Report Title: 12 Day Subchronic Percutaneous Toxicity in Rats

Test Type: Subchronic Dermal Toxicity

Conducting Laboratory and Location:

Test Substance(s): #G2877.01 – Solid deodorant with 7.5% Octopirox

Species: Rabbit

# of Animals: 3 male and 3 female

Test Conditions: Test material was applied dermally and undiluted at 2 ml/kg to rabbits 5 times/week for 10 applications.

Results: No deaths or signs of toxicity during the two weeks other than skin irritation due to the exaggerated exposure condition. Necropsy and hematology revealed no notable findings.

Study #: IRDC-191-143
Report Date: 06/20/89

Accession #: 35393

BIOLOGICAL SAFETY TEST SUMMARY REVIEW

Test Substance: BC-86 with 7.5% Octopirox

Test Substance Identification Number: G2877.01

Contract Laboratory: IR&DC Report #: 191-1439

Type of Study: 12-Day Subchronic Percutaneous Toxicity DRD #: BY0830

Toxicologist: B. S. Allgood Division: BYC

Date Report Written: 6-20-89 Date Rec'd by Operations Section: 6-23-89

[ ] This report was not selected for review by the Operations Section.

Operations Section Monitor: _____ Date: _____

This report has been reviewed and found in agreement with the Protocol and to comply with all applicable Federal Regulations:

Operations Section Monitor: G A Nixon Date: 6/24/89
G. A. Nixon

This report has been reviewed for specific scientific content:

HSD Scientific Reviewer: GR Johnson Date: 7/18/89
G. R. Johnson

This report has been reviewed for scientific quality and is summarized, with comments (if any), as follows: Where applicable, the retention limits for specimens to be returned to the P&G Archive are given.

G2877.01 was applied dermally and undiluted at 2 ml/kg to New Zealand white rabbits (3 ♂; 3 ♀) 5x/week for 10 applications. There were no deaths or signs of toxicity during the 2 wk. test other than marked dermal irritation due to the exaggerated exposure condition. Hematological measurements revealed no notable findings. Necropsy revealed no gross lesions.

Retention Limits (month & year)	
Slides:	N/A
Blocks:	N/A
Wet Tissues:	6/94
Teratology:	N/A

Divisional Toxicologist: B S Allgood Date: 7/20/89
G. S. Allgood

CIRCULATE BACK TO THE HSD SCIENTIFIC REVIEWER; THEN TO HSD LIAISON

This report is approved for entry into the Safety Data System and microfilming.

HSD Scientific Reviewer: GR Johnson Date: 7/21/89
G. R. Johnson

Corporate HSD Liaison: GR Johnson Date: 7/24/89
G. R. Johnson

Return to Marilyn Brown, Room 2N211, MVL

Entered into Safety Data System by MR Brown Date: 8-7-89

Microfilming Completed by _____ Date: _____

International Research
and Development Corporation
MATTAWAN, MICHIGAN, U.S.A. 49071 TELEPHONE (616) 668-3236

SPONSOR: The Procter & Gamble Company

TEST ARTICLE (ISIN): G2877.01

SUBJECT: 12-Day Subchronic Percutaneous Toxicity

DRD NO.: BY0830

DATE OF SUBMISSION: June 20, 1989

RECEIVED BY
JUN 23 1989
OPERATIONS SECTION

191-1439

"credence through research"

TABLE OF CONTENTS

		Page
I.	Summary	1
	A. Experimental Design/Methods	1
	B. Results and Conclusions	3
II.	Quality Assurance Statement	4
III.	Introduction	6
	A. Objective	6
	B. Species Selection	6
	C. Justification for Route of Administration	6
	D. Data Retention	6
IV.	Test Article	7
	A. Receipt and Description	7
	B. Storage Condition	7
	C. Dispensation	8
V.	In-Life Phase	9
	A. Methods	9
	1. Animal Acquisition and Maintenance	9
	2. Animal Selection Procedure	9
	3. Test Article Administration	10
	4. General Observations	11
	a. Mortality	11
	b. General Appearance, Behavior and Pharmacotoxic Signs	11
	c. Dermal Irritation	11
	d. Body Weights	12
	B. Results	12
	1. Mortality	12
	2. General Appearance, Behavior, Pharmacotoxic Signs	12
	3. Dermal Irritation	12
	4. Body Weights	13
VI.	Clinical Pathology	14
	A. Methods	14

TABLE OF CONTENTS
(Continued)

	Page
B. Results	14
C. References	16
VII. Anatomic Pathology	17
A. Methods	17
1. Macroscopic	17
2. Microscopic	17
B. Results	17
1. Macroscopic	17
2. Microscopic	18
VIII. Signatures	19
Table No.	
1. Summary of Dermal Observations	20- 21
2. Summary of Body Weight Values	22- 23
3. Summary of Hematological Values	24- 27
4. Incidence of Macroscopic Observations	28
5. Incidence of Microscopic Observations	29
APPENDIX A	
Record of Animal Fate and Disposition	30- 31
APPENDIX B	
Individual Dermal Scores	32- 46
APPENDIX C	
Individual Body Weights	47- 48
APPENDIX D	
Individual Hematological Values	49- 56
APPENDIX E	
Individual Animal Data Record: Pathology	57- 62
APPENDIX F	
Microscopic Tissue Inventory	63- 64
APPENDIX G	
Protocol and Protocol Addenda	65- 75

I. SUMMARY: 12-Day Subchronic Percutaneous Toxicity
IRDC Study 191-1439
Study Initiated January 3, 1989
Dosing Initiated January 4, 1989
Terminal Necropsy January 18, 1989

G2877.01 was applied dermally undiluted as received to New Zealand White rabbits five days per week for a total of 10 applications at a dose volume of 2 ml/kg. Control rabbits received deionized water by the same route. Summaries of the methods, results and conclusions are presented below.

A. EXPERIMENTAL DESIGN/METHODS

TEST ARTICLE

Identification: (TSIN#) G2877.01
(DRDN#) BYOR30

CONTROL ARTICLE

Identification: Deionized water

TEST SYSTEM/IN-LIFE EXAMINATIONS

Animals: New Zealand White rabbits; Mohican Valley Rabbitry, Inc., Loudonville, Ohio; approximately 3 months of age at study initiation.

Dosage Groups:

Dosage Level	Number of Rabbits Male	Number of Rabbits Female
Water Control	3	3
100% G2877.01	3	3

Randomization Procedure: Computerized random selection in a block design based on body weights.

Housing/Environmental Conditions:

Individually housed in stainless steel cages in a temperature, humidity and light (12 hour light/dark cycle) controlled room. Food and water available *ad libitum*.

Diet:	Certified Rabbit Chow® #5322, Purina Mills, Inc.
Observations:	Mortality twice daily; detailed observations once daily; dermal irritation scoring daily prior to each application.
Measurements:	Body weights pretest, week 1 and at terminal necropsy.

CLINICAL PATHOLOGY

Study Determinations:	Performed on all rabbits pretest and on day 14.
Hematology:	Hemoglobin, hematocrit, leukocyte count, erythrocyte count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count and differential white blood cell count.

ANATOMIC PATHOLOGY

Terminal Necropsy:	All surviving rabbits January 18, 1989.
Macroscopic Pathology:	On all rabbits. Tissues fixed in formalin.
Tissues Preserved:	All gross lesions.
Microscopic Pathology:	Hematoxylin and eosin stained paraffin blocks of all tissues from each group and sectioned at approximately 5 microns.
Tissues Examined:	All preserved tissues.

B. RESULTS AND CONCLUSIONS

The application of 100% G2877.01 (2 ml/kg) produced marked dermal irritation over the 2-week study period. While there were no overt signs of toxicity, animals of both sexes had reduced body weight gains.

There were no signs of systemic toxicity at necropsy, nor were there any notable findings in the 2-week hematology data. Gross lesions were limited to findings at the application site. Microscopically, these lesions included severe ulceration, exudate on the epidermal surface, acanthosis, hyperkeratosis, chronic dermatitis, edema and abscess formation.

To the best of my knowledge, there were no significant deviations from the Good Laboratory Practice Regulations which affected the quality or integrity of the study. This study was conducted in conformance with Good Laboratory Practice Regulations. This report accurately reflects the raw data obtained during the performance of the study.

Dale E. Johnson, Pharm.D., Ph.D., D.A.B.T. — Date 6/20/89
Scientific Director, Experimental
Toxicology Division
Study Director

191-1439

II. QUALITY ASSURANCE STATEMENT

Study Title: 12-Day Subchronic Percutaneous Toxicity
Test Article: G2877.01

The conduct of this study has been subjected to periodic inspections. The dates of inspection and the dates that findings were reported to management and the Study Director are listed on the following page.

This report has been reviewed by the International Research and Development Corporation Quality Assurance Department in accordance with the United States Food and Drug Administration Good Laboratory Practice Regulations of June 20, 1979 and as modified by the final rule effective October 5, 1987.

Approved By: Margery J. Witt, B.S.
Director of Quality Assurance
Date 6/26/89

191-1439

Quality Assurance Inspections

Dates of Inspections	Dates of Reports to Management	Dates of Reports to Study Director
1-04-89	4-14-89	4-14-89
1-10-89		
1-12-89		
1-17-89		
1-18-89		
1-31-89		
2-01-89		
2-03-89		
4-14-89		
5-04-89		
5-10-89		
5-11-89		

III. INTRODUCTION

The study described in this report was conducted in accordance with the standard operating procedures of the International Research and Development Corporation (IRDC) and the protocol as specified by the Sponsor. Procedures pertinent to this study are described in this report.

A. OBJECTIVE

To assess the cutaneous and systemic toxicity of a substance when it is repeatedly applied to intact skin over a period of 12 days.

B. SPECIES SELECTION

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

C. JUSTIFICATION FOR ROUTE OF ADMINISTRATION

The dermal route is, historically, an acceptable means of evaluating skin irritation and/or dermal absorption of the test article and is a possible route of human exposure.

D. DATA RETENTION

Unless otherwise specified in this report, all raw data, specimens and reports generated during the conduct of this study are retained in the Archives of the International Research and Development Corporation in Mattawan, Michigan.

IV. TEST ARTICLE

A. RECEIPT AND DESCRIPTION

The test article was received from the Procter & Gamble Company, Cincinnati, Ohio on December 29, 1988 as follows:

Label	Description
TEST SUBST. (TSIN) G2877.01 DIV. REQUEST DOC. (DRD) BY0830 DATE REC'D. (OPER SECTION) 10/12/88 TYPE OF TEST SUBACUTE PERC TOX GROSS WT. (INC. LID, CONT., LABEL) 1055.09 *TARE WT. 355.19 NET WT. 699.9 STORAGE CONDITIONS AMBIENT EXPIRATION DATE 8-19-89 HAZARD FLAMMABLE D.O.T. HAZARD NON-HAZARDOUS RETURN TO DIVISIONAL TOXICOLOGIST WHEN TEST IS COMPLETED *CONTAINER, LID, LABEL CAUTION: THE TOXICITY OF THIS MATERIAL HAS NOT BEEN COMPLETELY EVALUATED.	green solid (4 bottles)

PC #1 labeled as above. PC #2 had the following difference: GROSS WT 1073.15 g; TARE WT. 356.15; NET WT. 717.00; the letters HC0476594 left lower corner of label. PC #3 had the following differences: GROSS WT. 1046.09; TARE WT. 354.50; NET WT. 691.59; the letters HC0476-594 bottom of label. PC #4 had the following differences: GROSS WT. 663.48 g; TARE WT. 353.28 g; NET WT. 310.20; the letters HC0476-594 top of label.

B. STORAGE CONDITION

The batch of test article described was utilized throughout the study period and stored at room temperature.

C. DISPENSATION

An appropriate amount of the test article was dispensed undiluted as received, by the department performing the dosing procedure. The test material was warmed to approximately 40-55°C prior to being dispensed into syringes for individual dosage administration. Deionized water was dispensed for the control group.

Mark W. Griggs, B.S.
Manager, Test Material Control

6/20/89
Date

191-1439

V. IN-LIFE PHASE

A. METHODS

1. Animal Acquisition and Maintenance

Forty (40) male and 40 female New Zealand White rabbits were received from Mohican Valley Rabbitry, Inc., Loudonville, Ohio on December 20, 1988 and were approximately two months of age at receipt. From this initial group of animals, 9 male and 9 female rabbits were arbitrarily selected for possible use on this study. The rabbits were observed for evidence of disease and other physical abnormalities during a 15 day conditioning period. Each rabbit was identified by a Monel® metal ear tag bearing the individual animal number. Ear tags were verified at initiation, before and after blood collection, while transferring the animals to clean cages and prior to necropsy.

The rabbits were individually housed in stainless steel cages in a temperature (72 ± 0.9°F; mean ± S.D.), humidity (50 ± 16.3%; mean ± S.D.) and light (12 hour light/dark cycle) controlled room. Certified Rabbit Chow® #5322 (Purina Mills, Inc., St. Louis, Missouri) and water were available ad libitum.

Analysis of each lot of diet was performed by the manufacturer. The water supply of IRDC is analyzed quarterly for the presence of pesticides, heavy metals and coliforms. The results of these analyses are stored in the Archives of IRDC.

2. Animal Selection Procedure

Prior to randomization into study groups, the rabbits were bled for control hematological evaluation, weighed, sexed, clipped free of hair at the test site area and examined for evidence of disease and other physical abnormalities, including abnormalities in

the shaven test area. Based on those criteria, all 18 rabbits (males weighing from 2388-2731g and females weighing from 2580-2922g) were found to be acceptable for study use. The rabbits were randomized and placed into treatment groups as follows:

For each sex, the permanent animal identification numbers and corresponding body weights of the animals designated for use in the study were entered onto a magnetic disk, which was used as the data source for the following randomization procedure. A computerized sort developed a listing in order of ascending body weight and blocked into n blocks of x animals, where n = the number of animals per group and x = the number of groups. Animals in each block were then distributed among groups by means of a computer-generated list of x random numbers.

Test Article, Dosage Level	Number of Rabbits Male	Number of Rabbits Female
Water Control (Deionized Water)	3	3
G2877.01 100%	3	3

Randomization procedure excluded three males and three females due to group size.

3. Test Article Administration

Prior to study initiation, the hair was removed from the back of each rabbit (an area from shoulder to rump, approximately 15 cm wide) with an electric clipper. The hair was clipped as necessary during the study period to prevent the fur from becoming matted with the test article and to facilitate accurate observations. The skin of the rabbits remained intact.

Dosing was initiated on January 4, 1989 and the terminal necropsy was performed on January 18, 1989. The rabbits were dosed once daily, five days per study week for a total of 10 applications. Individual doses were adjusted once weekly based on the most current body weights.

The control article and test article were administered at a constant dosage volume of 2.0 ml/kg using a clean, 12 cc, plastic syringe, and a glass rod was used to evenly distribute the dose over the test site. Each dose covered approximately 100% of the test surface. Following administration, plastic restraint collars (E-Jay Saf-T Shields) were applied. The exposure time for each application was approximately 7 hours. Beginning study day 2, the test sites were washed with tepid tap water and dried with clean, disposable paper towels after collar removal; test sites were not washed or wiped on day 1. Collars were removed following the 7 hour period.

4. General Observations

a. Mortality

The rabbits were observed twice daily for mortality.

b. General Appearance, Behavior and Pharmacotoxic Signs

The rabbits were observed once daily for pharmacotoxic signs and other findings.

c. Dermal Irritation

The rabbits were observed prior to dosing for dermal irritation in accordance with the Sponsor designated scoring scale in the protocol.

If no dermal irritation was observed for an individual animal, a checkmark was recorded in the data to indicate that no dermal irritation was present. In this event, the individual scores in Appendix B are reported as "NE", i.e., dermal irritation not evident.

Where dermal irritation was present in any category for an individual animal, the irritation score was recorded as presented in the protocol. In this case, the numerical score recorded for each dermal parameter is presented in Appendix B.

d. Body Weights

Body weights were obtained and recorded one day prior to study initiation, weekly during the study period and prior to necropsy.

B. RESULTS

1. Mortality

A record of animal fate and disposition is presented in Appendix A.

All rabbits survived to study termination.

2. General Appearance, Behavior and Pharmacotoxic Signs

There were no visible abnormalities observed in any rabbit during the study period; therefore, no tabular data are presented.

3. Dermal Irritation

Dermal irritation is summarized in Table 1; individual dermal scores are presented in Appendix B.

There were no signs of dermal irritation observed at the application site of rabbits from the Water Control group.

Dermal irritation noted at the application site of the test article treated group included erythema, edema, atonia, desquamation, fissuring and eschar. Erythema and edema were observed in all rabbits from day 2, initially graded as slight and quickly increasing in severity to moderate on day 3 (erythema) or day 7 (edema) in most rabbits. Moderate erythema and edema persisted through termination. Eschar formation was observed in one animal (female #39381) on day 14.

Atonia was initially observed on day 6 in all rabbits and graded as moderate to marked through termination.

Fissuring, generally slight to moderate, was noted in all rabbits on days 13 and 14, and in some during days 6-10.

Female #39381 exhibited slight to moderate desquamation on days 6-14 and male #39347 exhibited red raised areas on days 9 and 10.

4. Body Weights

Body weights are summarized in Table 2; individual body weights are presented in Appendix C.

There were no remarkable changes observed in the control group body weights during the study period.

Several rabbits from the test article treated group lost approximately 40 grams body weight at week 1. By study termination, body weights in most of the rabbits from this group were greater than the week 1 values, four rabbits exhibited a weight gain at termination that exceeded the pretest value.

VI. CLINICAL PATHOLOGY

A. METHODS

Clinical laboratory studies were conducted on all animals prior to study initiation and at the termination of the study (Day 14). Blood samples were obtained from the central ear artery. Animals were allowed free access to food and water prior to blood sample collection. The hematological parameters listed below were determined using the instrument listed in accordance with the reference cited.

Summary of Clinical Pathology Determinations

Hematology Parameters	Sample Type	Instrument Used	Reference
Leukocyte Count	WB	Ortho ELT-8®	1
Erythrocyte Count	WB	Ortho ELT-8®	1
Hemoglobin	WB	Ortho ELT-8®	1
Hematocrit	WB	Ortho ELT-8®	1
MCV, MCH, MCHC	WB	Ortho ELT-8®	1
Platelets	WB	Ortho ELT-8®	1
Differential Leukocyte Count	WB	Light Microscope	2

WB = Whole Blood
MCV = Mean corpuscular volume
MCH = Mean corpuscular hemoglobin
MCHC = Mean corpuscular hemoglobin concentration

B. RESULTS

Hematological values are summarized in Table 3. Individual hematological values are presented in Appendix D.

Statistical analysis of the hematology data was not done due to the small sample size. However, a review of the mean values suggests there were no differences between animals in the control or treated groups for any parameter evaluated.

Prepared By: Dale E. Johnson, Pharm.D., Ph.D., D.A.B.T.
Study Director
Date: 6/20/89

Reviewed By: Robert G. Geil, D.V.M., A.C.V.P. Diplomate
Scientific Director of Pathology Division
Date: 6/20/89

191-1439

C. REFERENCES

1. Ortho ELP-8 Operator Reference Manual. Ortho Diagnostic Systems, Westwood, MA. 1979.

2. Miale, J. B. (1977). Laboratory Medicine Hematology. The C. V. Mosby Company, St. Louis, MO.

VII. ANATOMIC PATHOLOGY

A. METHODS

1. Macroscopic

All animals received a complete postmortem examination under the direct supervision of a pathologist. All animals were euthanized by intravenous sodium pentobarbital followed by exsanguination.

After a thorough external examination, each animal was opened and the contents of the abdominal, thoracic and cranial cavities were examined both in situ and after removal and dissection. All macroscopic abnormalities were recorded on the Pathology Record sheet.

Gross lesions from all animals were collected and placed in phosphate-buffered neutral formalin.

2. Microscopic

Gross lesions were processed for the preparation and microscopic examination of hematoxylin- and eosin-stained paraffin sections for all animals.

Following acceptance of the final report, all tissues will be sent to the Sponsor.

A four-step grading system of trace, mild, moderate and severe was used to define gradable lesions for comparison between dosage groups. A complete listing of organ and tissue accountability can be found in the Tissue Inventory (Appendix F).

B. RESULTS

1. Macroscopic

Macroscopic pathology data are summarized in Table 4. Individual macroscopic findings are presented in Appendix E.

All rabbits which received dermal applications of 100% G2877.01 had test article related skin changes at the application

site. These changes included escher formation, atonia, desquamation, edema and erythema. There were no macroscopic changes at the application site in control group rabbits.

2. Microscopic

Microscopic pathology data are summarized in Table 5. Individual microscopic findings are presented in Appendix F.

All rabbits which received applications of 100% G2877.01 had test article related skin changes at the application site, including severe ulceration. In addition, some also had exudate on the epidermal surface, acanthosis, hyperkeratosis, chronic dermatitis, edema and abscess formation. There were no microscopic changes at the application site in control group rabbits.

Prepared By: _____ _____
Robert G. Geil, D.V.M., A.C.V.P. Diplomate Date:
Scientific Director of Pathology Division

191-1439

VIII. **SIGNATURES**

Relevant sections of this report have been reviewed by the following personnel:

Gayle E. Denesey — 6/16/89
Gayle E. Denesey
Report Writer
Report Writing
Date

James R. Myer — 6/16/89
James R. Myer, B.S.
Manager, Acute, Ocular and Dermal Toxicology
Date

Malcolm Blair — 6/16/89
Malcolm Blair, Ph.D.
Associate Director of Research
Scientific Director, General Toxicology Division
Date

191-1439

TABLE 1. Cont.
Water Control

Summary of Dermal Observations
(Number of Animals Showing Signs)

Dermal Sign	Days 1	2	3	4	5	6	7	8	9	10	11	12	13	14
Erythema														
None	NA	6	6	NA	NA	6	6	6	6	6	NA	NA	6	6
Slight	NA			NA	NA						NA	NA		
Moderate	NA			NA	NA						NA	NA		
Marked	NA			NA	NA						NA	NA		
Edema														
None	NA	6	6	NA	NA	6	6	6	6	6	NA	NA	6	6
Slight	NA			NA	NA						NA	NA		
Moderate	NA			NA	NA						NA	NA		
Marked	NA			NA	NA						NA	NA		
Atonia														
None	NA	6	6	NA	NA	6	6	6	6	6	NA	NA	6	6
Slight	NA			NA	NA						NA	NA		
Moderate	NA			NA	NA						NA	NA		
Marked	NA			NA	NA						NA	NA		
Desquamation														
None	NA	6	6	NA	NA	6	6	6	6	6	NA	NA	6	6
Slight	NA			NA	NA						NA	NA		
Moderate	NA			NA	NA						NA	NA		
Marked	NA			NA	NA						NA	NA		
Fissuring														
None	NA	6	6	NA	NA	6	6	6	6	6	NA	NA	6	6
Slight	NA			NA	NA						NA	NA		
Moderate	NA			NA	NA						NA	NA		
Marked	NA			NA	NA						NA	NA		
Eschar														
No	NA	6	6	NA	NA	6	6	6	6	6	NA	NA	6	6
Yes	NA			NA	NA						NA	NA		
Exfoliation														
No	NA	6	6	NA	NA	6	6	6	6	6	NA	NA	6	6
Yes	NA			NA	NA						NA	NA		
Number of Animals	NA	6	6	NA	NA	6	6	6	6	6	NA	NA	6	6

191-1439

NA - Not applicable

TABLE 1.
100% G2877.01

Summary of Dermal Observations
(Number of Animals Showing Signs)

Dermal Sign	Days 1	2	3	4	5	6	7	8	9	10	11	12	13	14
Erythema														
None	NA			NA	NA						NA	NA		
Slight	NA			NA	NA						NA	NA		
Moderate	NA	6		NA	NA						NA	NA		
Marked	NA		6	NA	NA	6	6	6	6	6	NA	NA	6	6
Edema														
None	NA			NA	NA						NA	NA		
Slight	NA	6	2	NA	NA	1					NA	NA		
Moderate	NA		3	NA	NA	4					NA	NA		
Marked	NA		1	NA	NA	1	6	6	6	6	NA	NA	6	6
Atonia														
None	NA	6	6	NA	NA						NA	NA		
Slight	NA			NA	NA						NA	NA		
Moderate	NA			NA	NA	6	6	6	3	2	NA	NA		
Marked	NA			NA	NA				3	4	NA	NA	6	6
Desquamation														
None	NA	6	6	NA	NA	5	5	5	5	5	NA	NA	5	5
Slight	NA			NA	NA	1	1	1	1	1	NA	NA		
Moderate	NA			NA	NA						NA	NA	1	1
Marked	NA			NA	NA						NA	NA		
Fissuring														
None	NA	6	6	NA	NA	5	5	4	3	3	NA	NA	1	
Slight	NA			NA	NA	1	1	2	3	3	NA	NA	4	2
Moderate	NA			NA	NA						NA	NA	1	3
Marked	NA			NA	NA						NA	NA		1
Eschar														
No	NA	6	6	NA	NA	6	6	6	6	6	NA	NA	6	5
Yes	NA			NA	NA						NA	NA		1
Exfoliation														
No	NA	6	6	NA	NA	6	6	6	6	6	NA	NA	6	6
Yes	NA			NA	NA						NA	NA		
Red Raised Areas														
No	NA	6	6	NA	NA	6	6	6	5	5	NA	NA		
Yes	NA			NA	NA				1	1	NA	NA	6	6
Number of Animals	NA	6	6	NA	NA	6	6	6	6	6	NA	NA	6	6

191-1439

NA - Not applicable

TABLE 2. Males: Summary of Body Weight Values

Parameters Measured	WEEK OF STUDY	WATER CONTROL MEAN	WATER CONTROL S.D.	WATER CONTROL N	100% GP877.01 MEAN	100% GP877.01 S.D.	100% GP877.01 N
Body Weight grams	Pretest	2598	60.7	9	2656	69.2	3
	1	2826	147.6	3	2594	28.9	3
	Terminal	3169	166.2	3	2703	131.1	3

191-1439

S.D. - Standard Deviation
N - Number of Animals

TABLE 2. Cont.

Females: Summary of Body Weight Values

Parameters Measured	WEEK OF STUDY	WATER CONTROL MEAN	WATER CONTROL S.D.	WATER CONTROL N	100% G2877.01 MEAN	100% G2877.01 S.D.	100% G2877.01 N	
Body Weight grams	Pretest	2708	61.1	3	2703	30.0	3	
	1	3306	23.2	3	2715	119.4	3	N
	Terminal	3407	35.6	3	2878	220.5	3	N

191-1439

S.D. - Standard Deviation
N - Number of Animals

TABLE 3. Males: Summary of Hematological Values

Parameters Measured	DAY OF STUDY	WATER CONTROL MEAN	S.D.	N	100% GP877.01 MEAN	S.D.	N
Leukocytes	Pretest	7.6	1.17	3	9.2	0.70	3
$x10^3$/cmm	Terminal	7.7	1.27	3	10.4	2.75	3
Erythrocytes	Pretest	4.90	0.517	3	4.84	0.106	3
$x10^6$/cmm	Terminal	5.28	0.411	3	5.14	0.083	3
Hemoglobin	Pretest	12.3	0.90	3	12.7	0.45	3
g/dl	Terminal	13.3	0.71	3	12.8	0.42	3
Hematocrit	Pretest	36.7	2.95	3	37.2	1.50	3
%	Terminal	38.7	2.07	3	38.1	1.16	3
MCV	Pretest	75	1.7	3	77	1.5	3
microns^3	Terminal	74	2.1	3	74	1.0	3
MCH	Pretest	25.3	0.93	3	26.2	0.51	3
pg	Terminal	25.2	0.64	3	24.8	0.67	3
MCHC	Pretest	33.6	0.36	3	34.1	0.16	3
g/dl	Terminal	34.3	0.15	3	33.5	0.76	3
Platelets	Pretest	258	3.0	3	315	104.2	3
$x10^3$/cmm	Terminal	351	76.8	3	568	118.3	3

101-1439

S.D. - Standard Deviation
N - Number of Animals

TABLE 3. Cont.

Males: Summary of Hematological Values

Parameters Measured	DAY OF STUDY	WATER CONTROL MEAN	WATER CONTROL S.D.	WATER CONTROL N	100% 62877.01 MEAN	100% 62877.01 S.D.	100% 62877.01 N
Segmented Neutrophils $K10^2/cmm$	Pretest	2.1	0.91	3	2.7	0.50	3
	Terminal	1.6	0.59	3	3.4	2.28	3
Lymphocytes $\times 10^3/cmm$	Pretest	5.2	1.04	3	5.9	0.90	3
	Terminal	5.6	1.38	3	6.9	1.05	3

191-1439

S.D. - Standard Deviation
N - Number of Animals

TABLE 3. Cont.

Females: Summary of Hematological Values

Parameters Measured	Day of Study	Water Control Mean	Water Control S.D.	Water Control N	2006 62077.01 Mean	2006 62077.01 S.D.	2006 62077.01 N
Leukocytes $\times 10^3$/cmm	Pretest	10.0	1.25	3	8.9	1.69	3
	Terminal	7.5	1.50	3	10.5	3.94	3
Erythrocytes $\times 10^6$/cmm	Pretest	4.79	0.236	3	4.89	0.072	3
	Terminal	4.72	0.212	3	5.02	0.416	3
Hemoglobin g/dl	Pretest	12.5	0.26	3	12.9	0.26	3
	Terminal	12.3	0.75	3	12.9	0.61	3
Hematocrit %	Pretest	36.3	1.01	3	37.6	0.67	3
	Terminal	35.7	2.25	3	37.8	2.66	3
MCV microns^3	Pretest	76	2.0	3	77	1.7	3
	Terminal	75	1.5	3	75	1.5	3
MCH pg	Pretest	26.1	1.01	3	26.4	0.45	3
	Terminal	26.1	0.67	3	25.7	0.89	3
MCHC g/dl	Pretest	34.4	0.75	3	34.3	0.38	3
	Terminal	34.6	0.50	3	34.1	0.80	3
Platelets $\times 10^3$/cmm	Pretest	285	19.1	3	299	41.5	3
	Terminal	335	65.2	3	448	78.8	3

191-1439

S.D. - Standard Deviation
N - Number of Animals

TABLE 5. Cont.

Females: Summary of Hematological Values

Parameters Measured	DAY OF STUDY	WATER CONTROL MEAN	WATER CONTROL S.D.	WATER CONTROL N	1408 G2877.01 MEAN	1408 G2877.01 S.D.	1408 G2877.01 N
Segmented Neutrophils $\times 10^3$/cmm	Pretest	2.6	0.20	3	3.3	1.30	3
	Terminal	1.1	0.60	3	4.3	3.50	3
Lymphocytes $\times 10^3$/cmm	Pretest	6.3	1.18	3	5.3	0.55	3
	Terminal	6.2	1.40	3	5.9	1.42	3

191-1439

S.D. - Standard Deviation
N - Number of Animals

TABLE 4.

INCIDENCE OF MACROSCOPIC OBSERVATIONS
Terminal Sacrifice
Male and Female

SITE - Observation		Water Control Male	Female	1 M
NUMBER OF ANIMALS EXAMINED		3	3	
NUMBER WITHIN NORMAL LIMITS		3	2	
KIDNEY				
- Cyst, clear, mild			1	
SKIN, APPLICATION SITE				
- Desquamation, mild				
- Atonia, mild				
- Eschar, mild				
- Erythema,	- mild			
	- moderate			
- Edema,	- mild			
	- moderate			
- Fissuring,	- mild			
	- moderate			

191-1439

TABLE 5. Incidence of Microscopic Observations

SITE - Observation	Water Control Male	Water Control Female
KIDNEY	(0)	(1)
- Cyst, mild		1
SKIN, APPLICATION SITE	(0)	(0)
- Ulcer, severe		
- Exudate, mild		
- Acanthosis, mild		
- Dermatitis, chronic, mild		
- Hyperkeratosis, mild		
- Edema, mild		
- Abscess, mild		

( ) = Number of animals examined

191-1439

APPENDIX A

Record of Animal Fate and Disposition

Record of Animal Fate and Disposition

Group, Animal Number	Sex	Fate	Day	Clinical Pathology Interval of Analysis
Water Control:				
39326	M	SS	15	Pretest, Day 14
39340	M	SS	15	Pretest, Day 14
39352	M	SS	15	Pretest, Day 14
39377	F	SS	15	Pretest, Day 14
38378	F	SS	15	Pretest, Day 14
39391	F	SS	15	Pretest, Day 14
100% G2877.01:				
39330	M	SS	15	Pretest, Day 14
39347	M	SS	15	Pretest, Day 14
39355	M	SS	15	Pretest, Day 14
39367	F	SS	15	Pretest, Day 14
39379	F	S.	15	Pretest, Day 14
39381	F	SS	15	Pretest, Day 14

SS - Scheduled Sacrifice

APPENDIX B

Individual Dermal Scores

Water Control — Individual Dermal Scores

Dermal Sign:	Sex:	M	M	M	F	F	F
Erythema	Rabbit Number:	3	3	3	3	3	3
		9	9	9	9	9	9
		3	3	3	3	3	3
		3	4	5	7	7	9
		6	0	2	7	8	1
Day	Skin Treatment	I	I	I	I	I	I
1		NA	NA	NA	NA	NA	NA
2		NE	NE	NE	NE	NE	NE
3		NE	NE	NE	NE	NE	NE
4		NA	NA	NA	NA	NA	NA
5		NA	NA	NA	NA	NA	NA
6		NE	NE	NE	NE	NE	NE
7		NE	NE	NE	NE	NE	NE
8		NE	NE	NE	NE	NE	NE
9		NE	NE	NE	NE	NE	NE
10		NE	NE	NE	NE	NE	NE
11		NA	NA	NA	NA	NA	NA
12		NA	NA	NA	NA	NA	NA
13		NE	NE	NE	NE	NE	NE
14		NE	NE	NE	NE	NE	NE

191-1439

NA - Not Applicable
NE - Not Evident
I - Intact

Water Control — Individual Dermal Scores

Dermal Sign:	Sex:	M	M	M	F	F	F
Edema	Rabbit Number:	3	3	3	3	3	3
		9	9	9	9	9	9
		3	3	3	3	3	3
		2	4	5	7	7	9
		6	0	2	7	8	1
Day	Skin Treatment	I	I	I	I	I	I
1		NA	NA	NA	NA	NA	NA
2		NE	NE	NE	NE	NE	NE
3		NE	NE	NE	NE	NE	NE
4		NA	NA	NA	NA	NA	NA
5		NA	NA	NA	NA	NA	NA
6		NE	NE	NE	NE	NE	NE
7		NE	NE	NE	NE	NE	NE
8		NE	NE	NE	NE	NE	NE
9		NE	NE	NE	NE	NE	NE
10		NE	NE	NE	NE	NE	NE
11		NA	NA	NA	NA	NA	NA
12		NA	NA	NA	NA	NA	NA
13		NE	NE	NE	NE	NE	NE
14		NE	NE	NE	NE	NE	NE

191-1439

NA - Not Applicable
NE - Not Evident
I - Intact

Water Control — Individual Dermal Scores

Dermal Sign:	Sex:	M	M	M	F	F	F
Atonia	Rabbit Number:	3	3	3	3	3	3
		9	9	9	9	9	9
		5	3	3	3	3	3
		2	4	5	7	7	9
		6	0	2	7	8	1
Day	Skin Treatment	I	I	I	I	I	I
1		NA	NA	NA	NA	NA	NA
2		NE	NE	NE	NE	NE	NE
3		NE	NE	NE	NE	NE	NE
4		NA	NA	NA	NA	NA	NA
5		NA	NA	NA	NA	NA	NA
6		NE	NE	NE	NE	NE	NE
7		NE	NE	NE	NE	NE	NE
8		NE	NE	NE	NE	NE	NE
9		NE	NE	NE	NE	NE	NE
10		NE	NE	NE	NE	NE	NE
11		NA	NA	NA	NA	NA	NA
12		NA	NA	NA	NA	NA	NA
13		NE	NE	NE	NE	NE	NE
14		NE	NE	NE	NE	NE	NE

191-1439

NA - Not Applicable
NE - Not Evident
I - Intact

Water Control — Individual Dermal Scores

Dermal Sign:	Sex:	M	M	M	F	F	F
Desquamation	Rabbit Number:	3	3	3	3	3	3
		9	9	9	9	9	9
		3	3	3	3	3	3
		2	4	5	7	7	9
		6	0	2	7	8	1
Day	Skin Treatment	I	I	I	I	I	I
1		NA	NA	NA	NA	NA	NA
2		NE	NE	NE	NE	NE	NE
3		NE	NE	NE	NE	NE	NE
4		NA	NA	NA	NA	NA	NA
5		NA	NA	NA	NA	NA	NA
6		NE	NE	NE	NE	NE	NE
7		NE	NE	NE	NE	NE	NE
8		NE	NE	NE	NE	NE	NE
9		NE	NE	NE	NE	NE	NE
10		NE	NE	NE	NE	NE	NE
11		NA	NA	NA	NA	NA	NA
12		NA	NA	NA	NA	NA	NA
13		NE	NE	NE	NE	NE	NE
14		NE	NE	NE	NE	NE	NE

191-1439

NA - Not Applicable
NE - Not Evident
I - Intact

Water Control — Individual Dermal Scores

Dermal Sign:	Sex:	M	M	M	F	F	F
Fissuring	Rabbit Number:	3	3	3	3	3	3
		9	9	9	9	9	9
		3	3	3	3	3	3
		2	4	5	7	7	9
		6	0	2	7	8	1
Day	Skin Treatment	I	I	I	I	I	I
1		NA	NA	NA	NA	NA	NA
2		NE	NE	NE	NE	NE	NE
3		NE	NE	NE	NE	NE	NE
4		NA	NA	NA	NA	NA	NA
5		NA	NA	NA	NA	NA	NA
6		NE	NE	NE	NE	NE	NE
7		NE	NE	NE	NE	NE	NE
8		NE	NE	NE	NE	NE	NE
9		NE	NE	NE	NE	NE	NE
10		NE	NE	NE	NE	NE	NE
11		NA	NA	NA	NA	NA	NA
12		NA	NA	NA	NA	NA	NA
13		NE	NE	NE	NE	NE	NE
14		NE	NE	NE	NE	NE	NE

NA - Not Applicable
NE - Not Evident
I - Intact

Water Control — Individual Dermal Scores

Dermal Sign:	Sex:	M	M	M	F	F	F
Eschar	Rabbit Number:	3	3	3	3	3	3
		9	9	9	9	9	9
		3	3	3	3	3	3
		2	4	5	7	7	9
		6	0	2	7	8	1
Day	Skin Treatment	I	I	I	I	I	I
1		NA	NA	NA	NA	NA	NA
2		N	N	N	N	N	N
3		N	N	N	N	N	N
4		NA	NA	NA	NA	NA	NA
5		NA	NA	NA	NA	NA	NA
6		N	N	N	N	N	N
7		N	N	N	N	N	N
8		N	N	N	N	N	N
9		N	N	N	N	N	N
10		N	N	N	N	N	N
11		NA	NA	NA	NA	NA	NA
12		NA	NA	NA	NA	NA	NA
13		N	N	N	N	N	N
14		N	N	N	N	N	N

191-1439

NA - Not Applicable
N - No (none)
I - Intact

Water Control — Individual Dermal Scores

Dermal Sign:	Sex:	M	M	M	F	F	F
Exfoliation	Rabbit Number:	3	3	3	3	3	3
		9	9	9	9	9	9
		3	3	3	3	3	3
		2	4	5	7	7	9
		6	0	2	7	8	1
Day	Skin Treatment	I	I	I	I	I	I
1		NA	NA	NA	NA	NA	NA
2		N	N	N	N	N	N
3		N	N	N	N	N	N
4		NA	NA	NA	NA	NA	NA
5		NA	NA	NA	NA	NA	NA
6		N	N	N	N	N	N
7		N	N	N	N	N	N
8		N	N	N	N	N	N
9		N	N	N	N	N	N
10		N	N	N	N	N	N
11		NA	NA	NA	NA	NA	NA
12		NA	NA	NA	NA	NA	NA
13		N	N	N	N	N	N
14		N	N	N	N	N	N

191-1439

NA - Not Applicable
N - No (none)
I - Intact

100% G2877.01 Individual Dermal Scores

Dermal Sign:	Sex:	M	M	M	F	F	F
Erythema	Rabbit Number:	3	3	3	3	3	3
		9	9	9	9	9	9
		3	3	3	3	3	3
		3	4	5	6	7	8
		0	7	5	7	9	1
Day	Skin Treatment	I	I	I	I	I	I
1		NA	NA	NA	NA	NA	NA
2		2	2	2	2	2	2
3		3	3	3	3	3	3
4		NA	NA	NA	NA	NA	NA
5		NA	NA	NA	NA	NA	NA
6		3	3	3	3	3	3
7		3	3	3	3	3	3
8		3	3	3	3	3	3
9		3	3[a]	3	3	3	3
10		3	3[a]	3	3	3	3
11		NA	NA	NA	NA	NA	NA
12		NA	NA	NA	NA	NA	NA
13		3	3	3	3	3	3
14		3	3	3	3	3	3

191-1439

NA - Not Applicable
I - Intact
a - Red raised areas

100% G2877.01 Individual Dermal Scores

Dermal Sign:	Sex:	M	M	M	F	F	F
Edema	Rabbit Number:	3	3	3	3	3	3
		9	9	9	9	9	9
		3	3	3	3	3	3
		3	4	5	6	7	8
		0	7	5	7	9	1
Day	Skin Treatment	I	I	I	I	I	I
1		NA	NA	NA	NA	NA	NA
2		1	1	1	1	1	1
3		1	1	2	2	2	3
4		NA	NA	NA	NA	NA	NA
5		NA	NA	NA	NA	NA	NA
6		1	2	2	2	2	3
7		3	3	3	3	3	3
8		3	3	3	3	3	3
9		3	3	3	3	3	3
10		3	3	3	3	3	3
11		NA	NA	NA	NA	NA	NA
12		NA	NA	NA	NA	NA	NA
13		3	3	3	3	3	3
14		3	3	3	3	3	3

191-1439

NA - Not Applicable
I - Intact

100% G2877.01 Individual Dermal Scores

Dermal Sign:	Sex:	M	M	M	F	F	F
Atonia	Rabbit Number:	3	3	3	3	3	3
		9	9	9	9	9	9
		3	3	3	3	3	3
		3	4	5	6	7	8
		0	7	5	7	9	1
Day	Skin Treatment	I	I	I	I	I	I
1		NA	NA	NA	NA	NA	NA
2		0	0	0	0	0	0
3		0	0	0	0	0	0
4		NA	NA	NA	NA	NA	NA
5		NA	NA	NA	NA	NA	NA
6		2	2	2	2	2	2
7		2	2	2	2	2	2
8		2	2	2	2	2	2
9		2	2	3	2	3	3
10		3	2	3	2	3	3
11		NA	NA	NA	NA	NA	NA
12		NA	NA	NA	NA	NA	NA
13		3	3	3	3	3	3
14		3	3	3	3	3	3

NA - Not Applicable
I - Intact

100% G2877.01 Individual Dermal Scores

Dermal Sign:	Sex:	M	M	M	F	F	F
Desquamation	Rabbit Number:	3	3	3	3	3	3
		9	9	9	9	9	9
		3	3	3	3	3	3
		3	4	5	6	7	8
		0	7	5	7	9	1
Day	Skin Treatment	I	I	I	I	I	I
1		NA	NA	NA	NA	NA	NA
2		0	0	0	0	0	0
3		0	0	0	0	0	0
4		NA	NA	NA	NA	NA	NA
5		NA	NA	NA	NA	NA	NA
6		0	0	0	0	0	1
7		0	0	0	0	0	1
8		0	0	0	0	0	1
9		0	0	0	0	0	1
10		0	0	0	0	0	1
11		NA	NA	NA	NA	NA	NA
12		NA	NA	NA	NA	NA	NA
13		0	0	0	0	0	2
14		0	0	0	0	0	2

191-1439

NA - Not Applicable
I - Intact

100% G2877.01 Individual Dermal Scores

Dermal Sign:	Sex:	M	M	M	F	F	F
Fissuring	Rabbit Number:	3	3	3	3	3	3
		9	9	9	9	9	9
		3	3	3	3	3	3
		3	4	5	6	7	8
		0	7	5	7	9	1
Day	Skin Treatment	I	I	I	I	I	I
1		NA	NA	NA	NA	NA	NA
2		0	0	0	0	0	0
3		0	0	0	0	0	0
4		NA	NA	NA	NA	NA	NA
5		NA	NA	NA	NA	NA	NA
6		0	0	0	0	0	1
7		0	0	0	0	0	1
8		0	0	0	1	0	1
9		0	0	1	1	0	1
10		0	0	1	1	0	1
11		NA	NA	NA	NA	NA	NA
12		NA	NA	NA	NA	NA	NA
13		1	0	1	1	1	2
14		1	1	2	2	2	3

191-1439

NA - Not Applicable
I - Intact

APPENDIX C

Individual Body Weights

(Individual) Body Weight, Grams

GROUP, ANIMAL NO.	SEX	OBSERVATION PERIODS (day) Initiation	7	14
Water Control				
30126	M	2604	2882	2886
30340	M	2634	2818	3209
30352	M	2608	2977	3311
30377	F	2771	3132	3477
30378	F	2649	3080	3458
30391	F	2703	3084	3527
100% 02877.01				
30330	M	2606	2663	2783
30347	M	2731	2820	2963
30355	M	2641	2600	2794
30367	F	2732	2951	3124
30379	F	2672	2829	2817
30381	F	2704	2864	2805

191-1439

APPENDIX D

Individual Hematological Values

Codes for Individual Hematological Values

A - Erythrocyte Appearance Grades:

0 - Within normal limits
1 - 5 - 25% cells affected
2 - 26 - 50% cells affected
3 - 51 - 75% cells affected
4 - 76 - 100% cells affected

Other Notations

WBC - White blood cell = Leukocyte
NRBC - Nucleated red blood cell
RBC - Red blood cell
NS - None seen in 100 cell differential

Individual Hematological Values - Pretest

Group, Animal Number	Sex	Leukocytes $\times 10^3$ /cmm	Erythrocytes $\times 10^6$ /cmm	Hemoglobin g/dl	Hematocrit %	MCV microns^3	MCH pg	MCHC g/dl	Platelets $\times 10^3$ /cmm
WATER CONTROL:									
39226	M	8.9	5.17	12.0	38.3	74	23.0	33.7	261
39340	M	8.7	4.20	11.3	38.3	91	26.3	38.0	254
39352	M	7.1	5.22	12.8	38.1	74	24.5	33.3	288
39377	F	8.8	4.64	12.4	35.2	78	27.3	35.2	265
39378	F	9.9	4.81	12.3	38.5	76	25.6	33.7	303
39381	F	11.3	5.01	12.8	37.2	74	25.5	34.4	287
100% G2D77.01:									
39330	M	9.5	4.83	12.2	35.7	77	25.3	34.2	350
39347	M	9.7	4.97	12.7	37.2	75	25.6	34.1	221
39355	M	8.4	4.93	13.1	38.7	78	26.6	33.9	425
39367	F	7.5	4.87	13.1	37.6	76	26.4	34.7	259
39379	F	8.5	4.84	13.0	38.2	79	26.9	34.0	297
39381	F	10.8	4.85	12.6	36.9	76	26.0	34.1	342

191-1439

LM →

Individual Hematological Values - Pretest

Group, Animal Number	Sex	Segmented Neutrophils $\times 10^3$ /cmm	Band Neutrophils $\times 10^3$ /cmm	Lymphocytes $\times 10^3$ /cmm	Eosinophils $\times 10^3$ /cmm	Monocytes $\times 10^3$ /cmm	Basophils $\times 10^3$ /cmm	Other Cells $\times 10^3$ /cmm
WATER CONTROL:								
38328	M	2.8	NS	6.8	NS	0.3	NS	NS
38340	M	1.5	NS	4.0	NS	0.2	NS	NS
38362	M	1.1	NS	6.8	NS	0.3	NS	NS
38377	F	2.8	NS	6.7	0.2	0.4	NS	NS
38378	F	3.0	NS	5.5	NS	1.1	0.2	NS
38381	F	2.8	NS	7.7	NS	0.8	NS	NS
10MG GARZ.OIL:								
38330	M	2.2	NS	6.0	0.1	0.4	NS	NS
38347	M	3.2	NS	6.0	NS	0.3	0.2	NS
38358	M	2.7	NS	5.0	NS	0.8	NS	NS
38367	F	2.0	NS	5.0	NS	0.5	NS	NS
38379	F	3.2	NS	4.0	NS	0.3	0.1	NS
38381	F	4.0	NS	6.0	NS	0.2	NS	NS

181-1430

Individual Hematological Values - Pretest

Group, Animal Number	Sex	NRBC /100 WBC	Polychromasia[A]	Hypochromasia[A]	Poikilocytosis[A]	Anisocytosis[A]
WATER CONTROL:						
39326	M	0	0	0	0	0
39340	M	0	1	0	1	0
39352	M	0	0	0	0	0
39377	F	0	0	0	0	0
39378	F	0	0	0	0	0
39391	F	0	0	0	0	0
100% G2877-01:						
39330	M	0	0	0	0	0
39347	M	0	0	0	0	0
39355	M	0	0	0	0	0
39367	F	0	0	0	0	0
39379	F	0	0	0	0	0
39381	F	0	0	0	0	0

191-1439

Individual Hematological Values - Terminal

Group, Animal Number	Sex	Leucocytes $\times 10^3$ /cmm	Erythrocytes $\times 10^6$ /cmm	Hemoglobin g/dl	Hematocrit %	MCV microns^3	MCH pg	MCHC g/dl	Platelets $\times 10^3$ /cmm
WATER CONTROL:									
39328	M	8.8	6.81	13.0	40.4	72	24.6	34.4	394
39340	M	8.3	4.82	12.5	36.4	75	25.9	34.3	386
39362	M	7.9	5.41	13.4	39.3	73	24.6	34.1	262
39377	F	5.8	4.95	13.2	38.2	77	26.7	34.6	260
39378	F	8.5	4.93	11.8	33.8	75	24.3	35.1	380
39381	F	8.3	4.88	11.9	34.9	74	25.4	34.1	364
100% CZ877-01:									
39330	M	6.0	5.07	12.9	37.6	74	25.4	34.4	467
39347	M	5.6	5.11	12.3	37.3	73	24.1	33.0	452
39365	M	13.4	5.25	13.1	39.4	75	25.0	33.2	884
39367	F	7.7	4.84	12.6	36.1	75	26.0	34.9	500
39379	F	8.8	4.73	12.5	36.5	77	26.4	34.2	478
39381	F	15.0	5.60	13.6	40.9	74	24.3	33.3	359

191-1439

Individual Hematological Values - Terminal

Group, Animal Number	Sex	Segmented Neutrophils $\times 10^3$ /cmm	Band Neutrophils $\times 10^3$ /cmm	Lymphocytes $\times 10^3$ /cmm	Eosinophils $\times 10^3$ /cmm	Monocytes $\times 10^3$ /cmm	Basophils $\times 10^3$ /cmm	Other Cells $\times 10^3$ /cmm
WATER CONTROL:								
39328	M	1.8	NS	8.1	0.6	0.8	0.1	NS
39340	M	2.0	NS	4.0	0.1	0.1	0.2	NS
39362	M	0.9	NS	8.6	0.1	0.1	0.3	NS
39377	F	0.5	NS	5.2	0.1	0.1	NS	NS
39378	F	1.1	NS	7.3	NS	0.1	0.1	NS
39381	F	1.7	NS	6.3	0.2	NS	0.2	NS
100% G7877.01:								
39330	M	2.1	NS	5.4	0.2	0.1	0.2	NS
39347	M	2.0	NS	7.5	0.1	0.1	0.1	NS
39366	M	0.0	NS	8.6	0.3	0.5	NS	NS
39387	F	2.6	NS	4.3	0.2	0.1	0.2	NS
39379	F	1.0	NS	8.9	0.1	NS	NS	NS
39381	F	8.9	NS	6.6	0.2	NS	NS	NS

181-1459

Individual Hematological Values - Terminal

Group, Animal Number	Sex	NRBC /100 WBC	Polychromasia[A]	Hypochromasia[A]	Poikilocytosis[A]	Anisocytosis[A]
WATER CONTROL:						
39326	M	0	0	0	1	0
39340	M	0	0	0	0	0
39352	M	0	1	0	0	1
39372	F	0	0	0	1	0
39378	F	0	0	0	0	0
39391	F	1	0	0	0	0
1005 02877-01:						
39330	M	1	0	0	0	0
39347	M	0	0	0	0	0
39355	M	0	0	0	0	0
39367	F	0	1	0	0	1
39379	F	0	0	0	0	0
39381	F	2	0	0	0	0

191-1439

APPENDIX E

Individual Animal Data Record: Pathology

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rabbits

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Water Control				
38326	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Skin, Application Site	- Within normal limits.
			MICROSCOPIC:	
			ALL TISSUES	- HISTOPATHOLOGY NOT REQUIRED.
39340	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Skin, Application Site	- Within normal limits.
			MICROSCOPIC:	
			ALL TISSUES	- HISTOPATHOLOGY NOT REQUIRED.
38352	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Skin, Application Site	- Within normal limits.
			MICROSCOPIC:	
			ALL TISSUES	- HISTOPATHOLOGY NOT REQUIRED.
38377	F	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Skin, Application Site	- Within normal limits.
			MICROSCOPIC:	
			ALL TISSUES	- HISTOPATHOLOGY NOT REQUIRED.

[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS O=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rabbits

GROUP. ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
Water Control				
30378	F	S	MACROSCOPIC:	
			Kidney	- Cortex, cyst, clear, minute, bilateral, mild.
			Skin, Application Site	- Within normal limits.
			MICROSCOPIC:	
			Kidney	- Cyst, unilateral, mild; Corresponds to macroscopic observation.
30381	F	S	MACROSCOPIC:	
			All Tissues	- Within normal limits.
			Skin, Application Site	- Within normal limits.
			MICROSCOPIC:	
			ALL TISSUES	- HISTOPATHOLOGY NOT REQUIRED.

101-1438

[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rabbits

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
100% G3077.01				
20330	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Skin, Application Site	- Erythema, mild; Edema, mild; Fissuring, mild.
			MICROSCOPIC:	
			Skin, Application Site	- Ulcer, diffuse, severe; Corresponds to macroscopic observation.
20347	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Skin, Application Site	- Erythema, mild; Edema, moderate; Fissuring, mild; Atonia, mild.
			MICROSCOPIC:	
			Skin, Application Site	- Ulcer, diffuse, severe; Corresponds to macroscopic observation.
30355	M	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Skin, Application Site	- Erythema, moderate; Edema, moderate; Fissuring, mild; Atonia, mild.

[1]FATE CODES: S=SCHEDULED SACRIFICE M=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rabbits

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
1085 02877.01				
38855	M	S	MICROSCOPIC: Skin, Application Site	- Exudate, mild; Acanthosis, diffuse, mild; Ulcer, diffuse, severe; Corresponds to macroscopic observation.
38387	F	S	MACROSCOPIC: All Other Tissues Skin, Application Site	- Within normal limits. - Erythema, mild; Edema, mild; Fissuring, mild; Atonia, mild.
			MICROSCOPIC: Skin, Application Site	- Ulcer, diffuse, severe. Corresponds to macroscopic observation.
38378	F	S	MACROSCOPIC: All Other Tissues Skin, Application Site	- Within normal limits. - Erythema, mild; Edema, moderate; Fissuring, mild; Atonia, mild.
			MICROSCOPIC: Skin, Application Site	- Acanthosis, diffuse, mild; Dermatitis, chronic, diffuse, mild; Hyperkeratosis, diffuse, mild; Ulcer, diffuse, severe; Corresponds to macroscopic observation.

191-1449

[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rabbits

GROUP, ANIMAL NUMBER	SEX	FATE[1]	TISSUE:	OBSERVATIONS:
100% G7877.01				
59981	F	S	MACROSCOPIC:	
			All Other Tissues	- Within normal limits.
			Skin, Application Site	- Erythema, moderate. Edema, moderate; Desquamation, mild; Fissuring, moderate; Atonia, mild; Scbar, mild.
			MICROSCOPIC:	
			Skin, Application Site	- Edema, mild; Acanthosis, diffuse, mild; Dermatitis, chronic, diffuse, mild; Abscess, focal, mild; Ulcer, diffuse, severe; Corresponds to macroscopic observation.

[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

APPENDIX F

Microscopic Tissue Inventory

Microscopic Tissue Inventory
Terminal Sacrifice: Rabbits

	Water Control						100% Graff.01					
SEX:	M	M	M	F	F	F	M	M	M	F	F	F
FATE:	S	S	S	S	S	S	S	S	S	S	S	S
ANIMAL NUMBER:	2	3	3	8	3	3	2	3	3	2	3	3
	9	9	9	9	9	9	9	9	9	9	9	9
	3	3	3	8	8	3	8	3	3	8	3	3
	2	4	5	7	7	9	2	4	5	4	7	0
	0	0	2	7	8	1	0	7	5	7	9	1
ALL TISSUES	X	X	X	X		X						
Kidney					X							
Skin, Application Site							X	X	X	X	X	X

191-1430 Fates: O - Found dead E - Sacrificed in extremis S - Scheduled sacrifice

Codes: X - Microscopic observation or annotation
+ - Tissue present and within normal limits
0 - Tissue not appropriate for this sex
B - See EADR report
- - Tissue not examined
M - Tissue not in plane of section
A - Tissue is too autolyzed for diagnosis

Tissues listed below dashed line were examined due to the presence of a macroscopic change or appearance in the plane of section.

APPENDIX G

Procanol and Protocol Addenda

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

PROTOCOL DISTRIBUTION SHEET

Protocol Sheet No. 1 Study No. 191-1439 (TSIN# G2877.01) (DRD# BYD8301)

TITLE: 13-DAY SUBCHRONIC PERCUTANEOUS TOXICITY

ITEM	JUSTIFICATION
1	Study initiation.
2	Specification of animal source.
3	Test article identification.
4	Identification of the diet used.
5	Clarification of IRDC Quality Assurance procedures.
6	Clarification of the number of animals in each study group.
7	Clarification of the control group treatment.
8	Clarification of necropsy/sacrifice regimen.

ITEM	PROTOCOL REVISION OR CLARIFICATION
1	Conduct this study in accordance with the attached protocol. The letter of authorization is considered part of the protocol.
2	The source of the test animals is NVR, Inc., Loudonville, Ohio 44842. The rabbits will be 2-3 months of age at study initiation.
3	The test article is identified as G2877.01, IRDC 9881.
4	Certified Rabbit Chow® #5322, Purina Mills, Inc., will be used.

Study Director Dr. Dale E. Johnson

Signature 1/03/89
Date

IR90-49-5

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

PROTOCOL DISTRIBUTION SHEET

(TSIN# G2877.01)

Protocol Sheet No. 1 Study No. 191-1439 (DRD# BY0830)

TITLE: 14-DAY SUBCHRONIC PERCUTANEOUS TOXICITY

ITEM	PROTOCOL REVISION OR CLARIFICATION
5	All critical phases and the final report will be inspected. The critical phases may be defined by the IRDC Quality Assurance and Study Director.
6	There will be 6 animals (3 males and 3 females) in each of two study groups (control and test).
7	The control group will be dosed with IRDC deionized water at a dosage volume of 2 ml/kg.
8	Randomization/selection procedures following the IRDC Standard Operating Procedure will be used to determine which animals will be sacrificed each day and the order in which they will be sacrificed.

Approved By:

1/17/89

Sponsor's Representative Date

Study Director Dr. Dale E. Johnson

1/03/89

Signature Date

IR90-49-5

191-1439

THE PROCTER & GAMBLE COMPANY

December 27, 1988

Dr. Dale Johnson
International Research and
Development Corporation
500 North Main St.
Mattawan, Michigan 49071

Dear Dr. Johnson:

This is to authorize you to carry out the following study according to the attached protocol, and in agreement with the stipulations of our current Laboratory Services Agreement.

Notice: 1) This study is expected to be submitted to the following regulatory agency: FDA. The stipulations of the protocol are to be implemented in complete conformance with the FDA Good Laboratory Practice Regulations (21 CFR, Part 58).

2) Documentation of the derivation, characterization, and stability testing of the test substance will be the responsibility of the Sponsor

3) The test substance is to be used for research and development purposes only.

Test: 12-Day Subchronic Percutaneous Toxicity
Protocol No: Special Protocol Dated October 11, 1988
Test Substance No: G2877.01 Doc. Req. No.: BT0830
Physical Form: Solid

Dr. Dale Johnson
International Research and
Development Corporation
December 27, 1986
Page 2

Matters involving the scientific aspects of the work can be handled directly with the Sponsor's Divisional Toxicologist.

Dr. A. L. Kraus Telephone (513) 530-2410
The Procter & Gamble Company
11511 Reed Hartman Highway - Room HB2D33
Cincinnati, Ohio 45241

Complete both copies of the attached protocol by adding your study number, proposed start and completion dates, study cost and have the Study Director sign and date them. This study is scheduled to start the week of January 2, 1989. The Study Director should define the start and completion dates on the protocol. Retain one copy and return one copy to me, along with a letter stating that you agree to do the work specified in the attached protocol. Three copies of the draft report are needed as soon as possible, and are to be sent to me. Also, complete the attached animal accounting form and return it as instructed.

The invoice for this study and all unused samples are to be returned to the the following address (the cost of shipment should be included in the study cost):

Mr. James V. Matthews
The Procter & Gamble Company
11511 Reed Hartman Highway - Room HB2D31
Cincinnati, Ohio 45241

Sincerely,

THE PROCTER & GAMBLE COMPANY
Research & Development Department

G. A. Nixon
Professional Standards Department

nh
cc: Study File
A. L. Kraus
Quality Assurance Unit

12-DAY SUBCHRONIC PERCUTANEOUS TOXICITY

Issue Date: OCTOBER 11, 1988
SUPERSEDES ISSUE DATED: New

Test Substance Identification Number (TSIN) # 62877.01

Divisional Request Document Number (DRD) # Bye 230

Sponsor: The Procter & Gamble Company
Cincinnati, Ohio

Testing Facility: (To be filled in by Operations Section)
INTERNATIONAL RESEARCH & DEVELOPMENT CORPORATION
MATTAWAN, MICHIGAN 49071

Study # 191-1439 (To be filled in by Testing Facility)

Purpose: To assess the cutaneous and systemic toxicity of a substance when it is repeatedly applied to abraded skin over a period of 12 days.

Justification for Selection of Test System: Historically, the New Zealand albino rabbit has been the animal of choice due to the large amount of background information on this species.

Route of Administration of Test Substance and Reason for Choice: Applied topically to abraded skin. Historical. One of the possible routes of human exposure.

Diet and/or Water Analyses Required: None (no known contaminants expected which would interfere with this study)

Records to be Maintained: All records that would be required to reconstruct the study and demonstrate adherence to protocol.

12-DAY SUBCHRONIC PERCUTANEOUS TOXICITY CONT'D

Issue Date: OCTOBER 11, 1988

Test Substance(s)

TSIN #	DRD Number	Description: Color	Description: Physical Form	Expiration Date
62877.01	8y0030	GREEN	SOLID	8/89

Storage Conditions: (Check one)

[✓] Room temperature [ ] Refrigerator [ ] Freezer
[ ] Other _____

Hazards: (Check one)

[✓] None known. Take ordinary precautions in handling.
[ ] As follows:

Special Instructions: (Check one)

[✓] None
[ ] As follows:

Animals: Rabbits, New Zealand albino, obtained preferably from Hazleton Research Animals or, if not available from Hazleton, from a source that has been approved by the Sponsor and the Test Facility. There will be at least one test group for each test substance listed above plus one vehicle control group. Each test group will consist of six (6) animals (3 males, 3 females) weighing 2.0-3.0 kg.

Animal Care and Diet: Follow the approved Standard Operating Procedures of the Test Facility. [Acclimation period must be a minimum of seven (7) days.]

12-DAY SUBCHRONIC PERCUTANEOUS TOXICITY CONT'D

Issue Date: OCTOBER 11, 1988

Environmental Conditions: Follow the approved Standard Operating Procedures of the Test Facility. If the temperature or humidity fall out of SOP limits for more than two consecutive days, the Sponsor will be notified.

Animal Identification: Follow the approved Standard Operating Procedures of the Test Facility.

Group Assignment Methods and Pre-Dose Requirements: Rabbits will be selected from animals that have been acclimated in the laboratory a minimum of seven (7) days and have been used in no previous studies. Animals will be given a visual examination by a qualified individual and only those rabbits judged to be of acceptable health status will be selected for hematology screening.

Collect blood samples into collection tubes containing EDTA anti-coagulant, following the approved Standard Operating Procedures of the Test Facility. Specify the method used. Determine hemoglobin, hematocrit, white blood cell count, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, and differential white blood cell count. Eliminate those animals judged to have an abnormal hemogram as defined by the Standard Operating Procedures of the Test Facility. Dosing will be started within seven (7) days of the baseline blood collections.

Only animals weighing between 2.0-3.0 kg with an acceptable health status and normal hemogram will be randomized into test and control groups. Animals should be randomized into groups by weight and sex with 5 males and 5 females in each group according to the approved Standard Operating Procedures of the Test Facility.

Test Site Preparation: Clip the area on the back of each animal from shoulder to rump, approximately 12-15 cm wide, using a small animal clipper. Clip animals as needed while the test is in progress to prevent the test substance from matting in the hair.

Option [ ] Abrade the skin of the rabbits prior to each treatment with a clean clipper blade or other appropriate device by penetrating the horny layer of the epidermis without causing bleeding.

12-DAY SUBCHRONIC PERCUTANEOUS TOXICITY CONT'D

Issue Date: OCTOBER 11, 1988

Dose Preparation:

Test Group(s): (Check appropriate box)

[✓] Dose test substance undiluted
[ ] Dose as a ____% (w/w) solution/suspension of test substance in _____.

[ ] Dose as a ____% (w/v) solution/suspension of test substance in _____.

[ ] Dose per Special Instructions (see page 2)

Control Group

A control group should be [ ]; should not be [ ] included in this study. If included, the control substance _____ should be tested concurrently with the test substance at a dosage level of _____.

Dosing Instructions:

Apply appropriate concentration (see Dose Preparation) of test substance(s) or control substance daily, 5 days per week for 2 weeks (10 applications) at a dosage volume of 2 ml/kg of body weight.

Apply the substances with a syringe. Use Test Facility's Standard Operating Procedures to evenly distribute the substances over the clipped area. Record time of dosing. Weigh the animals once weekly and adjust the dose levels accordingly.

Restraining:

[ ] Do not restrain.

[✓] Restrain the animals to prevent oral ingestion. Remove the restraining device approximately 7 hours after the start of treatment.

Issue Date: OCTOBER 11, 1988

Washing:

[ ] Do not wash
[ ] Wash all test sites with tepid water approximately 7 hours post treatment. Gently dry with disposable paper towels or equivalent.
[✓] Wash animals with tepid water if significant amounts of test substance accumulates on the test sites. If any animals require washing, all animals should be washed and gently dried with disposable paper towels or equivalent. Record time and dates when animals are washed.

Grading:

Immediately prior to treatment each day (after day 1), grade the skin sites using the attached scale (Appendix 1), or a similar Draize skin reaction scoring system. If fissuring is noted on abraded animals, consult the Divisional Toxicologist for instructions on continued abrasion.

Note:

All animals that are caused undue stress or discomfort, as judged by the Study Director and the Test Facility Veterinarian, with the concurrence of the Divisional Toxicologist, should be sacrificed immediately for humane reasons.

Observations:

Observe all animals daily (7 days/week), up to the day of necropsy, recording all findings including any abnormalities. Necropsy all animals as soon as possible that are found moribund or dead during the course of the experiment. These necropsies will be supervised by a veterinarian. If necropsy is delayed, refrigerate the carcass until prosection begins. Record all observations. If possible, determine the cause of death and notify the Sponsor's Divisional Toxicologist. Collect tissues exhibiting gross observations from all animals which either die or are sacrificed prematurely. If any deaths occur after start of dosing, no replacement animals will be used without authorisation of Sponsor.

Necropsy:

Prior to initiation of the study, schedule the animals for necropsy with, as nearly as possible, an equal distribution as to sex and group number for each necropsy day. Randomization procedures following the

12-DAY SUBCHRONIC PERCUTANEOUS TOXICITY CONT'D

Issue Date: OCTOBER 11, 1988

Necropsy (Cont'd): Between day 12 and the day of necropsy, obtain blood samples via the technique used in the pre-study and analyze as described in the pretreatment hematology screening on page 3. Weight all animals on the first day of necropsy for use in assessing in-life body weight changes. Sacrifice the animals with an IV overdose of sodium pentobarbital. Exsanguinate prior to cessation of heart beat following the appropriate Standard Operating Procedure of the Test Facility. Necropsy all surviving animals and record all gross observations for all organs following the Standard Operating Procedure of the Test Facility. Take tissue specimens for any organs exhibiting gross observations. Any deviations from the protocol such as missing tissues, hematology results, etc., should be noted in the raw data. All scheduled necropsies will be supervised by a veterinary pathologist. All necropsy room assistants will be trained and qualified.

Histopathology: Trim all tissues collected (see Necropsy Section) and prepare paraffin blocks and H&E slides following the approved Standard Operating Procedures of the Test Facility. Slides of all tissues will be examined microscopically by a sponsor-approved veterinary pathologist.

Statistical Analysis: Due to the small number of animals on this study, calculate only means and standard deviations.

Protocol Changes: If it becomes necessary to change the approved protocol, verbal agreement to make this change should be made between the Study Director and the Sponsor. As soon as practical, this change and the reason for it should be put in writing and signed by both the Study Director and the Sponsor's Divisional Toxicologist. This document is then attached to the protocol as an addendum.

Report: Report dates of study initiation and termination, deaths, skin reactions, gross abnormalities, histopathological and hematological results. Pathologist's report should include a statement that in his opinion the quantity and quality of tissue taken was adequate to evaluate the study. This report shall conform to all requirements outlined in Section 58.185, Subpart J, Good Laboratory Practices Regulations.

12-DAY SUBCHRONIC PERCUTANEOUS TOXICITY CONT'D

Issue Date: OCTOBER 11, 1988

Retention of Histopathology Materials: All wet tissues, blocks and slides, including blood slides, collected at contract laboratories should be returned to the Sponsor for retention following acceptance of the final report. The Study Director will be notified in writing when the report has been accepted. Instructions for returning these materials are given in Appendix 2.

Quality Assurance: Quality assurance inspections shall consist of all critical phases as defined by the QAU and the Study Director or as defined by the Test Facility's SOP's. The final report will be reviewed by the QAU.

Sponsor: A Kuma Ph.D. — Divisional Toxicologist — 513-570-2410 Telephone No.

Date Approved by Sponsor's Divisional Toxicologist 10/7/88

Proposed Starting Date: 1/04/89

Defined as First day of dosing

Proposed Completion Date: 1/18/89

Defined as Day of necropsy

(To be completed by the Test Facility)

Study Director: Dale E. Johnson

Dale E. Johnson, Pharm. D., Ph. D.

Date: 1/03/89

Study Cost:

PROTOCOL - APPENDIX I

SCALE FOR EVALUATING SKIN REACTIONS *

Erythema (not including eschar area)
- 0 - None
- 1 - Slight (barely perceptible)
- 2 - Moderate (well defined)
- 3 - Severe (beet red)

Edema (not including eschar area)
- 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 (not including eschar area)
- 0 - Normal
- 1 - Slight (impairment of elasticity)
- 2 - Moderate (slow return to normal)
- 3 - Marked (no elasticity)

Desquamation (not including eschar area)
- 0 - None
- 1 - Slight (slight scaling without evidence of peeling)
- 2 - Moderate (large flakes with sloughing)
- 3 - Marked (pronounced flaking with denuded areas)

Fissuring (not including eschar area)
- 0 - None
- 1 - Slight (definite cracks in epidermis)
- 2 - Moderate (cracks in dermis)
- 3 - Marked (cracks with bleeding)

++Eschar
- N - No
- Y - Yes

++Exfoliation (sloughing of the eschar tissue)
- N - No
- Y - Yes

* Grades assigned should be based on the most severely affected area except when area is judged to be < 20% of the treatment site. Severe reactions occurring on < 20% of a site should be described in a footnote.

++ Discontinue scoring on portion of test site with eschar/exfoliation.

APPENDIX 2

INSTRUCTIONS FOR RETURN OF TERATOLOGY SPECIMENS, WET TISSUES, PARAFFIN BLOCKS, AND MICROSCOPIC SLIDES TO THE PROCTER & GAMBLE COMPANY

Wet Tissues: must be sealed in plastic bags (preferably heat-sealed). Bags such as "Kapak Pouches" by Skotchpak are excellent and available from most scientific supply houses. Place only one animal's tissues in a bag together with an amount of 10% buffered neutral formalin adequate to thoroughly moisten all tissues. Several seals should be made (with an identifying label written with waterproof ink which includes study number, group, animal number) between the seals.

Paraffin Blocks: should be placed on end (with the label visible) in numerical order by groups in special tray boxes which consists of a cardboard tray 16" x 9" x 2" plus a protective cardboard sleeve. These boxes will accommodate approximately 175 to 200 blocks and are available from John Green, Buckeye Box Co., 601 N. Hague Avenue, Columbus, Ohio 43204 (614-274-8484) (Part #WF-1). Label the end of the box to identify the contents. This permanent label should list the study number and groups.

Microscope Slides: labeled to indicate the study number, group and animal number must be packed in numerical order by groups in plastic boxes. Lids should be secured with tape. A packing material such as polyfoam, paper towels, etc. should be placed inside of the lid to prevent breakage. A permanent label should be placed on the outside of the lid identifying the study number and groups.

Teratology Specimens: All cleared specimens and soft tissue slices should be returned in appropriate containers (preferably plastic). See Wet Tissues instructions on labeling and sealing.

IMPORTANT

An itemized list should accompany each shipment. This list should indicate the following:

1. The number of units in the shipment; i.e., the number of shipping cartons.

2. The number of slides, blocks and individual containers of wet tissue or teratology specimens in study.

Contract Laboratories: Procter & Gamble will request (in writing) the return of specimens, indicating approximately when they should be shipped. All costs incurred in shipment of these materials to the sponsor should be included in the fixed study cost. When ready, please notify and send to:

Archive Technician
The Procter & Gamble Company
Miami Valley Laboratories - BK OON216
11810 E. Miami River Road
Ross (Butler County), Ohio 45061
Telephone: (513) 245-2288

BAD:nh

2/4/86

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION

PROTOCOL DISTRIBUTION SHEET

Protocol Sheet No. 2 Study No. 191-1439 (IRDC 890830) (ISIHC 62677.31)

TITLE: 12-DAY SUBCHRONIC PERCUTANEOUS TOXICITY

ITEM	JUSTIFICATION
1	Clarification of the test site skin treatment.
2	Clarification to allow warming of the test article prior to administration.

ITEM	PROTOCOL REVISION OR CLARIFICATION
1	The Sponsor clarified that the animals should have intact skin sites during the study.
2	The Sponsor authorized that the test material could be warmed so that it could be accurately measured into syringes. The material will be placed in a water bath heated to approximately 40-50°C. The material will be allowed to soften/melt and then dispensed into syringes for individual dose administration.

Approved by:

Sponsor's Representative Date

Study Director Dr. Dale E. Johnson

Signature Date 1/05/89

IR90-69-5

TEST SUBSTANCE CHARACTERIZATION REPORT

DAS: BY 0830

TSIN : 628770I

1. Test Article Name (Product/Ingredient)
BC-86 with 7.5% Octapirox

2. Brand Notebook: HC0476-594

3. Physical Form: Solid
Color: AQUA GREEN
Storage Conditions:
[X] Room Temperature [ ] Other _____

pH: ~9.10
Expiration Date: 8-17-89
Hazards: FLAMMABLE

4. Stability Testing is:
[ ] Completed [X] In Progress

5. DOT Hazard Classification: Non-Hazardous Regulatory Initials: [illegible]

These chemicals/test articles have been checked against the TSCA inventory list? [ ] Yes [ ] No

6. Formula Composition:

Component	CAS Number	Nominal Component Level	Nominal Calcul'd "Assay"	Actual Calcul'd "Assay"	Stock Code	Lot Number
DIPROPYLENE GLYCOL	110-98-5	28.400	28.400	28.388	45439	3
ETHANOL Rb	997021-01	24.000	24.000	24.004	45105	142
PPG-5 MYRISTYL ETHER	63793-60-2	17.500	17.500	17.495	47825	5
DS CYCLOMETHICONE Rb	997061-03-2	14.450	14.450	14.446	47777	1
OCTOPIROX	68890-66-4	7.500	7.500	7.521	52168	4
SODIUM STEARATE	822-16-2	6.000	6.000	5.996	48105	11
SOY BEAN (TA1154-1)		1.200	1.200	1.200	XP479	2
D&C GREEN						
No [illegible] SOLVENTICN		0.700	7 ppm	7 ppm	BX729	1
DMP (A.19e-2		0.200	0.200	0.200	XP439	1
SODIUM HYDROXIDE		0.650	250 ppm	250 ppm	45297	21
(Residual Water (and volatiles))		---	0.724	0.724		
Totals:		100.000	100.000	100.000		

(a) Use Chemical or CTFA names which uniquely identifies each component.

(b) CAS Numbers should be included whenever available. They are especially important for main components of the formula.

VA1/005/4 - 2/88 (FORM2.TXT)

DRD: BY 0830

TSIN: 62877.01

7. **ANALYSIS**

Date Submitted	Submitter Code Or Lab Notebook	Analysis	(X) *	Measured Value	Limits	Laboratory Testing Or Data Source
8-19-88	bF 309	MCT	X	Pass	Must Pass	BC Micro
8-19-88	8306-0972	% EtOH		23.1 %	22.1-24.5%	ANALYTICAL
8-18-88	HC0476-594	% Octopirox		753%	none established	R.K. Rose-3N49

* Analysis required by toxicologist or microbiologist

8.
Acceptable Microbial Susceptibility: [signature] 8/25/88
(Signature) (Date)

Made By: [signature] 2170 8-17-88
(Signature) (Phone No.) (Date Made)

Approval for Release: The test substance as made and characterized is a representative example of the intended formulation. Making records for plant-made product are being/have been obtained and evaluated by Products Research.

Process Development: [signature] 8/23/88
(Signature) (Date)

Products Research: [signature] 8/24/88
(Signature) (Date)

GMP Quality Assurance: K. L. Brotherton 8/25/88
(Signature) (Date)

(Attach batch records for GMP review)

1 finished products will be retained by Quality Assurance
(# samples)

9.
This substance has been appropriately characterized and is acceptable for testing outlined in the attached DRD.

Division Toxicologist: [signature] 9/1/88
(Signature) (Date)

VA1/005/5
2/88

INTERDEPARTMENTAL CORRESPONDENCE

FROM: A L Kerns DATE: 10/6/88

TO: Operations Section R/L:

SUBJECT: MONCLINICAL STUDY REGULATORY STATUS

Notification pertaining to: DRD # 840830

TSIM 62877.01

1. The study described in the above protocol is to be considered:

   [✓] Safety
   [ ] Regulated Safety
   [ ] Investigational

2. [✓] The data is expected to be submitted to the following regulatory agency:

   [✓] FDA
   [ ] EPA
   [ ] Other _____

   [ ] The data is not expected to be submitted to a regulatory agency. (Boxes #4 and #5 below need not be checked)

3. [✓] The test substance has been characterized and results are shown on the test substance characterization report (TSCR).

4. [✓] The method of synthesis, fabrication, or derivation of the test related substances has been documented (required for regulated studies).

5. [✓] Stability testing has been done or will be done on the test substance (required for regulated studies).

Sponsor's Divisional Toxicologist A L Kerns

Date: 10/6/88

bg: REGSTAT
10/23/86