

8(e)

CIBA-GEIGY

8EHQ-1292-8684

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December 30, 1992

Document Processing Center (TS-790)
 (Attention: Section 8(e) Coordinator)
 Office of Pollution Prevention and Toxics
 Environmental Protection Agency
 401 M St., SW
 Washington, DC 20460



8EHQ-93-8684
 INIT 01/07/93



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Dear Section 8(e) Coordinator:

Subject: TSCA 8(e) Notice - CGI 403

CIBA-GEIGY Corporation claims no information in this letter or the attached toxicity study as Confidential Business Information.

In accordance with EPA's March 16, 1978 policy statement on Section 8(e) reporting under the Toxic Substances Control Act, and EPA's June, 1991 TSCA Section 8(e) Reporting Guide, CIBA-GEIGY Corporation wishes to bring to the attention of the Environmental Protection Agency dermal sensitization results seen in the guinea pig with CGI 403. CGI 403, identified as TKA 40049 in the study, is bis(2,6-dimethoxybenzoyl)-2,4,4-trimethylpentylphosphine oxide. A CAS Registry Number has been requested from Chemical Abstracts Services but has not been received.

CGI 403 is an experimental photoinitiator for coatings. It has not yet been distributed outside of CIBA-GEIGY Corporation; we have conducted process development work in our facilities in the U.S. A PMN will be submitted soon. The present submission is a skin sensitization test (maximization test). Challenged animals showed a 70 and 90% positive response for the 24- and 48-hour observation period, respectively. Under the maximization scheme, this product would be classified as an extreme skin sensitizer. A copy of the study, entitled "Skin Sensitization Test in the Guinea Pig Maximization Test. Test No. 924186. TKA 40049 (CGI 403) Report", is enclosed.

CIBA-GEIGY Corporation will create a Material Safety Data Sheet and label to reflect this new information and to notify its workers in accordance with the OSHA Hazard Communication Standard (29 CFR 1910.1200).

Please call the undersigned if you have any questions about this submittal.

32 pgs.

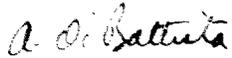
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Section 8(e) Coordinator
page 2 of 2

Very truly yours,

CIBA-GEIGY Corporation



Anthony DiBattista
Manager
Regulatory Affairs and Toxic Substance Compliance
Toxicology, Regulatory Auditing and Compliance.

Enclosure: Submitted study

Skin Sensitisation Test in the Guinea Pig

Maximisation Test

Test No. 924106

TKA 40049 (CGI 403)

Report

Study Director: Dr. med.vet. Ch. Hagemann

Testing Facility: CIBA-GEIGY Limited
Toxicology Services
Short-term Toxicology
4332 Stein / Switzerland

Test Guideline: OECD 406 / 84/449/EEC B.6.

Starting date: October 19, 1992

Completion date: November 3, 1992

Sponsor: CIBA-GEIGY Limited
Additives Division
4002 Basel / Switzerland

This report contains: 30 pages

Skin Sensitisation Test in the Guinea Pig
Test No.: 924166
Test Article: TKA 40015

2

0.1. Proprietary information

Proprietary information of CIBA-GEIGY Limited.
Not to be disclosed to third parties without previous consent
of CIBA-GEIGY Limited.

Skin Sensitisation Test in the Guinea Pig

3

Test No.: 924166
Test Article: TKA 40049

0.2. Certification of GLP and verification of the report

(Certification of Good Laboratory Practice and verification of a complete and unaltered copy of the report by the sponsor)

To the best of my knowledge and belief, the statement of compliance with Good Laboratory Practice found on page 4 of this report, and signed by the Study Director is truthful and accurate, and this report as provided by the testing facility is complete and unaltered.

For the Sponsor:

Signature:

V. Chiriac Date: *November 19, 1992*

9.3. Statement of compliance with Good Laboratory Practice

To the best of my knowledge and belief this study has been performed in compliance with Good Laboratory Practice (GLP) in Switzerland, Procedures and Principles, March 1986 (Verfahren und Grundsätze der Guten Laborpraxis (GLP) in der Schweiz), issued by the Swiss Federal Department of the Interior and the Intercantonal Office for the Control of Medicaments. These procedures are in essence consistent with:

- OECD Principles of Good Laboratory Practice (Council Decision 81/30, adopted on May 12, 1981, and the OECD Recommendation 83/95 concerning the 'Mutual Recognition of Compliance with Good Laboratory Practice', adopted on July 26, 1983).
- United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 160 (FIFRA); Federal Register, August 17, 1989.
- United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 792 (TSCA); Federal Register, August 17, 1989.
- Japan Ministry of Agriculture, Forestry and Fisheries, NohSan, Notification No. 3850, Agricultural Production Bureau, August 10, 1984.

Study director: Dr. med.vet. Ch. Hagemann

Signature:

Ch. Hagemann

Date:

November 3, 1992

Skin sensitisation test in the Guinea Pig
Test No.: 924166
Test Article: TKA 40049

5

0.4. Signatures

This report represents the results of the investigations compiled by the undersigned:

Study director: Dr. med.vet. Ch. Hagemann

Signature:

Ch. Hagemann Date: *November 3, 1992*

For facility
management:

Dr. phil. II W. Basler

Signature:

W. Basler Date: *November 3, 1992*

Skin Sensitisation Test in the Guinea Pig
Test No.: 924166
Test Article: TKA 40049

6

0.5. Reserved page for flagging statements

8

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Skin Sensitisation Test in the Guinea Pig
Test No.: 924166
Test Article: TKA 40049

7

Quality assurance statement

Test Article: TKA 40049
Study Title: Skin Sensitisation Test in the Guinea Pig
Test Number: 924166
Study Director: Dr. med.vet. Ch. Hagemann

I hereby certify that the following Quality Assurance activities were performed:

<u>QA-Activity</u>	<u>Date performed</u>	<u>Date reported</u>
Facility Inspection	17.09.92	30.09.92
Protocol Audit	21.10.92	21.10.92
Study Inspection	21.10.92	22.10.92
Final Report Audit	02.11.92	02.11.92

Quality Assurance Inspector: D. Baltisberger

Signature:

D. Baltisberger

Date:

12.11.92

Skin Sensitisation Test in the Guinea Pig
Test No.: 924166
Test Article: TKA 40049

8

1. SUMMARY AND CONCLUSION

70 and 90% of the animals were sensitised by TKA 40049 under the experimental conditions employed

According to the maximisation grading TKA 40049 showed an extreme grade of skin-sensitising (contact allergenic) potential in albino guinea pigs.

2. GENERAL

2.1. Introduction

At the request of the Additives Division of CIBA-GEIGY Limited, a sensitisation test in albino guinea pigs was performed to determine the contact allergenic potency of TKA 40049 in albino guinea pigs.

This test was based on the OECD Guideline No. 406, adopted May 12, 1981, adapted July 17, 1992, by the OECD Council, and on Annex V, Part B of Council Directive 79/831/EEC (Commission Directive 84/449/EEC of April 25, 1984).

Experimental starting date: September 22, 1992

Experimental termination date: October 22, 1992

Testing facility: CIBA-GEIGY Limited
Toxicology Services
Short-term Toxicology
4332 Stein/Switzerland

2.2. Archives

Archives are located at CIBA-GEIGY Limited, Werk Stein, CH-4332 Stein, Switzerland. Raw data, protocol and report will be stored at this location.

2.3. Distribution

Dr. H.J. Wendeli (for the sponsor)
Archives

Skin Sensitisation Test in the Guinea Pig

9

Test No.: 924166
Test Article: TKA 40049

2.4. Test material

Test article: TKA 40049
Batch No.: FZ Marly-WSH, dried
Trade name: CGI 403
Purity: see AC 925024
Physical properties: solid; light yellow
Storage conditions: room temperature
Validity: June, 1995
Test article received: August 17, 1992

2.5. Auxiliary compounds

- Physiological saline (0.9 %), sterile solution (Hausmann, St. Gallen, Switzerland)
- Bacto Adjuvant, Complete, Freund (Difco Lab. Detroit, Michigan USA)
- Vaseline (white petrolatum) Ph. H. VI (Siegfried AG, Zofingen, Switzerland)
- Oleum arachidis Ph. H. VI (Siegfried AG, Zofingen, Switzerland)

2.6. Test System

The albino guinea pig is the recommended species for skin sensitisation studies.

Animal strain: Pirbright White Strain (Tif: DHP)
Breeder: CIBA-GEIGY Limited
Animal Production
4332 Stein / Switzerland
Date of acclimatisation: September 17, 1992

2.7. Group Size and Husbandry

The test was performed on 10 male and 10 female guinea pigs in the test group and 5 males and 5 females in the control group, respectively, initially weighing between 346 to 444 g.

The animals were housed individually in Macrolon cages (Type 3) assigned to the different groups by means of random numbers generated by the random number generator, identified by individual ear tags, kept at a constant room temperature of $22 \pm 3^{\circ}\text{C}$, at a relative humidity of 30 to 70% and a 12 hours light cycle day.

The animals received a libitum standard guinea pig diet (NRFAG No. 345, Gossau) and fresh water.

All batches of the diet were checked for nutritive ingredients and contamination level by the manufacturer. Analytical results are available at the animal supply office.

The drinking water quality fulfilled the critical parameters in the specifications of the "Schweizerisches Lebensmittelbuch" (Edition 1972). The results of the routine chemical examination of water at source (Grundwasserfassung Stein) as conducted periodically by the water authority (Baudepartement des Kantons Aargau Abteilung Gewaesserschutz) are available to CIBA-GEIGY Limited, as well as the results of inhouse chemical analysis by the analytical laboratories of the Pharmaceutical Division, CIBA-GEIGY Limited.

2.8. Sensitivity of strain

The sensitivity of the strain is checked every six months with a known sensitiser, such as 2,4-dinitrochlorobenzene, para-phenylene-diamine or potassium-dichromate.

The results of the latest positive control test are presented in Appendix 3 of this report.

3. METHODS

3.1. Reason for selection

The maximisation test has been selected, because it is one of the recommended tests in the OECD guideline 406, adopted May 12, 1981, adapted July 17, 1992, as well as in Annex V, Part B of Council Directive 79/831/EEC (Commission Directive 84/449/EEC of April 25, 1984), and because the sensitivity of the method is well known. The test has been performed according to the original protocol of Magnusson and Kligman (J. invest. Dermatol. 52, 268-276, 1969; Contact Dermatitis 6, 46-50, 1980).

3.2. Test procedure

3.2.1. Induction procedure (weeks 1 and 2)

The induction was a two-stage operation. First, intradermal injections (into the neck region); second, closed patch exposure over the injection sites one week later.

First induction week, intradermal injection

Three pairs of intradermal injections (0.1 ml per injection) were made simultaneously into the shaved neck of the guinea pigs as follows:

- adjuvant/saline mixture 1:1 (v/v)
- test article TKA 40049 in Oleum arachidis (w/v)
- test article TKA 40049 in the adjuvant/saline mixture (w/v)

Second induction week, epidermal application

In the second week of induction TKA 40049 was incorporated in vaseline (w/w) and applied on a filterpaper patch to the neck of the animals (patch 2x4 cm; approx. 0.4 g paste per patch; occluded administration for 48 hours).

3.2.2. Rest period

During weeks 3 and 4 no treatments were performed.

3.2.3. Challenge (week 5)

The animals were tested on the flank with TKA 40049 in vaseline (w/w) and the vehicle a one (patch 2x2 cm; approx. 0.2 g paste per patch; occluded administration for 24 hours).

3.2.4. Control group

A control group of 10 animals (5 m, 5 f) was treated with adjuvant and the vehicle during the induction period. During the challenge period the group was treated with the vehicle as well as with the test article to check the maximum subirritant concentration of the test article in adjuvant treated animals.

3.3. Concentrations

3.3.1. Intradermal Induction

The concentration for the intradermal injections was selected on account of the solubility of the test article in standard vehicles and its local and systemic tolerability in a pretest. The following concentrations of test article have been prepared for intradermal injection:

5 % in Oleum arachidis.

Since 5% TKA 40049 in Oleum arachidis could be injected and was well tolerated, this concentration was used for the intradermal induction.

- 5% TKA 40049 in Oleum arachidis (w/v)

- 5% TKA 40049 in the adjuvant/saline mixture (w/v)

3.3.2. Epidermal Applications (induction and challenge)

The concentrations for the epidermal applications were selected on account of the primary irritation potential of the test article. The following concentrations of TKA 40049 have been examined on separate animals for the determination of the maximum subirritant concentration (see also Table 4):

1, 5, 10, 20, 30, and 50% in vaseline.

Skin Sensitisation Test in the Guinea Pig

13

Test No.: 924166
Test Article: TKA 40049

The tested concentrations did not induce erythema reactions, therefore the following concentration was selected:

Epidermal induction

Concentration of test article: 50%
Vehicle: vaseline

No skin irritation was observed in the pretest. Therefore the application site was pretreated with 10% sodium-laurylsulfate (open application) 24 hours prior to the epidermal induction application.

Epidermal challenge

Concentration of test article: 50%
Vehicle: vaseline

3.4. Observations and records

Induction reactions

After the intradermal and the epidermal induction application irritant reactions are normally induced by the adjuvant, the high test article concentration, or the sodium lauryl sulfate pretreatment. Because most of the reactions are treatment related and not compound related, the reactions are only described in special cases in the section of results.

Challenge reactions

Twenty four and forty eight hours after removing the dressings, the challenge reactions were graded according to the Draize scoring scale (Appendix 1).

General

The sensitising potential of TKA 40049 was classified according to the grading of Magnusson and Kligman (Appendix 2).

The body weight was recorded at start and end of the test.

4. RESULTS

The incidence of positive animals per group, the individual challenge reactions and the evaluation of the primary skin irritation potential are listed in Tables 1, 2, 3 and 4.

The individual animal weights at start and end of the test are listed in Table 5.

Under the experimental conditions employed, 70 and 90% of the animals of the test group showed skin reactions 24 and 48 hours after removing the dressings, respectively.

TKA 40049 is, therefore, classified as an extreme sensitiser in albino guinea pigs according to the grading of Magnusson and Kligman.

5. TABLES

TABLE 1

Number of positive animals per group after occlusive
epidermal application

Control group:

	after 24 hours	after 48 hours
vehicle control	0/10	0/10
test article	0/10	0/10

Test group:

	after 24 hours	after 48 hours
vehicle control	0/20	0/20
test article	14/20	18/20

TABLE 2

Challenge reactions after epidermal application
(CONTROL GROUP)

DRAIZE Score 24 hours after removal of the dressing

Vehicle control

Male animals 81 82 83 84 85

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Female animals 86 87 88 89 90

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Test article control

Male animals 81 82 83 84 85

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Female animals 86 87 88 89 90

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Skin Sensitisation Test in the Guinea Pig
Test No.: 924166
Test Article: TKA 40049

17

DRAIZE Score 48 hours after removal of the dressing

Vehicle control

Male animals 81 82 83 84 85

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Female animals 86 87 88 89 90

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Test article control

Male animals 81 82 83 84 85

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Female animals 86 87 88 89 90

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

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Skin Sensitisation Test in the Guinea Pig

18

Test No.: 924166
 Test Article: TKA 40049

TABLE

Challenge reactions after epidermal application
 (TEST GROUP)

DRAIZE Score 24 hours after removal of the dressing

Vehicle control

Male animals	61	62	63	64	65	66	67	68	69	70
Erythema score:	0	0	0	0	0	0	0	0	0	0
Edema score:	0	0	0	0	0	0	0	0	0	0

Female animals	71	72	73	74	75	76	77	78	79	80
Erythema score:	0	0	0	0	0	0	0	0	0	0
Edema score:	0	0	0	0	0	0	0	0	0	0

Test article

Male animals	61	62	63	64	65	66	67	68	69	70
Erythema score:	1	1	1	2	0	0	2	2	2	0
Edema score:	0	0	0	0	0	0	0	0	0	0

Female animals	71	72	73	74	75	76	77	78	79	80
Erythema score:	1	1	2	2	1	0	1	1	0	0
Edema score:	0	0	0	1	0	0	0	0	0	0

Skin Sensitisation Test in the Guinea Pig
Test No.: 924166
Test Article: TKA 40049

19

DRAIZE Score 48 hours after removal of the dressing

Vehicle control

Male animals	61	62	63	64	65	66	67	68	69	70
Erythema score:	0	0	0	0	0	0	0	0	0	0
Edema score:	0	0	0	0	0	0	0	0	0	0

Female animals	71	72	73	74	75	76	77	78	79	80
Erythema score:	0	0	0	0	0	0	0	0	0	0
Edema score:	0	0	0	0	0	0	0	0	0	0

Test article

Male animals	61	62	63	64	65	66	67	68	69	70
Erythema score:	1	2	1	2	1	0	1	2	2	1
Edema score:	0	1	0	1	0	0	0	1	0	0

Female animals	71	72	73	74	75	76	77	78	79	80
Erythema score:	1	2	2	2	1	1	1	1	0	1
Edema score:	0	1	0	2	0	0	0	0	0	0

TABLE 4

Evaluation of the primary skin irritation potential

Procedure: On each animal 2 concentrations of TKA 40049 were applied simultaneously on the left and right flank. A naive skin site served as control (not reported).

score 24 hours score 48 hours
after removing the dressing

concentrations of TKA 40049 in vaseline (%)

Animal No. / sex	01 % er/ed	05 % er/ed	01 % er/ed	05 % er/ed
1 male	0/0	0/0	0/0	0/0
2 female	0/0	0/0	0/0	0/0
Animal No. / sex	10 % er/ed	20 % er/ed	10 % er/ed	20 % er/ed
3 male	0/0	0/0	0/0	0/0
4 female	0/0	0/0	0/0	0/0
Animal No. / sex	30 % er/ed	50 % er/ed	30 % er/ed	50 % er/ed
5 male	0/0	0/0	0/0	0/0
6 female	0/0	0/0	0/0	0/0

ed = edema, er = erythema

Test No.: 924166
 Test Article: TKA 40049

TABLE 5

Individual animal bodyweights in g - males

CONTROL GROUP			TEST GROUP		
Animal No.	weight		Animal No.	weight	
	at start	at end		at start	at end
81	403	653	61	422	556
82	365	588	62	371	639
83	380	603	63	394	576
84	389	588	64	370	581
85	362	565	65	400	640
			66	412	607
			67	393	504
			68	417	587
			69	384	578
			70	444	673
Mean	380	599		401	614
Std. Dev.	17.0	32.9		23.4	35.5

Individual animal bodyweights in g - females

CONTROL GROUP			TEST GROUP		
Animal No.	weight		Animal No.	weight	
	at start	at end		at start	at end
86	390	551	71	392	583
87	366	534	72	350	523
88	441	603	73	406	530
89	404	548	74	361	517
90	414	502	75	391	528
			76	404	576
			77	425	594
			78	346	486
			79	419	593
			80	408	600
Mean	403	568		390	553
Std. Dev.	27.9	32.5		28.3	40.5

6. APPENDICES

APPENDIX 1

Evaluation of skin reactions

Evaluation of skin reactions according to Draize in Appraisal of the Safety of chemicals in Food, Drugs and Cosmetics (1959), The US Association of Food and Drug Officials (AFDO).

Erythema and eschar formation

No erythema.....	0
Very slight erythema (barely perceptible).....	1
Well defined erythema.....	2
Moderate to severe erythema.....	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth).....	4

Edema formation

No edema.....	0
Very slight edema (barely perceptible).....	1
Slight edema (edges of area well defined by definite raising).....	2
Moderate edema (raised approximately 1 mm).....	3
Severe edema (raised more than 1 mm and extending beyond area of exposure).....	4

APPENDIX 2

Maximisation grading

Sensitisation rate (%)	Grade	Classification
0 - 8	I	weak
9 - 28	II	mild
29 - 64	III	moderate
65 - 80	IV	strong
81 - 100	V	extreme

25

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Skin Sensitisation Test in the Guinea Pig
Test No.: 924166
Test Article: TKA 40049

24

APPENDIX 3

Reference values with Potassiumdichromate

Test No. 910032

Experimental starting date: January 21, 1992
Experimental completion date: February 21, 1992

The following concentrations of the reference compound and vehicles were used:

Intradermal induction

Concentration of compound: 0.2%
Vehicle: physiological saline

Epidermal induction

Concentration of compound: 5%
Vehicle: vaseline

Epidermal challenge

Concentration of compound: 1%
Vehicle: vaseline

Skin Sensitisation Test in the Guinea Pig

25

Test No.: 924166
Test Article: TKA 40049

**Number of positive animals per group after occlusive
epidermal application**

Control group:

	after 24 hours	after 48 hours
vehicle control	0/10	0/10
test article	0/10	0/10

Test group:

	after 24 hours	after 48 hours
vehicle control	0/10	0/10
test article	7/10	6/10

Skin Sensitisation Test in the Guinea Pig

26

Test No.: 924166
Test Article: TKA 40049

Challenge reactions after epidermal application
(CONTROL GROUP)

DRAIZE Score 24 hours after removal of the dressing

Vehicle control

Male animals 141 142 143 144 145

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Female animals 146 147 148 149 150

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Test article control

Male animals 141 142 143 144 145

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Female animals 146 147 148 149 150

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

26

Skin Sensitisation Test in the Guinea Pig

27

Test No.: 924166
Test Article: TKA 40049

DRAIZE Score 48 hours after removal of the dressing

Vehicle control

Male animals 141 142 143 144 145

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Female animals 146 147 148 149 150

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Test article control

Male animals 141 142 143 144 145

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Female animals 146 147 148 149 150

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Skin Sensitisation Test in the Guinea Pig

28

Test No.: 924166
Test Article: TKA 40049

Challenge reactions after epidermal application
(TEST GROUP)

DRAIZE Score 24 hours after removal of the dressing

Vehicle control

Male animals	121	122	123	124	125

Erythema score:	0	0	0	0	0
Edema score:	0	0	0	0	0

Female animals	131	132	133	134	135

Erythema score:	0	0	0	0	0
Edema score:	0	0	0	0	0

Test article

Male animals	121	122	123	124	125

Erythema score:		0	0	0	1
Edema score:	0	0	0	0	0

Female animals	131	132	133	134	135

Erythema score:	2	1	2	1	1
Edema score:	0	0	1	0	1

Skin Sensitisation Test in the Guinea Pig
Test No.: 924166
Test Article: TKA 40049

29

DRAIZE Score 48 hours after removal of the dressing

Vehicle control

Male animals 121 122 123 124 125

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Female animals 131 132 133 134 135

Erythema score: 0 0 0 0 0
Edema score: 0 0 0 0 0

Test article

Male animals 121 122 123 124 125

Erythema score: 0 0 0 0 1
Edema score: 0 0 0 0 0

Female animals 131 132 133 134 135

Erythema score: 2 1 1 2 2
Edema score: 0 0 0 0 0

31

0 0 3 2

TABLE OF CONTENTS

	Page
0.1 Proprietary information.....	2
0.2 Certification of GLP and verification of the report..	3
0.3 Statement of compliance with Good Laboratory Practice	4
0.4 Signatures.....	5
0.5 Reserved page for flagging statements.....	6
1 SUMMARY AND CONCLUSION.....	8
2 GENERAL.....	8
2.1 Introduction.....	8
2.2 Archives.....	8
2.3 Distribution.....	8
2.4 Test material.....	9
2.5 Auxiliary compounds.....	9
2.6 Test System.....	9
2.7 Group Size and Husbandry.....	10
2.8 Sensitivity of strain.....	10
3 METHODS.....	11
3.1 Reason for selection.....	11
3.2 Test procedure.....	11
3.3 Concentrations.....	12
3.4 Observations and records.....	13
4 Results.....	14
5 TABLES.....	15
Table 1: Incidences.....	15
Table 2: Epidermal reaction scores, control group.....	15
Table 3: Epidermal reaction scores, test group.....	15
Table 4: Evaluation of the primary irritation potential.....	20
Table 5: Individual animal weight in g.....	21
6 APPENDICES.....	22
Appendix 1: Evaluation of skin reactions according to Draize.....	22
Appendix 2: Maximisation Grading.....	23
Appendix 3: Reference values.....	24

32