T-3989

AR226-0224

28 Day Percutaneous Absorption Study with FC-129 in Albino Rabbits

Experiment No.: 0979AB0627

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, BS — Date
Advanced Toxicologist
Study Director

Reviewed By:

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-129 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 1.75 to 2.42 kg. The test article was administered by dermal application to ten male and ten female rabbits at a dosage level of 5,000 mg/kg body weight for a 24 hour exposure period.[a] Six mortalities were noted which occurred between days two and three. The untoward behavioral reactions which were noted during the 28 day study consisted of lethargy, hypoactivity, prostration and blood was noted the urine. Onset of the reactions occurred from day 1 to day 6 and all reactions subsided by day 7 or death precluded recovery. Body weight losses were noted in two of the animals which survived the observation period. Necropsies of animals which died acutely, generally revealed pale, mottled livers and blood in the urine with one animal exhibiting a dark green spot on the brain. Necropsies were also performed on animals which survived the study period and revealed no visible lesions, with the exception of one animal which had an atrophic spleen. Preliminary serum analysis (see Appendix V) indicates dermal absorption of FC-129 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[b] was to determine the percutaneous absorption potential of FC-129 in male and female albino rabbits. The study, which was initiated at Riker Laboratories, Inc., St. Paul, Minnesota on October 24, 1979

a A preliminary rangefinder study was conducted to determine the appropriate dosage level to be used in this study.

b Riker Toxicity Experiment No.: 0979AB0627, Test Method 699

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.

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, 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 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

ACUTE DERMAL RANGEFINDER TOXICITY STUDY - ALBINO RABBITS

with FC-129

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	9B2593	2.22	1.29	0/4	0
	M	9B2591	2.19	1.44		
	F	9B2689	2.07	1.41		
	F	9B2646	2.26	2.03		
2000	M	9B2594	2.10	1.76	0/4	0
	M	9B2597	2.09	2.00		
	F	9B2684	2.17	2.14		
	F	9B2687	2.02	1.87		
1000	M	9B2574	2.20	2.31	0/4	0
	M	9B2577	2.29	2.37		
	F	9B2690	2.37	2.24		
	F	9B2693	2.16	2.18		

[a] Test article was dosed undiluted

TABLE 2

ACUTE PERCUTANEOUS ABSORPTION TOXICITY STUDY - ALBINO RABBITS

with FC-129

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	9B3056	2.20	1.82	1.78	2.18	1/10	10
	M	9B3062	2.40	1.97	2.11	2.41		
	M	9B3057	2.42	2.14	2.43	2.75		
	M	9B3063	2.10	(2 Days)	----	----		
	M	9B3072	1.75	1.91	2.12	2.44		
	M	9B3077	2.04	2.04	2.05	2.30		
	M	9B3032	2.04	1.59	1.73	2.18		
	M	9B3038	2.38	2.15	2.37	2.45		
	M	9B3033	2.36	2.23	2.23	2.60		
	M	9B3039	2.28	1.98	2.25	2.42		
5000	F	9B2985	2.23	(3 Days)	----	----	5/10	50
	F	9B2991	2.17	(3 Days)	----	----		
	F	9B2936	2.23	(2 Days)	----	----		
	F	9B2942	2.00	1.61	1.56	1.84		
	F	9B2960	2.37	(2 Days)	----	----		
	F	9B2966	2.07	1.70	2.05	2.43		
	F	9B2955	1.87	1.89	2.15	2.44		
	F	9B2967	2.04	1.81	2.05	2.33		
	F	9B2937	1.98	1.72	2.04	2.32		
	F	9B2943	2.05	(2 Days)	----	----		

[a] Test article was dosed undiluted

Necropsy

Necropsies performed on animals which died acutely, generally revealed pale mottled liver and blood in urine, with one animal having a dark green spot on the brain. Animals which were sacrificed upon termination of the study revealed no visible lesions, with the exception of one animal which had an atrophic spleen.

TABLE 3

ACUTE DERMAL RANGEFINDER TOXICITY STUDY - ALBINO RABBITS

with FC-129

Summary of Reactions

Dose (mg/kg)	Sex	Reaction	Number Affected / Number Dosed	Time of Onset [a] Following Dose Administration	Cessation of Reaction [b] Following Dose Administration	Time of Death Following Dose
5000	M	Hypoactivity	2/2	Day 9	until termination	---
	F	No significant reactions		---	---	---
2000	M	No significant reactions		---	---	---
	F	No significant reactions		---	---	---
1000	M	No significant reactions		---	---	---
	F	No significant reactions		---	---	---

[a] Time when first animal in the dose group exhibited the reaction
[b] Time when no animal in the dose group exhibited the reaction

TABLE 4

ACUTE PERCUTANEOUS ABSORPTION TOXICITY STUDY - ALBINO RABBITS

with FC-129

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	Hypoactivity	1/10	Day 6	Day 7	
		Lethargy	2/10	Day 5	Day 6	
		Prostration	1/10	Day 1	Until death	Day 2
		Blood in urine	1/10	Day 1	Until death	Day 2
5,000	F	Hypoactivity	4/10	Day 1	Day 3	
		Prostration	1/10	Day 1	Until death	Day 2
		Blood in urine	2/10	Day 1	Until death	Day 2

[a]/[b] Time when first animal in the dose group exhibited the reaction
[a]/[b] Time when no animal in the dose group exhibited the reaction

APPENDIX I
PROTOCOL

TEST: Single Dose 28 Day Percutaneous Absorption Study
SPONSOR: 3M Commercial Chemicals Division
CONDUCTED BY: Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minnesota
TEST ARTICLE: FC-129 Lot 510
CONTROL ARTICLE: N/A
PROPOSED STARTING/COMPLETION DATE OF STUDY: 11-79 / 1-80
TEST SYSTEM AND SOURCE: New Zealand White Albino Rabbits
Pel Freez, Inc., Rogers, Arkansas
Sex: M+F
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 /kpe 11/7/79
Sponsor Date

K D O'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-129
CONTROL ARTICLE: N/A
PROPOSED STARTING/COMPLETION DATE OF STUDY: 11/79 - 1/80
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 5(C), 2,000, 1,000 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

KD Malley 11/2/79
Study Director Da

APPENDIX I (Concluded)
Amendment to Protocol

Riker Experiment No.: 0979AB0627

1. The 1-5 minute, 60 and 120 minute observations will be omitted due to the nature of the range finder.

K.D. Smalley 10/24/79
Study Director Date

2. The study designation numbers will be changed from 004 (K.L. Zahnow) to 009 (K.D. Smalley)

K.D. Smalley 10/24/79
Study Director Date

3. The weight range is extended to 1.7-30 kg in order to initiate the study

K.D. Smalley 11/20/79
Study Director Date

4. Due to delays in sponsor serum analyses and report processing, the completion date is extended to 3/80

K.D. Smalley 7/16/80
Study Director Date

5. _____

Study Director Date

6. _____

Study Director Date

7. _____

Study Director Date

8. _____

Study Director Date

11.

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 Study Director
Dr. V. Pothapragada	Commercial Chemicals Chemist
G. C. Pecore	Supervisor Animal Laboratory

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.