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TOXICOLOGY

28 Day Percutaneous Absorption Study
with FC-98
in Albino Rabbits

Experiment No.:

0979AB0630

Conducted At:

Safety Evaluation Laboratory
Riker Laboratories, Inc.
St. Paul, Minnesota

Dates Conducted:

October 25, 1979 to December 17, 1979

Conducted By:

K. D. O'Malley 3/11/81
K. D. O'Malley, BS Date
Advanced Toxicologist
Study Director

Reviewed By:

K. L. Ebbens 3/15/81
K. L. Ebbens, BS Date
Supervisor, Acute Toxicology

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

Summary

A 28 day percutaneous absorption study with FC-98 was conducted from October 25, 1979 to December 17, 1979 at Riker Laboratories, Inc., St. Paul, Minnesota using male and female albino rabbits ranging in body weights from 1.88 to 2.30 kg. The test article was administered by dermal application to ten male and ten female rabbits each a dosage level of 5,000 mg/kg body weight for a 24 hour exposure period.^a 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 with no visible lesions noted. Preliminary serum analysis (see Appendix V) indicates dermal absorption of FC-98 in albino rabbits, however, due to the limited number of samples analyzed, no concrete conclusion may be drawn.

Introduction

The objective of this study^b was to determine the percutaneous absorption potential of FC-98 in male and female albino rabbits. The study, which was initiated at Riker Laboratories, Inc., St. Paul, Minnesota on October 25, 1979 and completed on December 17, 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 A preliminary rangefinder study was conducted to determine the appropriate dosage level to be used in this study.

^b Riker Toxicity Experiment No.: 0979AB0630, Test Method 699

Method

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, Kalston 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 pharmacotoxic 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

4.

ACUTE DERMAL RANGEFINDER TOXICITY STUDY - ALBINO RABBITS
with FC-98
Mortality and Body Weight Data

Dose ^a (mg/kg)	Sex	Animal Number	Individual Body Weights (kg)		<u>Number Dead</u>	Percent Dead
			<u>Test Day Number</u>		<u>Number Tested</u>	
			0	14		
5000	M	9B2599	2.37	2.53	0/4	0
	M	9B2602	2.41	2.62		
	F	9B2617	2.42	2.31		
	F	9B2614	2.15	2.52		
1000	M	9B2605	2.22	2.51	0/4	0
	M	9B2608	2.47	2.55		
	F	9B2618	2.25	2.16		
	F	9B2621	2.35	2.45		

^a Test article was dosed as a suspension in water

ACUTE PERCUTANEOUS ABSORPTION TOXICITY STUDY - ALBINO RABBITS

with FC-98

Mortality and Body Weight Data

Dose ^a (mg/kg)	Sex	Animal Number	Individual Body Weights (kg)				<u>Number Dead</u> Number Tested	Percent Dead
			Test Day Number					
			0	7	14	28		
5000	M	9B3041	2.16	2.58	2.47	2.63	0/10	0
	M	9B3047	2.30	2.03	2.27	2.68		
	M	9B3053	2.16	2.13	2.45	2.79		
	M	9B3059	2.15	2.10	2.33	2.54		
	M	9B3042	2.30	2.15	2.47	2.79		
	M	9B3049	2.11	1.96	2.11	2.37		
	M	9B3055	2.19	2.22	2.47	2.75		
	M	9B3061	2.18	2.22	2.31	2.46		
	M	9B3045	2.30	2.33	2.52	2.79		
	M	9B3051	2.22	2.15	2.38	2.70		
5000	F	9B2921	2.25	2.03	2.25	2.66	1/10	10
	F	9B2927	2.12	2.00	2.29	2.78		
	F	9B2933	2.18	1.87	2.01	2.37		
	F	9B2939	1.99	1.72	2.09	2.42		
	F	9B2923	2.08	1.99	2.30	2.65		
	F	9B2929	1.88	1.72	1.90	2.21		
	F	9B2935	2.11	2.14	2.33	2.85		
	F	9B2941	2.02	2.13	2.25	2.48		
	F	9B2925	2.12	1.98	1.70	<u>b</u>		
	F	9B2931	1.94	1.94	2.14	2.37		

^a Test article was dosed as a suspension in water^b Animal sacrificed on day 14 due to accidental back injury inflicted during the day 7 bleeding periodNecropsy

Necropsies performed on all animals upon termination of the study revealed no visible lesions. Animal 9B2925 which was sacrificed on day 14 due to posterior paralysis, also revealed no visible lesions.

TABLE 3

ACUTE DERMAL RANGEFINDER TOXICITY STUDY - ALBINO RABBITS

with FC-98

Summary of Reactions

Dose (mg/kg)	Sex	Reaction	Number Affected		Time of Onset Following Dose Administration	Cessation of Reaction Following Dose Administration		Time of Death Following Dose
			Number	Dosed				
5000	M	No significant reactions noted			----		----	----
	F	No significant reactions noted			----		----	----
1000	M	No significant reactions noted			----		----	----
	F	No significant reactions noted			----		----	----

TABLE 4

ACUTE PERCUTANEOUS TOXICITY STUDY - ALBINO RABBITS

with FC-98

Summary of Reactions

Dose (mg/kg)	Sex	Reaction	Number Affected		Time of Onset Following Dose Administration	Cessation of Reaction Following Dose Administration		Time of Death Following Dose
				Number Dosed				
5000	M	No significant reactions noted			----		----	----
	F	No significant reactions noted			----		----	----

APPENDIX I
PROTOCOL

8.

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-98 Lot 315
CONTROL ARTICLE: N/A
PROPOSED STARTING/COMPLETION DATE OF STUDY: 11-79 / 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 5,000 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 / 11/7/79
Sponsor Date

W. O. O'Malley / 11/7/79
Study Director Date

TEST: Acute Dermal Toxicity Ranges Finding Study
SPONSOR: 3M Commercial Chemical
CONDUCTED BY: Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minne
TEST ARTICLE: EC-98
CONTROL ARTICLE: N/A
PROPOSED STARTING/COMPLETION DATE OF STUDY: 11/79 - 1/80
TEST SYSTEM AND SOURCE: New Zealand White Albino Rabbits Sex: 2/16
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 500, 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 animal. 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 stored 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 _____

K. D. M. Kelly
Study Director _____ 11/20/79
D

1. Due to the unavailability of rabbits, the 2,000 mg/kg dosage group will be omitted in the remaining studies.

K.D. Malley 10/24/98
 Study Director Date

2. The 1-minute and 15-minute observations were deleted in the remaining studies due to the type of study.

K.D. Malley 10/30/99
 Study Director Date

3. The study director's corresponding number for the body in the study will be changed to K.D. Malley (09) from (04) in all studies.

K.D. Malley 11/12/99
 Study Director Date

4. The weight range was extended to 1.8-30 kg in order to initiate the study.

K.D. Malley 11/20/99
 Study Director Date

5. Due to a delay in report processing and sponsor communication, the completion date is extended to 3/98.

K.D. Malley 7/16/98
 Study Director Date

- 6.
- Study Director Date

- 7.
- Study Director Date

- 8.
- Study Director Date

Principal Participating Personnel Involved in the Study

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

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 IVQuality 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.

APPENDIX 5

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 comparative 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:k1h

R. A. Prokop - 236-2B

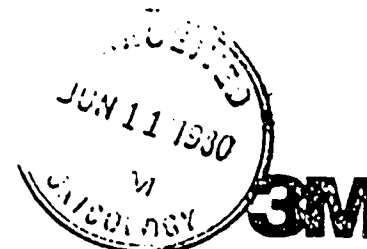
L. D. Winter - 236-2B

15.

APPENDIX B (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



Reference: Commercial Chemicals Division Analytical Request
 #15669

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

Compound	TOTAL F, ppm			
	Females		Males	
	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

Compound	Females			Males		
	Day 7	Day 14	Day 28	Day 7	Day 14	Day 28
	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 Bellido and
 D. F. Hagen, Anal. Biochem; 87, 545, 1978).

V. A. Bunnelle
 V. A. Bunnelle

VAB/hc

V. Pothapragada
 V. Pothapragada

Read and Reviewed
 by L. D. Winter

[Signature]