SafePharm Laboratories

13F-SFA-MONOMER:

ACUTE DERMAL IRRITATION IN THE RABBIT

SPL PROJECT NUMBER: 1458/0062

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QUALITY ASSURANCE REPORT

This study type is classed as short-term. The standard test method for this study type ("General Study Plan" in OECD terminology) was reviewed for compliance once only on initial production. Inspection of the routine and repetitive procedures that constitute the study is carried out as a continuous process designed to encompass the major phases at or about the time this study was in progress.

This report has been audited by Safepharm Quality Assurance Unit, and is considered to be an accurate account of the data generated and of the procedures followed.

In each case, the outcome of QA evaluation is reported to the Study Director and Management on the day of evaluation. Audits of study documentation, and process inspections appropriate to the type and schedule of this study were as follows:

	15 June 2004	Standard Test Method Compliance Audit
	23 January 2007	Test Material Preparation
	09 January 2007	Animal Preparation
	09 January 2007	Dosing
	13 January 2007	Assessment of Response
§	20 March 2007	Draft Report Audit
§	Date of QA Signature	Final Report Audit

§ Evaluation specific to this study

..... DATE: 03 APR 2007

For Safepharm Quality Assurance Unit*

***Authorised QA Signatures:**
Head of Department:
Deputy Head of Department:
Senior Audit Staff:

GLP COMPLIANCE STATEMENT

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106 as amended by SI 2004/0994)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 2004/9/EC and 2004/10/EC.

These international standards are acceptable to the Regulatory agencies of the following countries: Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Republic of Korea, Luxembourg, Mexico, The Netherlands, New Zealand, Norway, Poland, Portugal, Slovenia, South Africa, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the United States of America.

This report fully and accurately reflects the procedures used and data generated.

..... DATE: 28/3/07

Study Director

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SUMMARY

Introduction. The study was performed to assess the irritancy potential of the test material to the skin of the New Zealand White rabbit. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 404 "Acute Dermal Irritation/Corrosion" (adopted 24 April 2002)
- Method B4 Acute Toxicity (Skin Irritation) of Commission Directive 2004/73/EC

Results. A single 4-hour, semi-occluded application of the test material to the intact skin of three rabbits produced very slight erythema. One treated skin site appeared normal at the 24-hour observation and the remaining two treated skin sites appeared normal at the 72-hour observation.

3-minute and 1-hour semi-occluded applications of the test material to the intact skin of one rabbit produced no evidence of skin irritation.

Conclusion. The test material produced a primary irritation index of 0.3 and was classified as a mild irritant to rabbit skin according to the Draize classification scheme.

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1. INTRODUCTION

The study was performed to assess the irritancy potential of the test material following single, 3-minute, 1 and 4-hour, semi-occluded applications to the intact rabbit skin. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 404 "Acute Dermal Irritation/Corrosion" (adopted 24 April 2002)
- Method B4 Acute Toxicity (Skin Irritation) of Commission Directive 2004/73/EC

The albino rabbit has been shown to be a suitable model for this type of study and is recommended in the test method. The results of the study are believed to be of value in predicting the likely skin irritancy potential of the test material to man.

The study was performed between 17 January 2007 and 26 January 2007.

2. TEST MATERIAL

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	13F-SFA-MONOMER
Description	:	clear colourless liquid
Batch number	:	061115
Date received	:	24 November 2006
Storage conditions	:	room temperature in the dark

The integrity of supplied data relating to the identity, purity and stability of the test material is the responsibility of the Sponsor.

2.2 Preparation of Test Material

For the purpose of the study the test material was used as supplied.

The absorption of the test material was not determined.

2.3 Measurement of pH

The pH of the test material was determined prior to commencement of the study and found to be as follows:

Preparation	pH Measurement	
	immediately	after 10 minutes
Undiluted as Supplied	approximately 5.0	not applicable
90% v/v aqueous preparation of the test material	4.4	4.0

3. METHODS

3.1 Animals and Animal Husbandry

Three New Zealand White rabbits were supplied by an accredited supplier. At the start of the study the animals were in the weight range of 2.0 to 3.5 kg and were twelve to twenty weeks old. After an acclimatisation period of at least five days each animal was given a number unique within the study which was written with a black indelible marker-pen on the inner surface of the ear and on the cage label.

The animals were individually housed in suspended cages. Free access to mains drinking water and food (Certified Rabbit Diet) was allowed throughout the study. The diet and drinking water were considered not to contain any contaminant of a level that might have affected the purpose or integrity of the study.

The temperature and relative humidity were set to achieve limits of 17 to 23°C and 30 to 70% respectively. Any occasional deviations from these targets were considered not to have affected the purpose or integrity of the study. The rate of air exchange was at least fifteen changes per hour and the lighting was controlled by a time switch to give twelve hours continuous light (06:00 to 18:00) and twelve hours darkness.

The animals were provided with environmental enrichment items which were considered not to contain any contaminant of a level that might have affected the purpose or integrity of the study.

3.2 Procedure

On the day before the test each rabbit was clipped free of fur from the dorsal/flank area using veterinary clippers. Only animals with a healthy intact epidermis by gross observation were selected for the study.

One rabbit was initially treated. Three suitable sites were selected on the back of the rabbit. At each test site a quantity of 0.5ml of the test material was introduced under a 2.5 cm x 2.5 cm cotton gauze patch and placed in position on the shorn skin. Each patch was secured in position with a strip of surgical adhesive tape. To prevent the animal interfering with the patches, the trunk of the rabbit was wrapped in an elasticated corset for the duration of the 1 and 4 hour exposure periods.

One patch was removed at each of three time points: 3 minutes, 1 hour and 4 hours after application. Any residual test material was removed by gentle swabbing with cotton wool soaked in 74% Industrial Methylated Spirits.

After consideration of the skin reactions produced in the first animal, two additional animals were treated with 0.5 ml of test material. One patch was applied to the back of each rabbit, and was allowed to remain in contact with the skin for a period of four hours.

Approximately one hour following the removal of the patches, and 24, 48 and 72 hours later, the test sites were examined for evidence of primary irritation and scored according to the following scale:

EVALUATION OF SKIN REACTIONS

Erythema and Eschar Formation	**Value**
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beef redness) to eschar formation preventing grading of erythema	4

Oedema Formation	
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well-defined by definite raising)	2
Moderate oedema (raised approximately 1 millimetre)	3
Severe oedema (raised more than 1 millimetre and extending beyond the area of exposure)	4

Any other skin reactions, if present, were also recorded.

3.3 Interpretation of Results

Calculation of Primary Irritation Index and Grading of Irritancy Potential Using the Draize Scheme

The scores for erythema and oedema at the 24 and 72-hour readings were totalled for the three test rabbits (12 values) and this total was divided by six to give the primary irritation index of the test material. The test material was classified according to the following scheme devised by Draize J H (1959) "Dermal Toxicity" In: Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. Association of Food and Drug Officials of the United States, Austin, Texas, p.47:

Primary Irritation Index	Classification of Irritancy
0	Non-irritant
> 0 to 2	Mild irritant
> 2 to 5	Moderate irritant
> 5 to 8	Severe irritant

If irreversible alteration of the dermal tissue is noted in any rabbit, as judged by the Study Director, which include ulceration and clear necrosis or signs of scar tissue, the test material is classified as corrosive to rabbit skin. Classification according to Draize may, therefore, not be applicable.

4. ARCHIVES

Unless instructed otherwise by the Sponsor, all original data and the final report will be retained in the Safepharm archives for five years, after which instructions will be sought as to further retention or disposal.

5. RESULTS

5.1 4-Hour Exposure Period

The individual scores for erythema/eschar and oedema are given in Table 1.

Very slight erythema was noted at two treated skin sites one hour after patch removal and at two treated skin sites at the 24 and 48-hour observations.

One treated skin site appeared normal at the 24-hour observation and the remaining two treated skin sites appeared normal at the 72-hour observation.

5.2 1-Hour Exposure Period

The individual scores for erythema/eschar and oedema are given in Appendix 1.

No evidence of skin irritation was noted during the study.

5.3 3-Minute Exposure Period

The individual scores for erythema/eschar and oedema are given in Appendix 1.

No evidence of skin irritation was noted during the study.

6. CONCLUSION

The test material produced a primary irritation index of 0.3 and was classified as a MILD IRRITANT to rabbit skin according to the Draize classification scheme. No corrosive effects were noted.

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Table 1 Individual Skin Reactions Following 4-Hour Exposure

Skin Reaction	Observation Time	Individual Scores – Rabbit Number and Sex			Total
		65608 Male	65654 Male	65655 Male	
Erythema/Eschar Formation	1 Hour	0	1	1	(2)
	24 Hours	1	0	1	2
	48 Hours	1	0	1	(2)
	72 Hours	0	0	0	0
Oedema Formation	1 Hour	0	0	0	(0)
	24 Hours	0	0	0	0
	48 Hours	0	0	0	(0)
	72 Hours	0	0	0	0
Sum of 24 and 72-hour Readings (S)	:	2			
Primary Irritation Index (S/6)	:	2/6 = 0.3			
Classification	:	MILD IRRITANT			

( ) = Total values not used for calculation of primary irritation index

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Appendix 1 Individual Skin Reactions Following 1-Hour and 3-Minute Exposures

Skin Reaction	Observation Time	Individual Scores - Rabbit Number and Sex	
		65608 Male	
		1-Hour Exposure	3-Minute Exposure
Erythema/Eschar Formation	1 Hour	0	0
	24 Hours	0	0
	48 Hours	0	0
	72 Hours	0	0
Oedema Formation	1 Hour	0	0
	24 Hours	0	0
	48 Hours	0	0
	72 Hours	0	0

Appendix 2 Statement of GLP Compliance in Accordance with Directive 2004/9/EC

THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE IN ACCORDANCE WITH DIRECTIVE 2004/9/EC

LABORATORY

SafePharm Laboratories Ltd.
Shardlow Business Park
London Road
Shardlow
Derby
DE72 2GD

TEST TYPE

Analytical Chemistry
Environmental Fate
Environmental Toxicity
Mutagenicity
Phys/Chem Testing
Toxicology

DATE OF INSPECTION

30th August 2005

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of the UK GLP Compliance Programme.

At the time of inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

/05.

Head, UK GLP Monitoring Authority