T-3988
AR226-0156

28 Day Percutaneous Absorption Study

with FC-99

in Albino Rabbits

Experiment No.: 0979AB0633

Conducted At: Safety Evaluation Laboratory
Riker Laboratories, Inc.
St. Paul, Minnesota

Dates Conducted: October 24, 1979 to December 18, 1979

Conducted By: K. D. O'Malley 3/4/81
K. D. O'Malley, BS Date
Advanced Toxicologist
Study Director

Reviewed By: K L Ebbens 3/5/81
K. L. Ebbens, BS Date
Supervisor, Acute Toxicology

dc: M. T. Case
K. L. Ebbens
F. D. Griffith
W. C. McCormick

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Summary

A 28 day percutaneous absorption study with FC-99 was conducted from October 24, 1979 to December 18, 1979 at Riker Laboratories, Inc., St. Paul, Minnesota using male and female albino rabbits ranging in body weight from 1.78 to 2.35 kg. (A preliminary rangefinder study was conducted to determine the appropriat dosage level to be used.) The test article was administered by dermal application to ten male and ten female rabbits each at a dosage level of 5000 mg/kg body weight for a 24 hour exposure period. No mortalities, untoward behavioral reactions or body weight losses were noted during the 28 day study. Necropsies were performed on all animals upon termination of the study and no visible lesions were noted. Preliminary serum analysis (Appendix V) indicates dermal absorption of FC-99 in albino rabbits, however, due to the limited number of samples analyzed by the sponsor, no concrete conclusion may be drawn.

Introduction

The objective of this study[a] was to determine the percutaneous absorption potential of FC-99 in male and female albino rabbits. The study, which was initiated at Riker Laboratories, Inc., St. Paul, Minnesota on October 24, 1979 and completed on December 18, 1979, was not conducted to support a government submission or marketing permit and is therefore not regulated by the Good Laboratory Practice Regulation of 1978. The raw data generated by the Study Director and the final report are stored in the conducting laboratory's archives.

[a] Riker Toxicity Experiment No.: 0979AB0633, Test Method 699

Method and Results

Young adult albino rabbits of the New Zealand breed[a] were used in this test. All animals were held under quarantine for several days prior to testing with only animals which appeared to be in good health and suitable as test animals at the initiation of the study used. The rabbits were housed individually in stainless steel, wire-bottomed cages and maintained on a standard laboratory ration[b] with food and water available ad libitum.

An initial rangefinding study was conducted using two male and two female rabbits for each dosage level. The trunk of each animal was clipped free of hair and the test article placed on the surface of the intact skin which covered approximately 40% total body surface area. After administration of the test article, a flexible plastic collar was fitted on each animal and the trunk wrapped with impervious plastic sheeting which will occlude the test article. The animals were returned to their cages for a 24 hour period after which time the test article was removed from the dermal surface of the animals. The animals were observed for pharmacotoxic reactions both during the exposure period (immediately post dose administration, one and two hours) and after removal of the test article (daily for 14 days following dose administration) with all reactions recorded (Table 3). Initial and final body weights were also recorded (Table 1).

The information derived from the initial rangefinder was used in determining the dosage level for the 28 day percutaneous study. Preparation of 10 male and 10 female animals for dosing and application of the test article were conducted in the same manner as the rangefinder study with the exception of the collection of blood samples from the orbital sinus plexus prior to application and again on days 1, 7, 14 and 28 after initiation of the study for serum which was frozen for sponsor analysis. After the 24 hour exposure

[a] Pel Freez, Inc., Rogers, AR
[b] Purina Rabbit Chow, Ralston Purina, St. Louis, MO

period the test article was removed from the dermal surface of the animals and the animals returned to their cages for the following 28 days. Initial, 7, 14 and 28 day body weights were recorded (Table 2) as were any pharmaco-toxic signs noted during the 28 day observation period (Table 4). A gross necropsy was conducted on all animals sacrificed on day 28 and all findings recorded (Table 2). The protocol, principal personnel involved in the study, composition characteristics, and Quality Assurance statement are contained in Appendices I - IV.

TABLE 1

ACUTE DERMAL RANGEFINDER TOXICITY STUDY - ALBINO RABBITS

with FC-99

Mortality and Body Weight Data

Dose[a] (mg/kg)	Sex	Animal Number	Individual Body Weights (kg) Test Day Number 0	14	Number Dead / Number Tested	Percent Dead
5000	M	9B2586	2.45	2.42	0/4	0
	M	9B2589	2.00	1.44		
	F	9B2682	2.00	1.63		
	F	9B2652	2.00	1.34		
2000	M	9B2592	2.25	2.02	0/4	0
	M	9B2595	1.97	1.71		
	F	9B2688	2.35	2.17		
	F	9B2691	2.02	2.04		
1000	M	9B2587	2.36	2.22	0/4	0
	M	9B2590	2.08	2.17		
	F	9B2683	2.28	2.20		
	F	9B2655	2.05	2.13		

[a] Test article was dosed undiluted

TABLE 2

ACUTE PERCUTANEOUS ABSORPTION TOXICITY STUDY - ALBINO RABBITS

with FC-99

Mortality and Body Weight Data

Dose[a] (mg/kg)	Sex	Animal Number	Individual Body Weights (kg) Test Day Number 0	7	14	28	Number Dead / Number Tested	Percent Dead
5000	M	9B3064	2.10	1.77	2.00	2.25	0/10	0
	M	9B3067	1.78	1.77	1.96	2.25		
	M	9B3070	2.25	2.11	2.25	2.52		
	M	9B3073	2.09	1.74	1.99	2.41		
	M	9B3065	2.11	2.08	2.35	2.65		
	M	9B3068	2.14	2.15	2.48	2.62		
	M	9B3071	2.05	2.07	2.32	2.48		
	M	9B3075	2.24	2.01	2.34	2.47		
	M	9B3066	1.99	1.89	2.19	2.46		
	M	9B3069	2.22	2.13	2.35	2.62		
5000	F	9B2920	2.00	1.77	2.00	2.30	0/10	0
	F	9B2926	2.07	1.92	2.21	2.35		
	F	9B2932	2.35	2.05	2.35	2.51		
	F	9B2938	2.07	1.63	1.97	2.22		
	F	9B2922	1.97	1.85	2.05	2.25		
	F	9B2928	2.22	1.69	1.98	2.25		
	F	9B2934	2.23	2.15	2.20	2.35		
	F	9B2940	2.01	1.56	1.52	2.09		
	F	9B2924	2.25	2.13	2.30	2.55		
	F	9B2930	2.08	1.99	1.84	2.08		

[a] Test article was dosed undiluted

Necropsy

Necropsies performed upon termination of the study revealed no visible lesions

TABLE 3

ACUTE DERMAL RANGEFINDER TOXICITY - ALBINO RABBITS

with FC-99
Summary of Reactions

Dose (mg/kg)	Sex	Reaction	Number Affected / Number Dosed	Time of Onset Following Dose Administration	Cessation of Reaction Following Dose Administration	Time of Death Following Dose
5,000	M	No significant reactions		---	---	---
	F	No significant reactions		---	---	---
2,000	M	No significant reactions		---	---	---
	F	No significant reactions		---	---	---
1,000	M	No significant reactions		---	---	---
	F	No significant reactions		---	---	---

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TABLE 4

ACUTE PERCUTANEOUS ABSORPTION TOXICITY STUDY - ALBINO RABBITS

with FC-99

Summary of Reactions

Dose (mg/kg)	Sex	Reaction	Number Affected / Number Dosed	Time of Onset Following Dose Administration	Cessation of Reaction Following Dose Administration	Time of Death Following Dose
5,000	M	No significant reactions		---	---	---
	F	No significant reactions		---	---	---

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TEST: Single Dose 28 Day Percutaneous Absorption Study
SPONSOR: 3M Commercial Chemical Division
CONDUCTED BY: Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minnesota
TEST ARTICLE: FC-99
CONTROL ARTICLE: N/A
PROPOSED STARTING/COMPLETION DATE OF STUDY: 11-29 / 1-80
TEST SYSTEM AND SOURCE: New Zealand White Albino Rabbits Sex: M+F
Pel Freez, Inc., Rogers, Arkansas Number: 10+10
Weight Range: 2-3 kg

OBJECTIVE: The objective of this study will be to determine the percutaneous absorption potential of the test article in albino rabbits. Rabbits were selected as the test system for their historical use in dermal absorption studies, ease of handling and general availability.

METHOD: The animals, selected from a larger colony by health and body weight, will be randomly housed in standard wire-mesh cages in temperature and humidity controlled rooms with food[a] and water offered ad libitum. Each animal will be assigned a numbered ear tag, which will correspond to a card affixed to the outside of the cage. The trunk of each animal will be clipped free of hair and the test article applied as a single dosage of 5000 mg/kg to intact skin covering approximately 10% total body surface area. A flexible plastic collar[b] will be fitted on each animal and the trunk wrapped with impervious plastic sheeting, which will occlude the test article. The animals will then be returned to their cages for a 24 hour exposure period after which the test article will be removed. Prior to the application, blood samples will be collected from the orbital sinus plexus and again on days 1, 7, 14, and 28 after initiation of the study for serum which will be frozen for sponsor analysis. A gross necropsy will be conducted on all animals which may die during the conduct of the study as well as all animals sacrificed on day 28. All gross findings will be recorded and tissue samples of liver, spleen, brain, kidney and bone marrow (sternum) will be fixed in 10% buffered formalin for possible future microscopic examination. Initial, 7, 14, and 28 day body weights will be recorded as well as any pharmacotoxic signs noted during the conduct of the study. All raw data, other than the blood analysis data which will be the responsibility of the sponsor, and the final report will be stored in the Riker Laboratory's Archives, St. Paul, Minnesota.

[a] Purina Rabbit Chow, Ralston Purina, St. Louis, Missouri
[b] The collar will be worn for the duration of the study to reduce oral ingestion of residual test article.

W. C. McCormick/vdt 11/7/79
Sponsor Date

K D Malley 11/7/79
Study Director Date

TEST: Acute Dermal Toxicity Rangefinding Study
SPONSOR: 3M Commercial Chemical Divisio
CONDUCTED BY: Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minnesot
TEST ARTICLE: FC-99
CONTROL ARTICLE: N/A
PROPOSED STARTING/COMPLETION DATE OF STUDY: 11/29 - 12/80
TEST SYSTEM AND SOURCE: New Zealand White Albino Rabbits Sex: ♂♀
Pel-Freez, Inc., Rogers, Arkansas Number: 2/2
Body Weight Range: 2.3 kg

OBJECTIVE: The objective of this study will be to approximate the acute dermal toxicity of the test article in albino rabbits. Rabbits were selected as the test system for their sensitivity of response, historical data, ease of handling and general availability.

METHOD: The animals, selected from a larger colony by health and weight, will be randomly housed in standard wire-mesh cages in temperature and humidity controlled rooms with food[a] and water offered ad libitum. Each animal will be assigned a numbered ear tag, which will correspond to a card affixed to the outside of the cage. The trunk of each animal will be clipped free of hair and the test article placed on the surface of the intact skin at single dosages of 5000, 2000, 1000 mg/kg, however, if these dosage levels do not adequately characterize the toxicity of the test article, additional animals will be administered the test article at supplemental dosage levels. Any additional dosage levels will be documented and filed with this protocol. The test article will be administered to the animals in the form received from the sponsor. After administration of the test article, a flexible plastic collar[b] will be fitted on each animal and the trunk wrapped with impervious plastic sheeting which will occlude the test article. The animal will be returned to their cages for a 24 hour exposure period after which time the test article will be removed from the dermal surface of the animals. The animals will be observed for pharmacotoxic reactions both during the exposure period (immediately post dose administration, one and two hours) and after removal of the test article (daily for 14 days following dose administration) with all reactions being recorded. Initial and final body weights will also be recorded. The acute median lethal dose (LD50) of the test article will be approximated. All raw data and the final report will be stor in the Riker Laboratories Archives, St. Paul, Minnesota.

[a] Purina Rabbit Chow, Ralston Purina, St. Louis, Missouri

[b] The collar will be worn for the duration of the study to reduce oral ingestion of residual test article.

N/A
Sponsor Date

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Study Director Da

Riker Experiment No.: 0979ABCK

APPENDIX I (Concluded)
Amendment to Protocol

1. Due to analysis of blood samples the proposed completion date will be extended to 3/81

K D O'Malley 10/10/79
Study Director Date

2. The Study director # corresponding number will be changed from K L Ebben (04) to K D O'MALLEY (09)

K D O'Malley 10/10/79
Study Director Date

3. Due to the type of study the 1-30min, 60min, 120min observations will not be taken on the range finder

K D O'Malley 10/10/79
Study Director Date

4. To expidite the study the weight range will be extended to 1.7 - 3.0 Kg

K D O'Malley 10/24/79
Study Director Date

5. _____
Study Director Date

6. _____
Study Director Date

7. _____
Study Director Date

8. _____
Study Director Date

APPENDIX II

Principal Participating Personnel Involved in the Study

Name	Function
K. L. Ebbens, BS	Supervisor, Acute Toxicology
K. D. O'Malley, BS	Advanced Toxicologist
Dr. V. Pothapragada	Study Director Commercial Chemicals Chemist
G. C. Pecore	Supervisor Animal Laboratory

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APPENDIX III

Composition Characteristics

This study is not regulated by the Good Laboratory Practice Regulation of 1978 and therefore information pertaining to composition characteristics is not applicable for inclusion in this study.

APPENDIX IV

Quality Assurance Statement

This study is not regulated by the Good Laboratory Practice Regulation of 1978 and therefore a statement signed and prepared by the Quality Assurance group is not applicable. This study was, however, audited by the Quality Assurance group.

In addition to the data audit, different significant phases for studies underway in the Toxicology Laboratory are inspected weekly on a recurring cycle, and the facilities are examined by Laboratory Quality Assurance on a three month schedule.

Internal Correspondence

cc: D. R. Ricker 53-4

FC: F. D. Griffith - 220-2E
F. A. Uhel - 220-2E

APPENDIX V

To: K. L. EBBENS - RIKER SAFETY EVALUATION LAB - 203-1

From: W. C. McCORMICK - MEDICAL DEPT. - TOXICOLOGY SERVICES - 220-2E

Subject: SKIN ABSORPTION STUDIES ON FC-143, FC-95, FC-99, FC-134, FC-135, FC-128, FC-129 and FC-98

Date: JUNE 27, 1980

3M

Please consider this an authorization for your laboratory to release the dermal toxicity/skin absorption studies conducted on the above mentioned compounds.

It is understood that the studies are being issued in an incomplete form insofar as the fluorochemical analysis of the serum samples have not been completed and will not be included in the report. Preliminary serum sample analysis indicates absorption of the compounds. The serum data analysis are not sufficient enough to draw any concrete conclusions concerning comparitive toxicity. However, the animal data you have generated addresses this matter in a broader context. It is not certain when the remaining samples will be analyzed and their completion should not hold up your report any longer.

Thank you for your patience in this matter.

W. C. McCormick

WCM:klh

Internal Correspondence

cc: E. B. Caldwell - 220-2E-02
R. A. Prokop - 236-2B
L. D. Winter - 236-2B

APPENDIX V (Concluded)

COMMERCIAL CHEMICALS DIVISION
ANALYTICAL LAB REPORT #146

To W. C. MCCORMICK - 220-2E-02

From V. POTHAPRAGADA AND V. BUNNELLE - 236-3A

Subject RIKER SKIN ABSORPTION STUDY

Date June 9, 1980

RECEIVED JUN 11 1980 M TOXICOLOGY 3M

Reference: Commercial Chemicals Division Analytical Request #15669

For lack of time, only a selected set of serum samples was analyzed.

	TOTAL F, ppm			
	Females		Males	
Compound	Day 1	Day 28	Day 1	Day 28
FC-129	26.1	69.6	11.4	23.3
FC-134	0.2	18.1	18.8	23.9
FC-128	4.4	16.5	1.6	10.5
FC-98	226.4	93.1	271.9	94.3
FC-135	6.9	20.8	2.3	7.6
FC-95	0.9	128.0	10.3	130.2
FC-99	42.5	111.5	129.1	73.5
	53.1	119.8	72.7	66.6

	Females			Males		
	Day 7	Day 14	Day 28	Day 7	Day 14	Day 28
FC-143	10.1	12.1	3.5	5.4	6.8	4.6

Method of Analysis: Oxygen Bomb/GC Technique (Jon Bellatti and D. F. Hagen, Anal. Biochem; 87, 545, 1978).

V. A. Bunnelle

V. A. Bunnelle

V. Pothapragada

Read and Reviewed by L. D. Winter

VAB/hc