Corning Hazleton Inc.
P.O. Box 7545
Madison, WI 53707-7545
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608.241.4471 608.241.7227 Fax

CORNING Hazleton

Sponsor:

3M
St. Paul, Minnesota

FINAL REPORT

Study Title:

Acute Dermal Toxicity Study of T-6342 in Rabbits (OECD Guidelines)

Author:

Steven M. Glaza

Study Completion Date:

October 24, 1995

Performing Laboratory:

Corning Hazleton Inc.
3301 Kinsman Boulevard
Madison, Wisconsin 53704

Laboratory Project Identification:

HWI 50800374

HWI 50800374

COMPLIANCE STATEMENT

Acute Dermal Toxicity Study of T-6342 in Rabbits
(OECD Guidelines)

This study was conducted in accordance with the Organization for Economic Cooperation and Development's Principles of Good Laboratory Practice, C(81)30(Final).

Steven M. Glaza
Study Director
Acute Studies
Corning Hazleton Inc.

10-24-95
Date

QUALITY ASSURANCE STATEMENT

This report has been reviewed by the Quality Assurance Unit of Hazleton Wisconsin, Inc., in accordance with the Organisation for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice, C(81)30(Final). The following inspections were conducted and findings reported to the Study Director and management. Written status reports of inspections and findings are issued to Hazleton management monthly according to standard operating procedures.

Inspection Dates			Date Reported to	Date to
From	To	Phase	Study Director	Management
08/31/95	08/31/95	Dose Administration	08/31/95	09/10/95
10/13/95	10/16/95	Data/Report Review	10/16/95	11/10/95

Representative, Quality Assurance Unit

10.24.95
Date

STUDY IDENTIFICATION

Acute Dermal Toxicity Study of T-6342 in Rabbits
(OECD Guidelines)

Test Material	T-6342
Sponsor	3M Toxicology Service Medical Department 3M Center, Bldg. 220-2E-02 P.O. Box 33220 St. Paul, MN 55133-3220
Sponsor's Representative	Roger G. Perkins, PhD 3M Toxicology Service Medical Department 3M Center, Bldg. 220-2E-02 P.O. Box 33220 St. Paul, MN 55133-3220 (612) 733-3222
Study Director	Steven M. Glaza Corning Hazleton Inc. P.O. Box 7545 Madison, WI 53707-7545 (608) 241-7292
Study Location	Corning Hazleton Inc. 3301 Kinsman Boulevard Madison, WI 53704
Study Timetable	
Study Initiation Date	August 25, 1995
Experimental (In-life) Start Date	August 31, 1995
In-life End Date	September 14, 1995
Experimental Termination Date	October 24, 1995
Study Completion Date	October 24, 1995

KEY PERSONNEL

Acute Studies

Steven M. Glaza
Study Director
Manager

Steven R. Sorenson
Study Coordinator

Patricia Padgham
In-life Supervisor

Rose M. Bridge
Report Supervisor

Toxicology Support

Kathy Myers
Manager

Calvin L. Horton
Supervisor

Quality Assurance

Sherry R. W. Petsel
Manager

Laboratory Animal Medicine

Cindy J. Cary, DVM
Diplomate, ACLAM
Supervisor

Anatomical Pathology

Thomas E. Palmer, PhD
Anatomical Pathologist

Deborah L. Pirkel/
Jack Serfort
Supervisors
Necropsy

Anne Mosher
Supervisor
Pathology Data

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SUMMARY

The test material, T-6342, was evaluated for its acute dermal toxicity potential in male and female rabbits when administered as a single topical application at a level of 2,000 mg/kg of body weight. The estimated dermal LD_{50} for male and female rabbits was determined to be greater than 2,000 mg/kg. All animals appeared normal throughout the study. All animals exhibited body weight gain during the study with the exception of one male which exhibited a weight loss of 29 g during the first week. The test material produced slight to moderate dermal irritation. The gross necropsy at termination revealed no visible lesions.

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 were in compliance with the Animal Welfare Act Regulations. 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-6342 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 Corning Hazleton (CHW) Standard Operating Procedure (SOP).

Safety Precautions

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

TEST SYSTEM

Test Animal

Adult albino rabbits of the Hra:(NZW)SPF strain were procured from HRP, Inc., Kalamazoo, Michigan on August 9, 1995.

Housing

After receipt, the animals were acclimated for a period of at least 7 days. During acclimation and throughout the study, the animals were individually housed in screen-bottom stainless steel cages. Environmental controls for the animal room were set to maintain a temperature of 19° to 23°C, a relative humidity of 50% ±20%, and a 12-hour light/12-hour dark lighting cycle. In cases where variations from these conditions existed, they were documented and considered to have had no adverse effect on the study outcome.

Animal Diet

The animals were provided access to water *ad libitum* and a measured amount of Laboratory Rabbit Diet HF #5326, PMI Feeds, Inc. The feed is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Samples of the water are periodically analyzed by CHW. There were no known contaminants in the feed or water at levels that would have interfered with or affected the results of the study.

Animal Selection and Preparation of Exposure Area

Five male and five female healthy, acclimated rabbits, weighing from 2,386 to 2,675 g, were used for a single dose level of 2,000 mg/kg of body weight. The animals were identified by animal number and corresponding ear tag throughout the study. On the day 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 on each animal's body weight on the day of test administration.

Treatment

The test material was applied to the intact skin on each animal's back at a dose level of 2,000 mg/kg of body weight. The test material was applied to the test site at a rate of approximately 0.03 g/cm^2 in a thin and uniform layer. The area of application (approximately 200 cm^2)was covered with a 9.5-cm x 21.0-cm, 4-ply gauze patch secured with paper tape and overwrapped with Saran Wrap® and Elastoplast® tape to provide an occlusive dressing. Collars were used to restrain the test animals during the 24-hour exposure period.

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.

Reason for Route of Administration

Historically, the dermal route has been the route of choice based on the method of Draize.[2]

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 application (Day 0), at Day 7, and at termination of the in-life 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 in-life phase, all animals were euthanized, subjected to an abbreviated 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 an original signed copy of the final report will be retained in the archives of CHW in accordance with CHW SOP.

RESULTS

Mortality

A summary of the survival rate is in Table 1. No mortality was observed during the study. The estimated dermal LD_{50} for male and female rabbits was determined to be greater than 2,000 mg/kg of body weight.

Body Weights

Individual and mean body weights and body weight gains are in Table 2. All animals exhibited body weight gain throughout the study with the exception of one male which exhibited a weight loss of 29 g during the first week.

Clinical Signs

Individual clinical signs are in Table 3. All animals appeared normal throughout the study.

Dermal Reactions

Individual dermal irritation observations are in Table 4. Dermal irritation (based on the most severe score for each animal at any time point) consisted of slight to moderate erythema, edema, and atonia, and slight desquamation, coriaceousness, and fissuring. No other dermal irritation was observed.

Pathology

Individual gross necropsy pathology findings are in Table 5. A summary report by the study pathologist is on Page 12. There were no visible lesions observed at necropsy.

DISCUSSION

The acute dermal toxicity of T-6342 was evaluated in male and female rabbits when administered as a single topical application at a level of 2,000 mg/kg of body weight. The estimated dermal LD_{50} for male and female rabbits was determined to be greater than 2,000 mg/kg. All animals appeared normal throughout the study. All animals exhibited body weight gain during the study with the exception of one male which exhibited a weight loss of 29 g during the first week. The test material produced slight to moderate dermal irritation. The gross necropsy at termination revealed no visible lesions.

SIGNATURE

Steven M. Glaza
Study Director
Acute Studies

10-24-95
Date

REFERENCES

1. "Acute Dermal Toxicity," *Organisation for Economic Cooperation and Development's Guidelines for Testing of Chemicals*, Section 402 (adopted May 12, 1981).

2. 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 (1959).

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 follow this report. There were no visible lesions in any of the animals.

Thomas E. Palmer, PhD
Pathologist

10-24-95
Date

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Table 1

Mortality Summary

Dose Level (mg/kg)	Sex	Mortality Result No. Died/ No. Dosed
2,000	M	0/5
2,000	F	0/5

Table 2

Individual and Mean Body Weights/Body Weight Gains (g)

Animal Number	Day 0 Weight	Day 7		Day 14	
		Weight	Gain*	Weight	Gain*
		Males (2,000 mg/kg)			
F56261	2,553	2,524	-29	2,642	89
F56271	2,481	2,562	81	2,582	101
F56265	2,391	2,393	2	2,480	89
F56266	2,526	2,577	51	2,707	181
F56267	2,529	2,613	84	2,714	185
Mean	2,496	2,534	38	2,625	129
		Females (2,000 mg/kg)			
F56268	2,534	2,685	151	2,770	236
F56269	2,448	2,484	36	2,555	107
F56264	2,386	2,512	126	2,536	150
F56270	2,675	2,679	4	2,684	9
F56274	2,487	2,521	34	2,582	95
Mean	2,506	2,576	70	2,625	119

* Gain from the Day 0 body weight.

Table 3

Individual Clinical Signs

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
					Males (2,000 mg/kg)													
F56261	Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
F56271	Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
F56265	Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
F56266	Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
F56267	Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
					Females (2,000 mg/kg)													
F56268	Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
F56269	Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
F56264	Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
F56270	Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
F56274	Appeared normal	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

✓ Condition existed.

Table 4

Individual Dermal Irritation Observations

Animal Number	Observation	Observation Period (Day) 1	3	7*	10	14*
		Males				
F56261	Erythema	1	1	1	1	1
	Edema	1	0	0	0	0
	Atonia	1	0	0	0	0
	Desquamation	0	0	0	1	0
	Coriaceousness	0	0	0	0	0
	Fissuring	0	0	1	0	0
F56271	Erythema	1	0	0	0	0
	Edema	1	0	0	0	0
	Atonia	0	0	0	0	0
	Desquamation	0	0	0	0	0
	Coriaceousness	0	0	0	0	0
	Fissuring	0	0	0	0	0
F56265	Erythema	1	1	0	0	0
	Edema	1	0	0	0	0
	Atonia	1	0	0	0	0
	Desquamation	0	0	0	0	0
	Coriaceousness	0	0	0	0	0
	Fissuring	0	0	0	0	0
F56266	Erythema	1	1	2	1	1
	Edema	1	0	0	0	0
	Atonia	1	0	0	0	0
	Desquamation	0	0	0	1	0
	Coriaceousness	0	0	0	0	0
	Fissuring	0	0	0	0	0
F56267	Erythema	1	0	0	0	0
	Edema	0	0	0	0	0
	Atonia	1	0	0	0	0
	Desquamation	0	0	0	0	0
	Coriaceousness	0	0	0	0	0
	Fissuring	0	0	0	0	0

* Animals shaved before dermal observation.

Table 4 (Continued)

Individual Dermal Irritation Observations

Animal Number	Observation	Observation Period (Day) 1	3	7*	10	14*
		Females				
F56268	Erythema	1	1	2	2	1
	Edema	1	1	1	1	0
	Atonia	1	0	0	0	0
	Desquamation	0	0	0	1	1
	Coriaceousness	0	0	1	0	0
	Fissuring	0	0	1	1	0
F56269	Erythema	1	2	2	2	2
	Edema	1	2	2	2	1
	Atonia	2	1	0	0	0
	Desquamation	0	0	0	1	1
	Coriaceousness	0	0	1	0	0
	Fissuring	0	0	0	1	0
F56264	Erythema	1	1	1	0	0
	Edema	1	0	0	0	0
	Atonia	0	0	0	0	0
	Desquamation	0	0	0	0	0
	Coriaceousness	0	0	0	0	0
	Fissuring	0	0	0	0	0
F56270	Erythema	1	2	2	2	1
	Edema	1	2	2	1	1
	Atonia	0	0	0	0	0
	Desquamation	0	0	0	1	1
	Coriaceousness	0	0	1	0	0
	Fissuring	0	0	0	1	0
F56274	Erythema	1	1	2	1	0
	Edema	0	1	1	1	0
	Atonia	0	0	0	0	0
	Desquamation	0	0	0	1	0
	Coriaceousness	0	0	1	0	0
	Fissuring	0	0	0	0	0

* Animals shaved before dermal observation.

Table 5

Individual Pathology Comments

Dose Level: 2,000 mg/kg of Body Weight

Animal Number	Sex	Test Day		Necropsy Observation
		Died	Sacrificed	
F56261	M	-	14	No visible lesions.
F56271	M	-	14	No visible lesions.
F56265	M	-	14	No visible lesions.
F56266	M	-	14	No visible lesions.
F56267	M	-	14	No visible lesions.
F56268	F	-	14	No visible lesions.
F56269	F	-	14	No visible lesions.
F56264	F	-	14	No visible lesions.
F56270	F	-	14	No visible lesions.
F56274	F	-	14	No visible lesions.

- Not applicable.

APPENDIX A

Protocol
Protocol Amendment No. 1
Protocol Amendment No. 2

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. 50800374

Enclose with samples and send to:
Hazleton Wisconsin
3301 Kinsman Boulevard
Madison, Wisconsin 53704

Submitted by: ROGER G. PERKINS
Date Sample Sent: 6/7/95
Company: 3M
Invoice to: _____
P.O. Number: _____
Number of Reports Required: 3

Full GLP Compliance: X Yes ___ No
___ FDA (21 CFR 58)
___ EPA (TSCA—40 CFR 792)
___ EPA (FIFRA)—40 CFR 160)
X OECD

Sample Name: T-6342
Physical Description: liquid 07-1405-5 light colored
Special Handling Precautions: SEE MSDS

Storage Requirements: X Room Temperature
___ Refrigerated
___ Other _____

Disposal: X 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
X 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
X TP2070 OECD screen; 5M-5F at 2.0 g/kg
___ Conduct defined study if death occurs at 2.0 g/kg
Special instructions: _____

Primary Skin Irritation

___TP3208 FHSA; 6 rabbits-1 abraded, 1 intact site/rabbit
___TP3014 EPA; 6 rabbits-1 intact site/rabbit
X 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
X 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 Magnussun-Kligman maximization
___TP2008 Buehler sensitization
___TP6289 Photoallergenic contact dermatitis (Armstrong)
Special instructions: _____

For Hazleton Use Only

Protocol Issue Date: 8-25-95
Study Director: Steven M. Hays

White copy—Hazleton Yellow copy—Submitter

HAZLETON
WISCONSIN
POST OFFICE BOX 7545
MADISON WISCONSIN 53707-7545

a CORNING Laboratory Services Company

Sponsor:

3M
St. Paul, Minnesota

PROTOCOL TP2070

Study Title:

Acute Dermal Toxicity Study in Rabbits
(OECD Guidelines)

Date:

June 1, 1993

Performing Laboratory:

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

Laboratory Project Identification:

HWI 50800374

STUDY IDENTIFICATION

Acute Dermal Toxicity Study in Rabbits
(OECD Guidelines)

HWI No.	50800374
Test Material	(See sample submittal form)
Sponsor	3M Toxicology Services 220-2E-02 3M Center St. Paul, MN 55144
Sponsor's Representative	John L. Butenhoff, PhD 3M Toxicology Services 220-2E-02 3M Center St. Paul, MN 55144 (612) 733-1962
Study Director	Steven M. Glaza Hazleton Wisconsin, Inc. P.O. Box 7545 Madison, WI 53707-7545 (608) 241-7292
Study Location	Hazleton Wisconsin, Inc. Building No. 3 3802 Packers Avenue Madison, WI 53704
Proposed Study Timetable	
Experimental Start Date	Week of 8-28-95
Experimental Termination Date	Week of 9-11-95
Final Report Date	Week of 10-23-95

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 of rabbits

3. Regulatory Compliance
This study will be conducted in accordance with the following Good Laboratory Practice Regulations/Standards/Guidelines:

[ ] Conduct as a Nonregulated Study
[ ] 21 CFR 58 (FDA)
[ ] 40 CFR 160 (EPA-FIFRA)
[ ] 40 CFR 792 (EPA-TSCA)
[X] 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 5, 1988 (Japanese MOHW)

All procedures in this protocol are in compliance with the Animal Welfare Act Regulations. In the opinion of the Sponsor and study director, the study does not unnecessarily duplicate any previous work.

4. Quality Assurance
For regulated studies, 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) and policies.

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). Samples of test material/vehicle mixture(s) (if applicable) for concentration, solubility, homogeneity, and stability analyses will be taken before administration if requested by the Sponsor. These samples (if taken) will be sent to the Sponsor after experimental termination for possible analysis.

D. Storage
(See sample submittal form)

E. Reserve Samples
Studies of less than 4 weeks in experimental duration will not have reserve samples retained.

Reserve sample(s) of each batch/lot of test material will be taken if this study is more than 4 weeks in experimental duration.

The test material reserve sample will be stored at HWI in a freezer set to maintain a temperature of below 0°C for 10 years per HWI SOP. The Sponsor will be contacted after 10 years for disposition in accordance with the appropriate regulatory Good Laboratory Practices.

F. Retention
Any unused test material will be discarded after issuance of the final report, unless directed otherwise by the Sponsor.

G. Safety Precautions
As required by HWI SOPs and policies

6. Experimental Design

A. Animals

(1) Species
Rabbit

(2) Strain/Source
Hra:(NZW)SPF/Hazleton Research Products, Inc.

(3) Age at Initiation
Adult

(4) Weight at Initiation
2.0 to 3.0 kg

(5) Number and Sex
5 males and 5 females for the initial dose level
5 males and/or 5 females for any additional dose levels (if required)

(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
Ad libitum from an automatic system. Samples of the water are analyzed by HWI for total dissolved solids, hardness, 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 19 to 23°C, a relative humidity of 50% ±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 HWI SOPs. An adequate number of extra animals will be purchased so that no animal in obviously poor health is placed on test.

(9) 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.

B. Dose Administration

(1) Dose Level
A single dose of 2,000 mg/kg of body weight 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 2,000 mg/kg

level, additional dose levels may be added at the direction of the study director in order to meet the objectives of the study.

(2) Preparation of Exposure Area
On the day before test material application, the back of each rabbit will be clipped free of hair with an electric clipper. Not less than 10% of the total body surface area will be clipped. The animals will be clipped as needed throughout the study.

(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 a liquid, the test material will be applied undiluted. If a solid, the test material will be moistened with 0.9% saline. Aerosol materials will be discharged into a beaker and administered as a liquid. The area of application will be wrapped with a 10.0-cm x 10.0-cm gauze bandage secured with paper tape around all edges, overwrapped with Saran Wrap®, and secured with Elastoplast® tape to provide an occlusive dressing. The rabbits will be collared during the 24-hour application period.

(4) Reason for Route of Administration
Historically, the dermal route has been the route of choice based on the method of Draize.

(5) Removal of Test Material
Approximately 24 hours after test material application, the bandages and collars will be removed, and the residual test material will be removed using water or an appropriate solvent, if necessary.

C. Observation of Animals

(1) Clinical Observations
At approximately 1, 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 directed by the study director.

(2) Reading of Dermal Irritation
Approximately 30 minutes after bandage removal, the initial dermal irritation reading will be made and

recorded as the Day 1 reading (Attachment 1). 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.

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

D. Pathology
At termination of the experimental phase, surviving animals will be euthanized. All animals, whether dying during the study or euthanized, will be subjected to an abbreviated gross necropsy examination and all abnormalities will be recorded. After necropsy, the animals will be discarded and no tissues will be saved.

E. Statistical Analyses
Other than LD_{50} 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
Procedures
Dates of experimental initiation and termination
Tabulation of mortality data by sex and dose level
Description of any toxic effects/dermal irritation
Tabulation of mean body weights by sex and dose level
LD_{50} values by sex with 95% confidence intervals (when applicable)
Gross pathology findings/gross pathology report (when applicable)

8. Location of Raw Data, Records, and Final Report
Original data, or copies thereof, will be available at HWI 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, including those items listed below will be retained in the archives of HWI according to HWI SOP.

Protocol and protocol amendments
Dose preparation records
In-life records
  Body weights
  Dose administration
  Observations
Anatomical pathology records
Study correspondence
Final report (original signed copy)

The following supporting records will be retained at HWI but will not be archived with the study data.

Animal receipt/acclimation records
Water analysis records
Animal room temperature and humidity records
Refrigerator and freezer temperature records
Instrument calibration and maintenance records

PROTOCOL APPROVAL

John L. Butenhoff

July 27, 1993

John L. Butenhoff, PhD
Sponsor's Representative
3M

Date

Steven M. Glaza

6-1-93

Steven M. Glaza
Study Director
Acute Toxicology
Hazleton Wisconsin, Inc.

Date

Rebecca S. Nelson

6/1/93

Representative
Quality Assurance Unit
Hazleton Wisconsin, Inc.

Date

(TP2070.3M)

Attachment 1

Scoring Scale for Acute Dermal Reactions

Erythema

0 - None
1 - Slight
2 - Moderate
3 - Severe

Edema

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

Atonia

0 - None
1 - Slight (slight impairment of elasticity)
2 - Moderate (slow return to normal)
3 - Marked (no elasticity)

Desquamation

0 - None
1 - Slight (slight scaling)
2 - Moderate (scales and flakes)
3 - Marked (pronounced flaking with denuded areas)

Coriaceousness

0 - None
1 - Slight (decrease in pliability)
2 - Moderate (leathery texture)
3 - Marked (tough and brittle)

Fissuring

0 - None
1 - Slight (definite cracks in epidermis)
2 - Moderate (cracks in dermis)
3 - Marked (cracks with bleeding)

HWI No. 50800374

PROTOCOL AMENDMENTS

Amendment No. 1

Effective August 25, 1995

Portion of Protocol Being Modified: Page 2, Study Location

Reason for Modification: To identify the location where the study will be conducted, replace this section with the following change:

Modification: Study Location — Hazleton Wisconsin, Inc.
3301 Kinsman Boulevard.
Madison, WI 53704

Study Director Approval: Steven M Ellis 8-25-95

(G21/01-07-91)

HWI No. 50800374

PROTOCOL AMENDMENTS

Amendment No. 2

Effective August 28, 1995

Portion of Protocol Being Modified: Page 6, 6. Experimental Design; B. Dose Administration; (3) Dose Administration.

Reason for Modification: To correctly identify the size of the gauze bandage used to wrap the area of application.

Modification: Replace the seventh sentence of this section with the following change: The area of application will be wrapped with a 4-ply gauze bandage (approximately 9.5-cm x 21-cm) secured with paper tape around all edges, overwrapped with Saran Wrap®, and secured with Elastoplast® tape to provide an occlusive dressing.

Study Director Approval: Steven M. Klaja 10-9-95

(G21/01-07-91)