Study Coordinator	<u>Steven R. Sorenson</u>	SS
Annette R. Turner	Senior Clerk	<u>Annette R. Turner</u>	AT
Lara M. Weeden	Clerk	<u>Lara M. Weeden</u>	LW
Kevin Crossman	Lab Animal Caretaker	<u>Kevin Crossman</u>	KC
Rose M. Bridge	Report Supervisor	<u>Rose M. Bridge</u>	RB
William J. Kolman	Lab Animal Caretaker	<u>William J. Kolman</u>	BK

HWI No.: 21005233

ACUTE DERMAL APPLICATION / BODY WEIGHT RECORD

Test Material: T-5656 (T-5618) ①
 Physic Description: CLEAR COLORLESS LIQUID Initiated in Room No.: 103
 Vehicle: NA Mfg./Lot No. Exp.: NA / NA / NA
 Species/Source Strain/Location: Rabbit/Hra:(NZW)SPF/ALL Date Received: 10-21-92
 Dose Level: 1500 mg/kg Tech/Date/Time Clipped: JH / 14:10 / 11-16-92
 Storage conditions of test material: ROOM TEMPERATURE

Dose Calculations				Compound Preparation Weights		
Animal Number	Body Weight (kg)	Dose Level (mg/kg)	Dose ② Animal (g)	Tare Weight (g)	Total Weight (g)	Sample Weight (g)
✓ 3793	2.865	1500	4.30	7.86	12.16	4.30
3797	2.646		3.97	7.78	11.75	3.97
3798	2.767		4.15	7.90	12.05	4.15
3791	2.523		3.78	7.92	11.70	3.78
3792	2.766		4.15	7.82	11.97	4.15
3788	2.515		3.77	7.77	11.54	3.77
3794	2.828		4.24	7.77	12.01	4.24
3795	2.710		4.07	7.81	11.88	4.07
3796	2.592		3.89	7.77	11.66	3.89
✓ 3789	2.630	✓	3.95	7.79	11.74	3.95

Calculated by: KJ Date: 11-17-92 Conducted by: KJ Date: 11-17-92
 Verified by: JH Date: 11-17-92 Approved by: JH Date: 11-17-92
 Scale Used: SARTORIUS 2811002

Animal Number	Skin Prep	Sex	Animal Body Weights (g)		
			Study Day		
			0	7	14
✓ 3793	I	♂	2865	2925	3033
3797			2646	2609	2730
3798			2767	2795	2881
3791			2523	2445	2459
3792		↓	2766	2782	2891
3788		♀	2515	2428	2574
3794			2828	2721	2973
3795			2710	2714	2802
3796			2592	2471	2627
✓ 3789	↓	↓	2630	2641	2692
Technician	KJ	KJ	KJ	KJ	JH
Date: 1992	11/17	11/17	11/17	11/24	12/1
Scale Used:	A + D ③	JEFFRON	CS604465	CS604465	CS604465

① FORM CHANGE.
 KJ 11-17-92
 ② APPROXIMATE RATE OF EXPOSURE IS 0.04 g/cm²
 KJ 11-17-92
 ③ CLARIFICATION OF FOOTNOTE ②.
 AVERAGE DOSE = 9/cm²
 TEST SITE AREA 100cm x 100 cm
 ④ TEST MATERIAL FOR THIS STUDY IS IDENTIFIED BY T-5656 ONLY. THE T-5618 WAS THE IDENTIFICATION OF THIS MATERIAL FOR A PREVIOUS STUDY. SRS 1, 28-93

I - Intact
 A - Abraded (with a clipper blade)
 NA - Not applicable

(D2/03-01-92)

Final data review by/Date: JH / 12-7-92

HWI No.: 21005233

MORTALITY RECORD

Dose Level: 1500 mg/kg

Test Material: T-SLSL4

Animal Number	Observation Period (Days)															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
3793	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3797	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3798	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3791	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3792	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3796	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3795	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3794	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3796	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3789	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Technician	LN	LN	LN	LN	LN	LN	LN	LN	LN	LN	LN	LN	LN	LN	LN	LN
Time	7:50	11:05	7:55	14:20	14:00	7:30	14:10	7:05	14:10	7:05	14:10	7:30	14:10	7:30	14:10	7:10
Date 1992	11/10	11/18	11/19	11/20	11/20	11/21	11/21	11/22	11/22	11/23	11/23	11/24	11/24	11/25	11/25	11/25

NA - Not applicable.
 X - Dead.
 / - Alive.

Final data review by/Date: CH / 12-1-92

(04/03-01-92)

HWI No.: 21005233

Acute Dermal Irritation Observation

Test Material: T-SLASH Dose Level: 1500 mg/kg

	Observation Period (Days)										
	Males					Females					
		3	7	10	14	1	3	7	10	14	
	11/18	11/20	11/24	11/27	12/1	11/18	11/20	11/24	11/27	12/1	
	Animal No. F43793					Animal No. F43788					
Erythema	2	2	2	1	1	2	2	2	2	1	
Edema	2	1	1	1	0	2	2	3	1	1	
Atonia	0	0	1	0	0	3	1	2	1	0	
Desquamation	0	0	0	0	1	0	0	0	0	1	
Coriaceousness	0	0	1	0	0	0	0	1	1	0	
Fissuring	0	0	1	1	0	0	0	2	2	1	
	Animal No. F43797					Animal No. F43794					
Erythema	2	1	2	2	1	2	2	2	2	1	
Edema	2	1	1	1	0	3	2	2	2	1	
Atonia	2	1	2	1	1	2	1	2	2	1	
Desquamation	0	0	0	0	1	0	0	0	0	1	
Coriaceousness	0	0	1	1	0	0	0	2	1	0	
Fissuring	0	0	1	1	0	0	0	2	2	1	
	Animal No. F43798					Animal No. F43795					
Erythema	2	2	2	1	1	2	1	1	2	1	
Edema	2	1	1	1	0	2	1	1	1	0	
Atonia	2	1	1	1	0	1	1	1	1	0	
Desquamation	0	0	0	1	1	0	0	0	0	1	
Coriaceousness	0	0	1	0	0	0	0	1	1	0	
Fissuring	0	0	1	1	0	0	0	1	2	0	
	Animal No. F43791					Animal No. F43796					
Erythema	2	2	2	2	2	2	1	1	1	1	
Edema	2	2	2	1	0	2	1	1	1	0	
Atonia	1	1	2	1	0	2	1	1	0	0	
Desquamation	0	0	0	0	1	0	0	0	0	0	
Coriaceousness	0	0	1	0	0	0	0	1	1	0	
Fissuring	0	0	1	1	0	0	0	1	2	1	
	Animal No. F43792					Animal No. F43789					
Erythema	2	1	1	1	1	2	2	2	2	1	
Edema	3	2	2	1	0	3	1	1	1	0	
Atonia	2	1	2	1	0	1	1	1	1	0	
Desquamation	0	0	0	0	1	0	0	0	0	1	
Coriaceousness	0	0	1	0	0	0	0	1	1	0	
Fissuring	0	0	1	1	0	0	0	1	2	1	
Technician	K	K	K	AH	AK*	K	KA	K	AK	AK*	
Date	1992	11/18	11/20	11/24	11/27	12/1	11/18	11/20	11/24	11/27	12/1

A Subcutaneous hemorrhage B Blanching D Eschar
 N Possible necrotic area E Exfoliation

* Animal(s) shaved prior to dermal observation by technician.

(D5/11-03-92)

Final data review by/Date: JH 1/12-7-92

Sample Submittal Form

This form is to be used when submitting samples for routine acute testing. Special testing needs can be easily arranged by contacting the Acute Toxicology Department at (608) 241-4471, Ext. 7292, or the Client Service Center at (608) 241-7210.

HWI Study No. 21005233
Enclose with samples and send to:
Hazleton Wisconsin
3301 Kinsman Boulevard
Madison, Wisconsin 53704

Submitted by: JK DALLMS Date Sample Sent: HAZLETON HAS SAMPLE AS T-5618.
Company: 3M Invoice to: _____
P.O. Number: _____ Number of Reports Required: 3
Full GLP Compliance: Yes No FDA (21 CFR 58) EPA (FIFRA)—40 CFR 160
 EPA (TSCA)—40 CFR 792 OECD
Sample Name: T-5618
Physical Description: Clear, colorless liquid with white HVA component (over)
Special Handling Precautions: MSDS ATTACHED
Storage Requirements: Room Temperature Refrigerated Other _____
Disposal: Return to submitter Dispose of according to Hazleton SOPs

Tests

Acute Oral Toxicity in Rats

- TP8084 Up and down LD50 procedure
 - TP3206 FHSA screen; 5M-5F at 5.0 g/kg
 Conduct defined study if death occurs at 5.0 g/kg
 - TP3013 EPA screen; 5M-5F at 5.0 g/kg
 Conduct defined study if death occurs at 5.0 g/kg
 - TP2069 OECD screen; 5M-5F at 5.0 g/kg
 Conduct defined study if death occurs at 5.0 g/kg
- Special instructions: _____

Acute Dermal Toxicity in Rabbits

- TP3207 FHSA screen; 5M-5F at 2.0 g/kg
 - TP3016 EPA screen; 5M-5F at 2.0 g/kg
 - Conduct defined study if death occurs at 2.0 g/kg
 - TP2070 OECD screen; 5M-5F at 2.0 g/kg
 Conduct defined study if death occurs at 2.0 g/kg
- Special instructions: THANK YOU TO LSC, RSC, etc

For Hazleton Use Only

Protocol Issue Date: 11-16-92

Study Director: Steve Blago

White copy—Hazleton Yellow copy—Submitter

Primary Skin Irritation

- TP3208 FHSA; 6 rabbits-1 abraded, 1 intact site/rabbit
 - TP3014 EPA; 6 rabbits-1 intact site/rabbit
 - TP2071 OECD; 3 rabbits-1 intact site/rabbit
 - TP4206 DOT corrosivity; 6 rabbits-1 intact site/rabbit
 - TP7145 Phototoxicity; 6 rabbits-2 intact sites/rabbit
(one site with UVA exposure)
- Special instructions: _____

Primary Eye Irritation

- TP6360 Low-volume procedure; 6 rabbits unwashed
 - TP3209 FHSA; 6 rabbits unwashed
 - TP2012 1978 EPA; 6 rabbits unwashed, 3 washed
 - TP3015 1982 EPA; 6 rabbits unwashed
 - TP2072 OECD; 3 rabbits unwashed
 3 rabbits washed at 4 seconds
 3 rabbits washed at 30 seconds
- Special instructions: _____

Guinea Pig Sensitization

- TP2017 EPA Magnusson-Kligman maximization
 - TP6164 OECD Magnusson-Kligman maximization (EC)
 - TP2008 Buehler sensitization
 - TP6289 Photoallergenic contact dermatitis (Armstrong)
- Special instructions: _____



HAZLETON LABORATORIES AMERICA, INC.

3301 KINSMAN BLVD. - P.O. BOX 7545 - MADISON, WI 53707 - (608) 241-4471 - TLX 703956 HAZRAL MDS UD

Sponsor:

3M
St. Paul, Minnesota

PROTOCOL TP2070

Study Title:

Acute Dermal Toxicity Study in Rabbits
(OECD Guidelines)

Date:

August 18, 1989

Performing Laboratory:

Hazleton Laboratories America, Inc.
3301 Kinsman Boulevard
Madison, Wisconsin 53704

Laboratory Project Identification:

HLA 21005233

000 23

STUDY IDENTIFICATION

Acute Dermal Toxicity Study in Rabbits
(OECD Guidelines)

HLA Study No.	21005233
Test Material	(See sample submittal form)
Sponsor	3M Toxicology Services 220-2E-02 3M Center St. Paul, MN 55144
Sponsor's Representative	Frank D. Griffith, PhD 3M Toxicology Services 220-2E-02 3M Center St. Paul, MN 55144 (612) 733-7635
Study Director	Steven M. Glaza Hazleton Laboratories America, Inc. P.O. Box 7545 Madison, WI 53707 (608) 241-7292
Study Location	Hazleton Laboratories America, Inc. Building No. 3 3802 Packers Avenue Madison, WI 53704
Study Timetable	
In-Life Start Date	Week of 11-9-92
In-Life End Date	Week of 11-23-92
Final Report Date	Week of 1-4-93

0 0 0 2 4

1. Study Acute Dermal Toxicity Study in Rabbits (OECD Guidelines)
2. Purpose To assess the systemic toxicity and relative skin irritancy of a test material when applied to the skin
3. Regulatory Compliance This study will be conducted in accordance with the following Good Laboratory Practice Regulations/Standards:
 - 21 CFR 58 (FDA)
 - 40 CFR 160 (EPA-FIFRA)
 - 40 CFR 792 (EPA-TSCA)
 - C(81)30 (Final) (OECD)
 - Notification No. 3850, August 10, 1984 (Japanese MAFF)
 - Notification No. 313, March 31, 1982, and as amended by Notification No. 870, October 6, 1988 (Japanese MOHW)
4. Quality Assurance The protocol, in-life phase, and the final report will be audited by the Quality Assurance Unit in accordance with Hazleton Laboratories America, Inc. (HLA) Standard Operating Procedures (SOPs).
5. Test Material
 - A. Identification (See sample submittal form)
 - B. Physical Description (See sample submittal form)
 - C. Purity and Stability The Sponsor assumes responsibility for purity and stability determinations (including under test conditions). Analyses of test material vehicle mixture(s) for concentration, homogeneity, and stability will not be done unless specifically requested by the Sponsor.
 - D. Storage (See sample submittal form)
 - E. Retention Any unused test material will be discarded 30 days after issuance of the final report, unless directed otherwise by the Sponsor.
 - F. Safety Precautions As required by HLA SOPs

6. Experimental Design

A. Animals

- | | |
|-------------------------------|---|
| (1) Species | Rabbit |
| (2) Strain/Source | Hra:(NZW)SPF/Hazleton Research Products, Inc. |
| (3) Age at Initiation | Young adult (approximately 14 weeks old) |
| (4) Weight at Initiation | 2.0 to 3.0 kg |
| (5) Number and Sex | Five/sex |
| (6) Identification | Individual numbered ear tag |
| (7) Husbandry | |
| (a) Housing | Individually, in screen-bottom stainless steel cages (heavy gauge) |
| (b) Food | A measured amount of High Fiber Rabbit Chow [®] #5326 (Purina Mills, Inc.). The food is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. |
| (c) Water | <u>Ad libitum</u> from an automatic system. Samples of the water are analyzed by HLA for total dissolved solids, conductivity, and specified microbiological content and for selected elements, heavy metals, organophosphates, and chlorinated hydrocarbons. |
| (d) Contaminants | There are no known contaminants in the food or water that would interfere with this study. |
| (e) Environment | Environmental controls for the animal room will be set to maintain a temperature of 70°F \pm 3°, a relative humidity of 50% \pm 20%, and a 12-hour light/12-hour dark cycle. |
| (f) Acclimation | At least 7 days |
| (8) Selection of Test Animals | Based on health and body weight according to HLA SOPs. An adequate number of extra animals will be purchased so that no animal in obviously poor health is placed on test. |

(9) Justification

Historically, the New Zealand White albino rabbit has been the animal of choice because of the large amount of background information on this species.

B. Dose Administration

(1) Dose Level

A single dose of 2.0 g/kg will be administered to the intact skin of five males and five females. If no test material-related mortality is produced at this level, no further testing will be required. If any mortality occurs at the 2.0 g/kg level, additional dose levels may be added at the Sponsor's request. Each dose level will be given to five males and/or five females.

(2) Preparation of Exposure Area

The hair will be removed from the back of each rabbit with an electric clipper approximately 24 hours before test material application. Not less than 10% of the total body surface area will be shaved.

(3) Dose Administration

All animals will receive a single administration of test material. The dose will be based upon the animal's body weight just before administration of the test material. The area of application will be covered with as thin and uniform a layer as possible. If the test material is a solid, it will be moistened with 0.9% saline. The area of application will be wrapped with a gauze bandage secured with paper tape around all edges, overwrapped with Saran Wrap®, and secured with Elastoplast® tape. The rabbits will be collared during the 24-hour application period.

(4) Reason for Dosing Route

Historically, the dermal route has been the route of choice based on the method of Draize.

(5) Removal of Test Material

Twenty-four hours after test material application, the bandages will be removed, and the residual test material will be removed using water or an appropriate solvent, if necessary.

C. Observation of Animals

(1) Antemortem Observations

At 1.0, 2.5, and 4 hours after test material administration for clinical signs and mortality, daily thereafter for clinical signs, and twice daily (a.m. and p.m.) for mortality for at least 14 days. Observations may be extended when considered necessary.

(2) Reading of Dermal Irritation

Approximately 30 minutes after bandage removal, the initial dermal irritation reading will be taken. Additional dermal irritation readings will be made on Study Days 3, 7, 10, and 14. Individual dermal irritation records will be maintained for each animal (Attachment 1).

(3) Body Weights

Just before test material application, on Days 7 and 14, and at death (when survival exceeds 1 day)

D. Pathology

All test animals will be subjected to a gross necropsy examination, and abnormalities will be recorded.

E. Statistical Analyses

Other than LD₅₀ calculations (when applicable) no statistical analyses are required.

7. Report

A final report including those items listed below will be submitted:

Description of the test material
Description of the test system
Dates of study initiation and termination
Response data for mortality
Description of any toxic effects
Body weights by sex and dose levels
LD₅₀ values by sex with 95% confidence intervals (when applicable)
Gross necropsy findings

8. Maintenance of Raw Data and Records

Original data, or copies thereof, will be available at HLA to facilitate auditing the study during its progress and before acceptance of the final report. When the final report is completed, all original paper data and a copy of the final report will be retained in the archives of HLA.

PROTOCOL APPROVAL

Frank D. Griffith
Frank D. Griffith, PhD
Sponsor's Representative
3M

9-14-89
Date

Steven M. Glaza
Steven M. Glaza
Study Director
Acute Toxicology
Hazleton Laboratories America, Inc.

8-17-89
Date

Darcie S. Kollette
Representative
Quality Assurance Unit
Hazleton Laboratories America, Inc.

8/18/89
Date

(1486S)

2A

0029

Attachment 1

Scale for Scoring Skin Reactions

Erythema

- 0 - None
- 1.0 - Slight
- 2.0 - Moderate (well defined)
- 3.0 - Severe (beet red)

Edema

- 0 - None
- 1.0 - Slight (barely perceptible to well defined by definite raising)
- 2.0 - Moderate (raised approximately 1 mm)
- 3.0 - Severe (raised more than 1 mm)

Atonia

- 0 - None
- 1.0 - Slight (slight impairment of elasticity)
- 2.0 - Moderate (slow return to normal)
- 3.0 - Marked (no elasticity)

Desquamation

- 0 - None
- 1.0 - Slight (slight scaling)
- 2.0 - Moderate (scales and flakes)
- 3.0 - Marked (pronounced flaking with denuded areas)

Coriaceousness

- 0 - None
- 1.0 - Slight (decrease in pliability)
- 2.0 - Moderate (leathery texture)
- 3.0 - Marked (tough and brittle)

Fissuring

- 0 - None
- 1.0 - Slight (definite cracks in epidermis)
- 2.0 - Moderate (cracks in dermis)
- 3.0 - Marked (cracks with bleeding)

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0 0 3 0

HLA/HWI No. 21005333

PROTOCOL AMENDMENTS

Amendment No. 1
Effective September 1, 1990

For every occurrence in the protocol and raw data where "Hazleton Laboratories America, Inc. (HLA)" is stated, replace it with "Hazleton Wisconsin, Inc. (HWI)" as there was a company name change.

Amendment No. 2
Effective October 2, 1990

Page 2, Study Timetable. The study timetable specified should be considered as a *proposed* schedule of events.

Amendment No. 3
Effective October 2, 1990

Page 3, 4. Quality Assurance. To modify that originally given, replace "in-life phase" with the following underlined change:

The protocol, study conduct, and the final report will be audited by the Quality Assurance Unit in accordance with Hazleton Wisconsin (HWI) Standard Operating Procedures (SOPs).

Study Director Approval:

Steve Hago 11-6-92

HWT No. 21005233

PROTOCOL AMENDMENTS

Amendment No. 4
Effective November 6, 1992

Portion of Protocol Being Modified: Page 5, 6, Experimental Design;
B. Dose Administration; (1) Dose Level.

Reason for Modification: To clarify the dose level as provided by the Sponsor.

Modification: Replace "2.0 g/kg", with "1.5 g/kg" wherever listed.

Study Director Approval: *Steve Kelly* 11-6-92

Amendment No. _____
Effective _____

Portion of Protocol Being Modified: _____

Reason for Modification: _____

Modification: _____

Study Director Approval: _____

CERTIFICATE OF AUTHENTICITY

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