ISTITUTO DI RICERCHE BIOMEDICHE "ANTOINE MARXER" RBM S.p.A.
Sede Legale e Labor.: Via Ribes, 1 - 10010 Colleretto Giacosa (TO) - ITALY
Telef.: 0125/222111 - Telefax: 0125/222599 - C.P. 226 - 10015 Ivrea (TO)

RBM Exp. No. 970595

[redacted]

[redacted] ce $(C_3F_6O)_{2,5}-CF_2COO^-Na^+$

ACUTE DERMAL TOXICITY STUDY IN RATS

RBM EXP. No. 970595

EEC Guidelines (B.3)
OECD Guidelines (402)

Issued on March 23, 1998

[redacted]

long
2 copy

(3)

SPONSOR

AUSIMONT
Viale S. Pietro, 50/A
20021 BOLLATE (Milano)
Italy

PERFORMING LABORATORY

Istituto di Ricerche Biomediche
"Antoine Marxer" RBM S.p.A.
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RBM Exp. No. 970595

TITLE OF THE STUDY

"Acute dermal toxicity study in rats treated with the test article [redacted]

PURPOSE OF THE STUDY

The purpose of the study was to evaluate the acute dermal toxicity of the test article [redacted]

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RBM Exp. No. 970595

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This report consists of 30 pages.

Ivrea, March 23, 1998

Dr. Ping Yu
RBM Study Director

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FOREWORD

On behalf of **AUSIMONT - Viale S. Pietro, 50/A, 20021 BOLLATE Milano - Italy** - Istituto di Ricerche Biomediche "Antoine Marxer" RBM S.p.A., authorized by the Italian Health Authorities (1-2) to conduct safety studies, has performed an acute toxicity study by dermal route in Sprague Dawley Crl: CD(SD) BR rat (RBM-Experiment No. 970595), with the test article:

[redacted]

A sample of the substance used, along with pertinent documentation, is held in sufficient quantity in the RBM archives and is at the disposal of the Ministero della Sanità.

The undersigned declare that the experiment was conducted using the same batch of substance as that of the sample held on file.

For verification by the Ministero della Sanità, the undersigned moreover guarantee the identification and classification of all those materials, documents and recordings used in conducting the experiment, held on file for a period of at least 10 years from the date of this report. Following this time, they will be placed at the disposal of the Sponsor.

Dr. Roberto Maraschin

Scientific Director Recognized by the Italian Health Authorities as Responsible for General Toxicology Experimentation

Dr. Angelo Conz

General Manager of the Istituto di Ricerche Biomediche "Antoine Marxer" , RBM S.p.A.

Ivrea, March 23, 1998

(1): **Pharmaceuticals:**
Authorization dated March 12, 1976 in accordance with "Circolare 73", May 16, 1974

(2): **Chemicals:**
Authorization in accordance with DPR 927/81 (D.M. dated January 7, 1988 published in G.U. No. 12, dated January 16, 1988).

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QUALITY ASSURANCE STATEMENT

RBM Experiment number: 970595

Study title:

"Acute dermal toxicity study in rats treated with the test article [redacted]"

Studies of the type described in this report are conducted in a manner which involves frequent repetition of identical or similar procedures.

In compliance with the Principles of Good Laboratory Practice, at the time of this study, procedure-based inspections were made by the Q.A.U. of critical phases and procedures relevant to this type of study. For the inspection of any given procedure, studies were selected at random. All such inspections were reported promptly to the study director and to facility management.

Dates of inspection/audit	Dates of report to Study Director and Management
January 13, 1998	January 13, 1998
March 19, 1998	March 19, 1998

This report has been audited by the Q.A.U. and was found to be an accurate description of such methods and procedures as were used during the conduct of the study and an accurate reflection of the raw data.

Date of final report audit: March 31, 1998

Enrico Invernizzi
Head of Quality Assurance Unit

Date : March 31, 1998

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RBM MANAGEMENT DECLARATION OF GLP COMPLIANCE

Study No. 970595 entitled :

"Acute dermal toxicity study in rats treated with the test article [redacted]"

was performed in compliance with the OECD-GLP in the testing of chemicals, [C(81) 30 (final)], regulations also enforced by the Italian Health Authority [D.M. dated June 26, 1986 as published in G.U. No. 198, dated August 27, 1986 and D.L. January 27, 1992, No. 120 as published in G.U. (Supplement) No. 40, February 18, 1992].

Dr. Ping Yu
RBM Study Director

Dr. Angelo Conz
General Manager of the Istituto di Ricerche Biomediche "Antoine Marxer", RBM S.p.A.

Ivrea, March 31, 1998

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RBM Exp. No. 970595

SCIENTISTS INVOLVED IN THE STUDY

STUDY No. 970595

"Acute dermal toxicity study in rats treated with the test article [redacted]"

RBM Study Director	Dr. Ping Yu
Scientific Director Toxicology	Dr. Roberto Maraschin
Head of General Toxicology I Unit	Dr. Germano Oberto

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MATERIALS AND METHODS

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EXPERIMENTAL DESIGN

RBM Experiment No.:	970595
Test article:	[redacted]
Administration route:	epidermal
Exposure period:	about 24 hours
Duration of treatment period:	single administration
Duration of post-treatment observation period:	14 days after the 24-hour exposure period

The test method was in accordance with European Economic Community Guidelines - Annex to Commission Directive 92/69/EEC of July 31, 1992 adapting to technical progress for the seventeenth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (B.3) and with Organization for Economic Cooperation and Development Guidelines (section 4, subpart 402, Paris 1981 and subsequent revisions).

TEST SYSTEM

Species, strain and substrain:	Sprague Dawley Crl: CD (SD) BR rat
Justification for selection of the test system :	the Sprague Dawley rat was chosen as rodent species since it is an appropriate experimental model widely accepted by Health Authorities, with documented susceptibility to a wide range of toxic substances
Number and sex of animals:	5 males + 5 females treated at 2000 mg/kg
Body weight (at randomization):	Males: 283 - 325 g Females: 232 - 262 g

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Age (at randomization):	no more than three months
Supplier:	Charles River Italia S.p.A. Via Indipendenza, 11 22050 CALCO (Lecco) Shipping slips No.s 8504 (December 12, 1997) and 8353 (December 5, 1997)
Acclimatation:	more than 5 days before the start of the test. Animals were observed daily to ascertain their fitness for the study.
Housing:	5 animals/sex/cage in air-conditioned room. - Temperature: 22°C ± 2 - Relative humidity: 55% ± 10 - Air changes: about 20 / hour filtered on HEPA 99.97% - Light: 12 hour cycle (7 a.m. - 7 p.m.) - Cage size: grill cages 40.5x38.5x18h cm with stainless steel feeder. The waste that dropped through the grill bottom onto removable paper was periodically disposed of.
Animal identification:	by appropriately coloring different areas of the limbs. Cage card gave experiment number, dosage group, sex and date of administration.
Diet:	GLP 4RF21 top certificate pelleted diet produced by Charles River Italia's feed licencee Mucedola S.r.l., Settimo Milanese. The declare contents on the label, on dry matter basis (moisture 12%), were:

crude protein	18.50%
crude fat	3.00%
crude fiber	6.00%
crude ash	7.00%

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The diet was supplemented by the Producer with vitamins and trace elements. The Producer supplies a certificate of analysis for nutrients and contaminants, the levels of which are within the limits proposed by EPA-TSCA (44FR:44053-44093, July 26, 1979).
RBM has the animal feed re-analyzed at least twice a year for bacterial contamination.
The diet was available "ad libitum" to the animals.

Water: from the municipal water main system.
Water is filtered and distributed "ad libitum" to the animals by an automatic valve system.
Periodically drinking water is analyzed for microbial count, heavy metals, other contaminants (e.g. solvents, pesticides) and other chemical and physicals characteristics. The accepted limits of quality of the drinking water were those defined in EEC directive 80/778

Contaminants that might interfere with the objectives of the study were not expected to be present in the diet or drinking water.

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TEST ARTICLE IDENTIFICATION, CHARACTERIZATION AND FORMULATE

The test article was supplied by the Sponsor as follows:

Identification:	[redacted]
Batch:	18732/40
Characteristics:	white wax/solid
Purity:	>99%
Manufacturing date:	October 14, 1997
Expiry date:	December 2000
Storage conditions:	at room temperature

TEST DESCRIPTION

Administration route:	epidermal
Reason for selection of administration route:	possible accidental exposure in humans
Experimental design:	one group of 5 rats/sex, randomly selected, was administered a dosage of 2000 mg/kg (limit dose) of the test article. Individual dosages were based on body weight taken just before treatment.

Dose mg/kg		Treatment date	Final killing
2000	males:	January 15, 1998	January 30, 1998
2000	females:	January 23, 1998	February 7, 1998

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Preparation of animals skin:	approximately 24 hours before the test, fur was clipped from the dorsal and ventral area of the trunk of the test animals. Care was taken to avoid abrading the skin which could alter its permeability. An area of about 6x5 cm of the body dorsal surface was cleared for the application of the test article. This area corresponded to about 10% of the total body surface.
Administration of the test article:	the test article was applied uniformly onto a porous gauze which was moistened with 0.9% NaCl. The treated area was covered with the porous gauze dressing fixed to the skin with hypoallergenic non-irritating tape. The test site was further covered in a suitable manner in order to ensure that the animals could not ingest the test substance. At the end of the exposure period the residual test article was wiped off with water.
Observation period:	14 days after the 24-hour exposure period.
Observation of clinical signs and mortality:	at 30 minutes, 2, 4 and 6 hours on the first day after the administration (day 1) and then twice a day up to termination of the observation period.
Body weight:	twice pre-trial (at randomization and on day 1 just before administration) and on days 8 and 15. Volume of administration was based on day 1 body weight.
Gross pathology:	on all animals (fasted overnight) killed by excision of the femoral arteries, after i.p. overdosage anesthesia with 5% sodium pentobarbital, at the end of the observation period
Histology:	Histologic examination was not performed.
LD_{50} and its statistical limits:	LD_{50} was not calculated

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RECORD FILING

The protocol, a reserve sample of the test article used, the raw data bound in a register numbered 970595/1, the final report and all other documents pertinent to the conduct of this study, including records and reports of maintenance, cleaning, calibration and inspection of equipment, analysis of diet and water are filed at RBM premises for ten years from the issue date of this report and then sent to the Sponsor.

PROCEDURAL DETAILS

The study was conducted in accordance with the procedures described in the RBM Standard Operating Procedures (SOP's) collection.

Protection of animals used in the experiment is in accordance with Directive 86/609/EEC, enforced by the Italian D. L. No. 116 of January 27, 1992.

Physical facilities and equipment for accomodation and care of animals are in accordance with the provisions of EEC Council Directive 86/609.

The Institute is fully authorized by Competent Veterinary Health Authorities.

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RESULTS

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CLINICAL OBSERVATIONS

MORTALITY *(TABLE 1)*

Two out of 5 females died on day 13 or 14 of the study. No deaths occurred in males. The LD_{50} was not calculated and it was considered higher than 2000 mg/kg.

CLINICAL SIGNS *(TABLE 2 AND APPENDIX 1)*

Females showed piloerection and hunched posture, starting on days 8-9 of the observation period. No local abnormalities were seen in any animal.

BODY WEIGHT *(APPENDIX 2)*

Decrease in body weight (females)or retarted growth (males) was noted during the study period.

POST-MORTEM EXAMINATION

GROSS PATHOLOGY *(TABLE 3 AND APPENDIX 3)*

At the autopsy of animals which died before the end of the observation period congestion and ulcer of stomach, kidney medulla congestion and pale liver were found in one female. Another female showed pale liver and spleen decreased size. No appreciable changes were evident in the animals killed at the end of the observation period.

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SUMMARY AND CONCLUSIONS

Experimental data from a toxicity study in which Sprague Dawley Crl:CD(SD) BR rats received a single dermal administration of the test article [redacted] at the dosage of 2000 mg/kg (5 males and 5 females) are given in this report.

The test method was in accordance with European Economic Community Guidelines - Annex to Commission Directive 92/69/EEC of July 31, 1992 adapting to technical progress for the seventeenth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (B.3) and with Organization for Economic Cooperation and Development Guideline (section 4, subpart 402, Paris 1981 and subsequent revisions).

The test article was applied uniformly onto a porous gauze which was moistened with 0.9% NaCl and then, this porous gauze was fixed to the dorsal and ventral area of trunk of the rats (fur was clipped 24 hours previously). The individual dosages were based on body weight taken just before treatment.

The day of treatment was considered day 1 of the study. The animals were weighed twice before treatment (at randomization and on day 1 just before treatment) and on days 8 and 15. They were clinically observed for 14 days after the 24-hour exposure period. On day 16 all rats were killed (fasted overnight) by excision of the femoral arteries after i.p. overdosage anesthesia with 5% sodium pentobarbital and were submitted to a thorough autopsy.

No deaths occurred in males. Two out of 5 females died on day 13 or 14 of the study. Before death the two females showed piloerection and hunched posture (starting on days 8-9 of the observation period). Other females had similar symptoms. No local abnormalities were seen in any animal.

Decrease in body weight (females) or retarded growth (males) were noted during the study period.

At the autopsy of animals which died before the end of the observation period the main macroscopic findings were congestion and ulcer of stomach and pale liver. No appreciable changes were evident in the animals killed at the end of the observation period.

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In conclusion, the test article [redacted] when administered by dermal route to rats, induced delayed toxicity (20% mortality) with some changes (liver and stomach were mainly involved) at the limit dose of 2000 mg/kg. Females were more sensitive to treatment with the test article than males.

The **LD_{50}** by dermal route is **higher than 2000 mg/kg**.

Dr. Ping Yu
RBM Study Director

March 23, 1998

Dr. Roberto Maraschin
Scientific Director Recognized by the Italian Health Authorities as Responsible for General Toxicology Experimentation

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GROUP DATA

Test article: [redacted]
Title : Acute dermal toxicity study in rats
RBM exp. : 970595

TABLE 1. - Mortality and LD50 calculation (p. 1)

Males - Females

Dose (mg/kg)		2000
Treated animals		10
Day	13	1
	14	1
Total no.	(day 15)	2
Total (%)		20.0%

LD50 not calculable

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Title : Acute dermal toxicity study in rats
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TABLE 2. - Clinical signs (maximum daily frequency) (p. 1)
(no. of animals affected, from-to)

Males

Dose (mg/kg)	2000
no. of treated animals	5
No clinical signs	5 30m-15d

from-to (first-last observation in one or more animals)
Time : m (minutes) d (days)

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Test article: [redacted]
Title : Acute dermal toxicity study in rats
RBM exp. : 970595

TABLE 2. - Clinical signs (maximum daily frequency) (p. 2)
(no. of animals affected, from-to)

Females

Dose (mg/kg)	2000
no. of treated animals	5
Death	2 13d-14d
Piloerection	3 9d-13d
Hunched posture	5 8d-13d
Recovery	3 14d

from-to (first-last observation in one or more animals)
Time : d (days)

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Test article: [redacted]
Title : Acute dermal toxicity study in rats
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TABLE 3. - Gross pathology examination (p. 1)
(no. of cases, mean severity, %)

Final killing	Males
Dose (mg/kg)	2000
no. of animals	5
no. of animals without appreciable lesions	5

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Test article: [redacted]
Title : Acute dermal toxicity study in rats
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TABLE 3. - Gross pathology examination (p. 2)
(no. of cases, mean severity, %)

Dead or agonal sacrificed an.	Females
Dose (mg/kg)	2000
no. of animals	2
no. of animals without appreciable lesions	0
Kidneys	
medulla, congestion	1(3.0) 50.00%
Liver	
pale	2(3.0) 100.00%
Spleen	
decreased size	1(3.0) 50.00%
Stomach	
congestion	1(2.0) 50.00%
ulcer	1(3.0) 50.00%

Severity : 0(very slight) 1(slight) 2(moderate) 3(severe)

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Test article: [redacted]
Title : Acute dermal toxicity study in rats
RBM exp. : 970595

TABLE 3. - Gross pathology examination (p. 3)
(no. of cases, mean severity, %)

Final killing	Females
Dose (mg/kg)	2000
no. of animals	3
no. of animals without appreciable lesions	3

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APPENDICES

Test article: [redacted]
Title : Acute dermal toxicity study in rats
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APPENDIX 1. - Clinical signs incidence (p. 1)
(no. of animals affected)

Dose (mg/kg) 2000

Cage # 1M	Day	1				2		3		4		5		6		7		8		9		10		11		12		13		14		15	
	Time	30m	2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A
No clinical signs		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Cage # 2F	Day	1				2		3		4		5		6		7		8		9		10		11		12		13		14		15	
	Time	30m	2h	4h	6h	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A	M	A
Death																												1		1			
No clinical signs		5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5							2	2	2	2	3	3	3	3	3	3
Piloerection																				3	3	3	3	3	3	3	3	1	1				
Hunched posture																		5	5	5	5	5	5	3	3	3	3	1	1				

Time: m (minutes) h (hours) M (morning) A (afternoon)

Test article: [redacted]
Title : Acute dermal toxicity study in rats
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APPENDIX 2. - Body weight (g) (p. 1)
(individual)

Dose (mg/kg) 2000

Animal #		1M	2M	3M	4M	5M	6F	7F	8F	9F	10F
Week	day										
	0	298	304	325	283	286	244	261	234	262	232
1	1	300	310	331	290	292	249	263	237	258	238
2	8	319	350	391	333	333	206	194	163	218	218
3	15	328	362	398	383	341	210			223	225

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Test article: [redacted]
Title : Acute dermal toxicity study in rats
RBM exp. : 970595

APPENDIX 3. - Gross pathology examination (p. 1)
(individual)

Dead or agonal sacrificed an.

Dose (mg/kg) 2000

An#	Death day/code#	TISSUE	Gross observations
7F	13 M2	Kidneys	medulla, congestion, diffuse, severe
		Liver	pale, diffuse, severe
		Stomach	congestion, diffuse, moderate ulcer, focal, severe
8F	14 M2	Liver	pale, diffuse, severe
		Spleen	decreased size, diffuse, severe

Death code : M2(Natural death)

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Sede Legale e Labor.: Via Ribes, 1 - 10010 Colleretto Giacosa (TO) - ITALY
Telef.: 0125/222111 - Telefax: 0125/222599 - C.P. 226 - 10015 Ivrea (TO)

Test article: [redacted]
Title : Acute dermal toxicity study in rats
RBM exp. : 970595

APPENDIX 3. - Gross pathology examination (p. 2)
(individual)

Final killing

Dose (mg/kg) 2000

An#	Death day	T I S S U E	Gross observations
1M	16	General observation	no macroscopically appreciable lesions
2M	16	General observation	no macroscopically appreciable lesions
3M	16	General observation	no macroscopically appreciable lesions
4M	16	General observation	no macroscopically appreciable lesions
5M	16	General observation	no macroscopically appreciable lesions
6F	16	General observation	no macroscopically appreciable lesions
9F	16	General observation	no macroscopically appreciable lesions
10F	16	General observation	no macroscopically appreciable lesions

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LABORATORIES & CLINICS GROUP
BIOSCIENCE

REDACTED AS TO TRADE NAMES

RBM Via Ribes 1
10010 Colleretto Giacosa (TO)
Italy

Tel: 0125 222111
Fax: 0125 222599

[redacted]

[redacted]

$Ce(C_3F_6O)_{2,5}-CF_2COO^-\ H_5^+$

"SKIN SENSITIZATION TEST IN GUINEA-PIGS"

Maximization test

RBM EXP. No. 970590

EEC Guideline (B.6)
OECD Guideline (406)

Issued on April 21, 1998

SPONSOR

AUSIMONT S.p.A.
Via S. Pietro, 50/A
20021 Bollate (Milano)
Italy

PERFORMING LABORATORY

Istituto di Ricerche Biomediche
"Antoine Marxer" RBM S.p.A.
Via Ribes, 1
10010 - COLLERETTO GIACOSA (Torino)
Italy

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EXP. No. 970590

TITLE OF THE STUDY

"Skin sensitization test in guinea-pigs treated with the test article [redacted]".

PURPOSE OF THE STUDY

Assessment of the contact sensitizing potential of the test article.

TEST METHOD

The Magnusson's maximization test was followed (1, 2, 3).

The test method is in accordance with method B.6, Annex V to Directive 67/548 (EEC Directive 96/54, EEC Official Jurnal, No. L 248, September 30, 1996) and with Organization for Economic Cooperation and Development (OECD) Guidelines (section 4, subpart 406, Paris 1981 and subsequent updatings).

PRINCIPLE

Following initial exposure to the test article (the "induction" period), the animals are subjected, approximately two weeks after the last induction exposure, to a "challenge" application of the test compound in order to establish whether a hypersensitive state has been induced.

Sensitization is determined by examining the skin reaction to the challenge exposure.

SENSITIVITY CHECK OF THE DUNKIN HARTLEY GUINEA-PIG

The sensitivity check of the Dunkin Hartley albino guinea-pig is normally verified at RBM twice a year, as indicated in the Guidelines, at 6-month intervals.

The data obtained in the last check performed are attached (see Attachment No. 1). These data show a clear sensitization of animals by 2,4-dinitrochlorobenzene (DNCB), therefore the strain of Guinea pigs used at RBM is suitable for detecting the possible sensitizing potential of test materials.

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LABORATORIES & CLINICS GROUP BIOSCIENCE

RBM Exp. No. 970590

FOREWORD

On behalf of **AUSIMONT S.p.A., Via S. Pietro, 50/A - 20021 Bollate (Milano) - Italy**, Istituto di Ricerche Biomediche "Antoine Marxer" RBM S.p.A., authorized by the Italian Health Authorities (1-2) to conduct safety studies, has performed a skin sensitization test in guinea-pigs, RBM - Experiment No. 970590, treated with the test article:

[redacted]

A sample of the substance used, along with relative documentation, is held in sufficient quantity in the RBM archives at the disposal of the Ministero della Sanità.

The undersigned declare that the experiment was conducted using the same batch of substance as that of the sample held on file.

For verification by the Ministero della Sanità, the undersigned moreover guarantee the identification and classification of all those materials, documents and recordings used in conducting the experiment, held on file for a period of at least 10 years from the date of this report. Following this time, they will be placed at the disposal of the Sponsor.

Dr. Roberto Maraschin

RBM Scientific and Operative Director

Ivrea, April 21, 1998

(1): **Pharmaceuticals:**
Authorization dated March 12, 1976 in accordance with "Circolare 73", May 16, 1974

(2): **Chemicals:**
Authorization in accordance with DPR 927/81 (D.M. dated January 7, 1988 published in G.U. No. 12, dated January 16, 1988).

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LABORATORIES & CLINICS GROUP BIOSCIENCE

RBM Exp. No. 970590

QUALITY ASSURANCE STATEMENT

RBM Experiment number: 970590

Study title:

"Skin sensitization test in guinea-pigs treated with the test article [redacted]".

Studies of the type described in this report are conducted in a manner which involves frequent repetition of identical or similar procedures.

In compliance with the Principles of Good Laboratory Practice, at the time of this study, procedure-based inspections were made by the Q.A.U. of critical phases and procedures relevant to this type of study. For the inspection of any given procedure, studies were selected at random. All such inspections were reported promptly to the Study Director and to facility management.

This study was inspected on:

Dates of inspection/audit	Dates of report to Study Director and Management
February 16, 1998	February 16, 1998
April 17 and 18, 1998	April 18, 1998

This report has been audited by the Q.A.U. and was found to be an accurate description of such methods and procedures as were used during the conduct of the study and an accurate reflection of the raw data.

Date of final report audit: April 24, 1998

Enrico Invernizzi
Head of Quality Assurance Unit

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CERTIFICATION OF GLP COMLPIANCE

RBM Experiment No.: 970590

Study title: "**Skin sensitization test in guinea-pigs treated with the test article** [redacted]".

I hereby confirm that this study was conducted in accordance with the OECD [C(81) 30 (final)], Principles of Good Laboratory Practice (GLP).

The Sponsor is responsible for GLP compliance of any information supplied.

These principles were adopted by the EEC and incorpored into EEC Directive 88/320, that was legally enforced by the Italian Health Authority [D.M. dated June 26, 1986 as published in G.U. No. 198, dated August 27, 1986 and D.L. January 27, 1992, No. 120 as published in G.U. (Supplement) No. 40, February 18, 1992].

The final report fully and accurately reflects the raw data generated during the conduct of the study.

This report consists of 34 pages.

RBM Study Director

Dr. Enrico Vigna

Ivrea, April 24, 1998

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LABORATORIES & CLINICS GROUP
BIOSCIENCE

RBM Exp. No. 970590

SPONSOR IDENTIFICATION

AUSIMONT S.p.A.
Via S. Pietro, 50/A
20021 Bollate (Milano)
Italy

SCIENTISTS INVOLVED IN THE STUDY

"Skin sensitization test in guinea-pigs treated with the test article [redacted]".

RBM Study Director	Dr. Enrico Vigna	
RBM Senior Scientist for General Toxicology	Dr. Sergio Peano	
Centralized Pharmacy Head	Dr. Rita Bussi	
Pharmacy Service Head	Dr. Bruna Piccioli	

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MATERIALS AND METHODS

PRODUCT IDENTIFICATION AND CHARACTERIZATION

Test article (supplied by the Sponsor)

Identification:	[redacted]
Batch No.:	18732/40
Characteristics:	white wax/solid
Preparation date:	October 14, 1997
Expiry date:	December 2000
Storage conditions:	Room temperature
Purity:	>99%

The Sponsor reserves the right to divulge any other relevant data on test article characterization directly to Regulatory Agency(ies), when appropriate.

Vehicle characterization

Identification: deionized water

Adjuvant characterization

Identification:	Freund's complete adjuvant (FCA)
Batch No.:	86321 LA
Expiry date:	February 1999
Storage:	15-30°C, in the dark
Producer:	Difco Laboratories; Detroit Michigan-USA

PRELIMINARY TEST (Tolerability)

The preliminary test was performed on a total of 4 animals in order to select the highest concentration that causes mild irritation to be used in the induction phase and the highest concentration that proves not to be irritating for the challenge exposure.

Initially an aliquot of 0.1 ml of four different concentrations (2, 5, 10 and 15%) of the test article (vehicle = deionized water) were injected into four different areas of the shoulder region of two animals.

Three patches containing 0.3 ml of three different concentrations (15, 25 and 50%) of the test article (vehicle = deionized water) were applied for 24 hours in three different areas of the dorsal region of the same two animals treated intradermally.

The 50% concentration of the test article in deionized water was the highest concentration administrable to animals (see RBM internal communication dated February 5, 1998).

Twenty-four hours after the administration, the patches were removed and the animals were observed for up to 48 h for local reactions on the skin areas both of the intradermal injection and of the patch application.

All the four concentrations tested for intradermal injection resulted in eschar formation.

None of the three concentration assayed for the patch application were irritant.

On the basis of the results obtained, two additional animals were treated by intradermal injection with the test article concentrations of 0.1, 0.2 and 0.5% (for each concentration 0.1 ml was injected) in three different shoulder regions.

The 0.2 and 0.5% concentrations resulted in eschar formation, while the 0.1% concentration produced slight erythema.

Therefore in the experiment the test article was used at the concentration of 0.1% in the induction with the intradermal injection, at 50% in the booster (with sodium lauryl sulphate treatment in the previous day) and at 50% in the challenge application.

TEST ARTICLE FORMULATE PREPARATIONS

When necessary, an exact amount of [redacted] was weighed in a suitable container and made up to final volume with deionized water to obtain the concentration required.

For the injection in Freund's complete adjuvant (FCA) the test article was dissolved in water for injection at a concentration of 0.2% and then equal volume of FCA was added to obtain the concentration of 0.1% .

The test article formulates were prepared just prior to administration.

TEST SYSTEM

Species and strain:	Dunkin Hartley albino guinea-pigs
Justification for the selection of the test system:	Dunkin Hartley albino guinea-pig is the species generally recommended by Health Authorities as the experimental model for skin sensitization studies
Supplier:	Charles River Italia S.p.A. Via Indipendenza, 11 22050 Calco (Lecco) Shipping slip No. 00387, dated January 16, 1998 (preliminary study) Shipping slip No. 01195, dated February 13, 1998 (main study)
Number:	19 animals as follows: 10 animals for the treated group 5 animals for the control group 4 animals for the preliminary test
Body weight (and age):	between 369 and 418 g at the start of the experiment (corresponding to an age of about 6 weeks, animals were born on January 5, 1998 shipping slip No. 01195)
Sex:	male
Acclimatization:	6 days. Animals were observed daily to ascertain their fitness for the study
Housing (room H5/A):	2 or 3 animals/cage in an air-conditioned room - temperature: 22 ± 2°C - air changes: about 20/h filtered on HEPA 99.97% - relative humidity: 55 ± 10% - artificial light: 12 h cycle (7 a.m. - 7 p.m.) - cage: wire cages (40.5x38.5x18h) with a stainless steel feeder The waste that dropped through the wire bottom onto a removable paper was periodically disposed of.

Animal identification: by coloring different areas of the ears and paws.
A computerized randomization program was used to allocate the animals to groups.

Cage identification: by cage card giving the experimental number, starting day and group identification in indelible ink.

Diet: the standard GLP diet - certificate coded 8 GP 22, produced by Charles River Italia's feed licensee Mucedola S.r.l., Settimo Milanese, was used.
The declared contents, on the label, on dry matter basis (moisture 12%), were:

crude protein	19 %
crude fat	4 %
crude fiber	14.5 %
crude ash	7.5 %

The diet was supplemented by the Producer with vitamins and trace elements. According to the analytical certificates provided by the Supplier, the contents of the batch of diet used in this study were within ± 5% of the declared values and the presence and the levels of contaminants were within the limits proposed by EPA-TSCA (44FR: 44053-44093, July 26, 1979).
Animal feed, in compliance with RBM SOPs, is analyzed twice a year for bacterial contamination.
The diet was available "ad libitum" to the animals.

Water:

filtered water was distributed "ad libitum" to the animals by means of an automatic watering valve system. The drinking water came from the municipal water main.
Periodically, drinking water is analyzed to determine microbial count, heavy metals, other contaminants (e.g. solvents, pesticides) and other chemical and physical characteristics.
The accepted limits for the quality of drinking water are those defined in EEC Directive 80/778.
Contaminants that might interfere with the objectives of the study are not expected to be present either in the diet or in the water.
The analytical certificates of the animal feed and water are filed at RBM premises.

EXPERIMENTAL DESIGN

RBM Experiment No.:	970590
Date of preliminary test (tolerability):	February 5-7, 1998
Beginning of the study:	February 16, 1998
End of the study:	March 16, 1998
Experimental groups:	group 1 (treated animals), 10 males numbered from 1 to 10 group 2 (control animals), 5 males numbered from 11 to 15
Administration route:	intradermal injection and topical exposure by occlusive patch
Concentrations used:	0.1% for the intradermal injection 50% for the booster exposure 50% for the challenge application
Volume administered:	0.1 ml/injection site for the intradermal injection 0.3 ml/animal for the booster exposure 0.2 ml/animal for the challenge application
Observation of clinical signs:	daily
Body weight recording:	pre-trial and weekly thereafter

Induction phase: intradermal injection

Day -1: fur was clipped from an area of about 4x6 cm on the shoulder region with an electric clipper before injection.
Care was taken to avoid abrading the skin, which could alter the results of the study.

Day 0: each animal was given three pairs of intradermal injections in the skin area clipped the day before, so that on each side of the midline there was one row of three injections.

The injections were:

Group 1 (test article)
1) 0.1 ml FCA emulsion (1:1 mixture (v/v) FCA/water)
2) 0.1 ml test article
3) 0.1 ml test article in FCA (1:1 mixture (v/v) FCA/water)

In injection 3 the test article was dissolved in water for injection prior to mixing with FCA.
The concentration of the test compound was therefore equal to that used in injection 2.

Group 2 (vehicle)
1) 0.1 ml FCA emulsion (1:1 mixture (v/v) FCA/water)
2) 0.1 ml vehicle
3) 0.1 ml vehicle in FCA (1:1 mixture (v/v) FCA/water)

Twenty-four hours later the injection sites were observed for irritant effects.
The results were recorded.

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Induction phase: booster

Day 5: the area destined to receive the booster (that used for the induction), was clipped and treated with 0.5 ml of 10% sodium lauryl sulfate (Merck, batch L149860, expiry date September 1999) in vaseline oil (Carlo Erba, batch A908393768, expiry date July 2001), in order to create a local irritation and therefore to enhance skin permeability to the compound for the following day.

Day 6: a filter paper (3M Whatman, 2x4 cm) was fully-loaded with the test article or vehicle and applied to the skin areas clipped the day before. The patch was covered by an overlapping impermeable, hypoallergenic, plastic adhesive tape (3M Blenderm). This in turn was firmly secured by adhesive bandage (3M Micropore), wound around the torso of the animal.
The dressing was left in place for 48 hours.

Twenty-four hours after removal of the patches, the patch sites were observed for irritant effencts.
The results were recorded.

Challenge application

Day 19: an area of about 5x5 cm on both the flanks of the animals of the two groups was clipped.

Day 20: an occlusive patch (2x2 cm) loaded with the test article or vehicle were applied for 24 hours to the animals of the two groups.

Left flank: test article
Right flank: vehicle

Day 21: the patches were removed.

Days 22 and 23: approximately 21 hours after removing the patches the challenge areas were clipped and approximately 3 hours later (48 hours from the start of the challenge patch application) the skin was observed and any reaction recorded (day 22).
Twenty-four hours after the above observation a second observation was made and once again recorded (day 23).

ASSESSMENT OF SKIN REACTIVITY

Evaluation of skin reactions:

0 absent
1 discrete or patchy erythema
2 moderate and confluent erythema
3 intense erythema and swelling

Animals are considered positive if showing at least discrete or patchy erythema (score=1), while no reaction is seen in the control animals. The sensitization potential of test compound was calculated on the basis of the percentage of animals showing a response of 1 or greater.
The degree of sensitization was evaluated by the maximization procedures which classify it in the following five groups, ranging from weak (grade I) to extreme (grade V) according to the percentage of animals sensitized.

Percentage of animals showing sensitization	Grade	Classification
0 - 8	I	Weak
9 - 28	II	Mild
29 - 64	III	Moderate
65 - 80	IV	Strong
81 - 100	V	Extreme

RECORD FILING

The protocol, a reserve sample of the batch of the test article used, the raw data bound in a register numbered 970590/1, the final report and all other required document pertinent to the conduct of this study, including records and reports of maintenance, cleaning, calibration and inspection of equipment, will be filed at RBM premises for ten years from the issue date of this report and then sent to the Sponsor.

At the end of the ten-year archiving period, the Sponsor can request the extension of the storage of all materials or part of them for a further period. An appropriate agreement will be drawn up accordingly.

PROCEDURAL DETAILS

The study was conducted in accordance with the procedures described in the RBM Standard Operating Procedures (SOPs) collection.

Protection of animals used in the experiment is in accordance with Directive 86/609/EEC, enforced by the Italian D. L. No. 116 of January 27, 1992.

Physical facilities and equipment for accommodation and care of animals are in accordance with the provisions of EEC Council Directive 86/609.

The Institute is fully authorized by Competent Veterinary Health Authorities.

REFERENCES

(1): Klecak G.
"Identification of contact allergens: predictive tests in animals"
In: Dermatoxicology and Pharmacology, Marzulli F.N. and Maibach H.I. eds., Hemisphere Publishing Co. Washington DC., p. 313 - 316, 1977.

(2): Magnusson B. and Kligman A.M.
"The identification of contact allergens by animal assay. The guinea pig maximization test"
J. Invest. Dermatol., Vol. 52, p. 268-276, 1969.

(3): Magnusson B. and Kligman A.
"Usefulness of guinea pig tests for detection of contact sensitizers".
In: Dermatoxicology and Pharmacology, Marzulli F.N. and Maibach H.I. eds., Hemisphere Publishing Co. Washington DC, p. 551-559, 1977.

RESULTS

MORTALITY, CLINICAL OBSERVATIONS AND BODY WEIGHT

Five test article treated animals died during the second half of the study. Mortalities are given in the following scheme:

Animal No.	Experimental day of death
1	13
3	15
4	14
7	15
9	13

Before death (from day 11 onward) these five animals showed anorexia, they appeared thin, dehydrated and showed hunched posture and piloerection. Severe body weight decrease was also recorded (see Table 1).

Mortalities occurred 7-9 days after the topical application (48 hour duration) in the shoulder region of 0.3 ml of 50% test article concentration (booster).

The transdermal toxicity of the test article was increased by the topical application of sodium lauryl sulphate (0.5 ml/animal of the 10% concentration) at the treatment site on the day preceding the booster (as required by the protocol since the concentration selected for the booster did not result in skin changes in the preliminary test).

The Sodium lauryl sulphate applications clearly increased the permeability of the skin to the test article. In fact at the challenge the surviving animals were again treated with the 50% test article concentration and neither mortality and clinical signs nor local reactions were observed (while severe local reactions occurred in all animals when sodium lauryl sulphate was administered).

At the autopsy in all five animals emaciation, dehydration and empty stomach and empty intestine were found. Skin treatment sites appeared severely inflammed with crusts and desquamation.

The 5 animals surviving animals did not show general clinical signs, but at the skin treatment site severe erythema was observed. Body weight stasis or slight body weight decrease was recorded in 4 out of the 5 animals on days 13 and 19. However an additional body weight recording carried out on day 25 (i.e. after 5 days from the challenge) showed a general trend toward recovery.

EVALUATION OF SKIN SENSITIZATION

Twenty-four hours after the intradermal injections all animals were in good health and, as expected, at each injection site of FCA emulsion (FCA/water), FCA/vehicle and FCA/test article a swollen reddish area was seen. The injection of the test article at the concentration of 0.1% in the vehicle, caused slight irritation. No reaction was seen after injection of the vehicle alone.

Twenty-four hours after the removal of the 48-hour closed patch (booster), signs of severe irritation such as severe redness and thickening of the skin were observed in animals treated with the test article, while in controls slight skin thickening was observed as consequence of the sodium lauryl sulphate application.

Table 2 shows the results obtained at the challenge exposure in surviving animals with the test article [redacted] applied by an occlusive patch at the concentration of 50%.

No animals showed positive reactions at the challenge.

No skin reactivity was observed in the negative control group (see Table 3).

CONCLUSIONS

Contact sensitivity is a T-lymphocyte-mediated delayed hypersensitivity reaction.

The immunological events in skin sensitization can be separated into two main phases: development of sensitization and elicitation of clinical effects (e.g. erythema and edema) following subsequent exposure to the same compound.

The sensitizing potential of the test article [redacted] was assessed in guinea-pigs using the Magnusson test as described by Klecak (1), Magnusson B. and Kligman A. M. (2, 3).

All test article treated animals showed severe local irritation and half of them died within 7-9 days of the booster (topical application of 50% test article concentration). Local reactions and mortality were considered to be caused by increased transdermal absorption of the test article after sodium lauryl sulphate (SLS) application on the skin treatment sites on the day preceding the booster.

The death was preceded by anorexia, body weight loss, dehydration, hunched posture and piloerection. At autopsy empty stomach and empty intestine, dehydration, and emaciation were found. On skin treatment sites severe inflammation, with crusts and desquamation, was seen.

Surviving animals only showed body weight stasis or slight body weight decrease and local severe erythema and skin thickening. Body weight showed an evident trend towards recoveryat the end of the study.

No surviving animals treated with the test article showed either general and local clinical signs or a positive reaction at the challenge (topical application of 50% test article concentration without SLS application).

On the basis of this result, under the experimental conditions applied, [redacted] did not appear to possess sensitizing capacity; however, it should be considered that assesment was done on a limited (surviving) number of animals.

E. Vigna 21/4/98

Dr. Enrico Vigna

RBM Study Director

Peano 21/4/98

Dr. Sergio Peano

RBM Senior Scientist for General Toxicology

TABLES

Test article: [redacted]
Title : Skin sensitization test in guinea-pigs
RBM exp. : 970590

TABLE 1. - Body weight
(expressed in grams)

Group No.	Guinea-pig No.	Days				
		-1	5	13	19	25
1	1	389	419			
	2	369	433	411	415	493
	3	389	446	449		
	4	391	454	311		
	5	404	467	491	496	549
	6	381	446	463	514	556
	7	379	416	380		
	8	412	450	481	489	523
	9	418	473			
	10	395	450	436	440	509
2	11	389	414	461	497	552
	12	389	443	508	512	580
	13	391	433	507	567	612
	14	399	438	473	514	545
	15	387	414	463	525	567

Animal No. 1 found dead on day 13
Animal No. 3 found dead on day 15
Animal No. 4 found dead on day 14
Animal No. 7 found dead on day 15
Animal No. 9 found dead on day 13

Test article: [redacted]
Title : Skin sensitization test in guinea-pigs
RBM exp. : 970590
Vehicle : deionized water

TABLE 2. - Challenge in surviving treated animals

	Challenge			
	Day 22		Day 23	
Group 1 Guinea pig no.	Test article	Vehicle	Test article	Vehicle
2	0	0	0	0
5	0	0	0	0
6	0	0	0	0
8	0	0	0	0
10	0	0	0	0

Skin reaction was assessed according to the scores described in the test (see section assessment of skin reactivity)

No. of positive animals at the challenge: 0

Result: **NEGATIVE**

Test article: [redacted]
Title : Skin sensitization test in guinea-pigs
RBM exp. : 970590
Vehicle : deionized water

TABLE 3. - Challenge in control animals

	Challenge			
	Day 22		Day 23	
Group 2 Guinea pig no.	Test article	Vehicle	Test article	Vehicle
11	0	0	0	0
12	0	0	0	0
13	0	0	0	0
14	0	0	0	0
15	0	0	0	0

Skin reaction was assessed according to the scores described in the test (see section assessment of skin reactivity)

No. of positive animals at the challenge: 0

Result: **NEGATIVE**

ATTACHMENT

Attachment No. 1 (p.1)

SENSITIVITY CHECK OF THE DUNKIN HARTLEY GUINEA-PIG IN THE SKIN SENSITIZATION STUDY

Attachment No. 1 (p.2)

TITLE

Sensitivity check of the Dunkin Hartley guinea-pig in the skin sensitization study.

PURPOSE

To assure guinea-pigs' continuing responsiveness and that the technical aspects of the procedure are being correctly followed.

This sensitivity check is required by the pertinent OECD and EEC Guidelines.

TEST METHOD

Magnusson's maximization test was followed.

The test method is in accordance with method B.6, Annex V to Directive 67/548 (EEC Directive 96/54, EEC Official Journal, No. L 248, September 30, 1996) and with Organization for Economic Cooperation and Development (OECD) Guidelines (section 4, subpart 406, Paris 1981 and subsequent updatings).

PROCEDURAL DETAILS

The test is conducted in compliance with the OECD-GLP in the testing of chemicals, [C(81) 30 (final)], regulations also enforced by the Italian Health Authority [D.M. dated June 26, 1986 as published in G.U. No. 198, dated August 27, 1986 and D.L. January 27, 1992, No. 120, as published in G.U. (Supplement) No. 40, February 18, 1992].

EXPERIMENTAL DATE

The study was conducted in December 1997/January 1998.

POSITIVE CONTROL

Identification:	2,4- dinitrochlorobenzene (DNCB) chosen on the basis of the EEC Guideline indication
Batch No.:	VV 218627
Expiry date:	May 2000
Producer:	Merck (Germany)
Vehicles:	vaselin oil

CONCENTRATIONS USED

Magnusson test:	0.02% for the intradermal injection 0.4% for the booster exposure 0.2% for the challenge application

FORMULATE PREPARATION

Intradermal injection

DNCB was dissolved in vaselin oil to obtain the 0.02% concentration.

For the injection in Freund's Complete Adjuvant (FCA) DNCB was dissolved in FCA at the concentration of 0.04% and then an equal volume of water for injection was added to obtain the final concentration of 0.02%.

Topical application

Test article concentrations 0.4% and 0.2% in vaseline oil were prepared for the booster and the challenge, respectively.

Attachment No. 1 (p. 4)

TEST DESCRIPTION

Magnusson test:	2 administrations, one per week, the first one by intradermal injection, the second one by 48h patch application (induction phase), and one exposure, 24h patch, 14 days after the last induction phase (challenge application).

TEST SYSTEM

Species and strain:	Dunkin Hartley albino guinea-pigs
Number and sex:	5 males treated with the positive control
Supplier:	Charles River Italia S.p.A. Via Indipendenza, 11 22050 Calco (Lecco)
Housing:	2 or 3 animals/cage in an air-conditioned room - temperature: 22 ± 2°C - air changes: about 20/h filtered on HEPA 99.97% - relative humidity: 55 ± 10% - artificial light: 12 h cycle (7 a.m. - 7 p.m.) - cage: wire cages (40.5x38.5x18h) with a stainless steel feeder
Animal identification:	by coloring different areas of the ears and paws.
Diet:	standard GLP diet - certificate coded 8 GP 22 (produced by Charles River Italia's feed licensee Mucedola S.r.l., Settimo Milanese, Italia)
Water:	"ad libitum".

Attachment No. 1 (p. 5)

TABLE 1. - Skin sensitization test in guinea-pigs (Magnusson test)

	Challenge			
	Day 22		Day 23	
Guinea pig no.	Positive control	Vehicle	Positive control	Vehicle
1	2	0	1	0
2	2	0	1	0
3	3	0	2	0
4	3	0	2	0
5	3	0	2	0

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REDACTED AS TO TRADE NAMES

RESEARCH TOXICOLOGY CENTRE - ROMA

[redacted]

ACUTE DERMAL TOXICITY STUDY IN THE RAT

FINAL REPORT

RTC Study Number: 8833-005

RTC Report Number: 8833-005/T/215/2002

Sponsor:
AUSIMONT S.p.A.
Via Lombardia, 20
20021 Bollate (MI)
Italy

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Reg. Soc. Trib. di Roma n° 2828/72
Cod. Fisc. 00653120584
Partita IVA: 00920611001

RTC Report Number: 8833-005/T/215/2002

COMPLIANCE STATEMENT

We, the undersigned, hereby declare that the following report constitutes a true and faithful account of the procedures adopted, and the results obtained in the performance of this study. The aspects of the study conducted by Research Toxicology Centre S.p.A. were performed in accordance with:

A. Commission Directive 1999/11/EC of 8 March 1999 adapting to technical progress the principles of good laboratory practice as specified in Council Directive 87/18/EEC on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (adoption of the *"OECD principles on Good Laboratory Practice – as revised in 1997"*) and subsequent revisions.

B. Decreto Legislativo 27 gennaio 1992, n. 120 published in the Gazzetta Ufficiale della Repubblica Italiana 18 Febbraio 1992 (adoption of the Commission Directive of 18 December 1989 adapting to technical progress the Annex to Council Directive 88/320/EEC on the inspection and verification of Good Laboratory Practice (90/18/EEC) and subsequent revisions.

C. Longobardi, Biol.D.
(Study Director): Date : 09 - 08 - 2002

J. Brightwell, Ph.D.
(Scientific Director): Date : 9.08.2002

RTC Report Number: 8833-005/T/215/2002

QUALITY ASSURANCE STATEMENT

(Relevant to those aspects of the study conducted by Research Toxicology Centre S.p.A.)

Study phases monitored by RTC's QAU according to current relevant Standard Operating Procedures	Quality Assurance Inspections (Day Month Year)		
	Inspection	Report to Study Director	Report to Company Management
PROTOCOL CHECK	30.07.2001	30.07.2001	30.07.2001
PROTOCOL AMENDMENT (1) CHECK	08.08.2002	08.08.2002	08.08.2002
PROCESS-BASED INSPECTIONS			
Allocation	22.05.2002	-	19.06.2002
Dose preparation	18.04.2002	-	02.05.2002
Body weight	15.03.2002	-	23.04.2002
Dosing (dermal)	18.04.2002	-	29.04.2002
Clinical observations	17.05.2002	-	18.07.2002
Necropsy	31.05.2002	-	14.06.2002
Other routine inspections of a procedural nature were carried out on activities not directly related to this type of study. The relevant documentation is kept on file although specific inspection dates are not reported here.			
FINAL REPORT Review of this report by RTC's QAU found the reported methods and procedures to describe those used and the results to constitute an accurate representation of the recorded raw data.			Review completed 09.08.2002

pp Nora Astolfi

M. M. Brunetti, Biol.D.
(Head of Quality Assurance)

09.08.2002
Date

Contents

Tables

1. SUMMARY

The acute toxicity of [redacted] was investigated following administration of a single dermal dose to the rat.

A single dose of 2000 mg/kg was administered to a group of 5 male and 5 female animals for a 24 hour period. A 14 day period followed after which all animals were killed and subjected to a necropsy examination.

No mortality occurred in male animals and no significant clinical signs were noted. One female was found dead on day 14 of the observation period. Hunched posture and a thin appearance were noted in a single animal just on Day 15. Examination of the treated site showed erythema and a desquamation on the treated site.

Changes in body weight in both males and females showed severely reductions.

Necropsy examination revealed no internal abnormalities.
Skin/fur staining was noted in the early decedent animal.

These results indicate that the test item, [redacted] has a slight toxic effect in the rat following dermal exposure over a 24 hour period at a level of 2000 mg/kg. On the basis of the observed results, the LD50 is estimated to be in excess of 2000 mg/kg. European Directives concerning the classification, packaging and labelling of dangerous substances would indicate the following:-

Classification : Not required
Symbol : None indicated
R Phrase : None indicated

2. INTRODUCTION

The purpose of this study was to assess the acute toxicity of the substance following dermal administration of a single dose to the rat. This will allow hazard assessment as required by European Directives concerning the classification, packaging and labelling of dangerous substances (67/548/EEC and subsequent revisions).

The procedures used were designed to meet the requirements of the test for acute dermal toxicity described in OECD guideline Number 402, adopted on 24th February 1987. Methods were in agreement with European Directives described by COM(93)638, a compilation of Council Directive 67/548/EEC. The rat was used, being a species indicated in the guidelines for this test. The route of administration is a potential route of exposure during manufacturing, handling or use of the substance.

The study was carried out at: Research Toxicology Centre S.p.A.
Via Tito Speri, 12
00040 Pomezia (Roma)
Italy

On behalf of: AUSIMONT S.p.A.
Via Lombardia, 20
20021 Bollate (MI)
Italy

The study started on 1st June 2001 with signing of the protocol by the Study Director. The experimental work described in this report started on 17th April 2002 with allocation of animals to treatment and ended on 2nd May 2002 with termination of the study. The study was completed on the date shown against the Study Director signature at the front of this report.

3. TEST ITEM

Details of the test item received at RTC were as follows:

Name	:	[redacted]
Lot or Batch Number	:	90215/92
Purity	:	90%
Concentration of active ingredient	:	20% in water
Expiry date	:	February 2004
Received from	:	AUSIMONT S.p.A.
Date received	:	11th February 2002
Amount received	:	500 grams
Description	:	Colourless liquid
Container	:	Opaque plastic tank.
Storage at RTC	:	Ambient conditions
RTC reference number	:	6533

Detailed characterisation of the test item was not undertaken at the testing facility. The determination of the identity, strength, purity, composition, stability and method of synthesis and/or derivation of the test item was the responsibility of the Sponsor. An aliquot of the test item was taken and will be retained within the RTC archives for a period of 10 years prior to disposal.

The test item was used in the condition supplied.

During handling of the substance, precautions were taken to reduce possible operator exposure. These included, but were not limited to, use of a face mask, eye protection and the wearing of gloves.

4. METHODS

Any deviations from the protocol are detailed within the text of the report. No deviations occurred which were considered to have compromised the purpose or conduct of the study.

Dated and signed records were made of all activities relating to the day by day conduct and maintenance of the study.

4.1 Animal management

4.1.1 Animal supply

Healthy rats of the Hsd: Sprague Dawley SD strain were ordered from and supplied by Harlan Italy S.r.l., 33049 San Pietro al Natisone (UD), Italy. Animals were ordered weighing 176 to 200 grams and aged approximately 6 to 8 weeks with female animals nulliparous and non-pregnant. They appeared to be in an acceptable condition following arrival on 5th April 2002. A pre-dose acclimatisation period of at least 5 days was allowed during which time the health status of the animals was assessed. Following arrival animals were permanently identified by a combination of ear notch and tattoo on the feet.

4.1.2 Animal husbandry

Animals were individually housed in polycarbonate cages measuring 42 x 26 x 18 cm and equipped with a stainless steel mesh lid and floor. Cages were suspended over trays holding an absorbent material which was inspected daily and changed as necessary. Throughout the study each cage was identified by a colour coded label recording the study number, animal number and the details of treatment. This colour coding matched the corresponding colour coded formulation container.

Animal room controls were set to maintain temperature within the range of 22 ± 2°C and relative humidity within the range of 55 ± 15%. Actual conditions were recorded.

The room was lit by fluorescent tubes controlled to give an artificial cycle of 12 hours light and 12 hours dark each day.

4.1.3 Water and diet

Animals were offered drinking water supplied to each cage via a water bottle and a commercially available laboratory rodent diet (Altromin MT, Altromin, D-32770 Lage, Postfach 1120, Germany) *ad libitum* throughout the study.

There was no information to indicate that any component present in the drinking water or diet was at a level likely to interfere with the purpose or conduct of the study.

4.2 Experimental design

A single group of 5 male and 5 female animals were dosed at a level of 2000 mg/kg.

4.2.1 Selection and animal preparation

The required number of animals for the study was allocated to treatment. Individuals were identified within the study by a combination of ear notch (units) and tattoo on the feet. Males were identified with even numbers and females with odd numbers.

A single group of 5 males and 5 females were allocated to the study as follows:-

Dose level (mg/kg)	Animal number	
	Males	Females
2000	12, 14, 16, 18, 20	11, 13, 15, 17, 19

All animals were within a body weight range of 215 to 294 grams when prepared for dosing. The fur was removed from the dorsal surfaces of the trunk over an area estimated to be at least 10% of the total body surface of each animal. An electric clipper with suitable blade was used and care was taken to avoid any irritation or damage to the skin.

4.2.2 Dosing

On Day 1 of the study, the amount of supplied test item to be administered, at a dose level of 2000 mg/kg body weight, was calculated for each animal according to body weight. This was spread onto the prepared skin site using a patch of surgical gauze measuring 2.5 x 2.5 cm. The gauze patch was then placed onto the animal's skin, with the test item in direct contact with the skin. A strip of aluminium foil was placed over the treated site and the whole assembly held in place by encircling the trunk of the animal with a length of elastic adhesive bandage. All animals were treated in the same manner.

After a period of 24 hours, the adhesive bandage and gauze dressings were removed. The treated skin was washed gently with warm water to remove residual test item.

4.2.3 Mortality and morbidity

Throughout the study all animals were checked twice daily.

4.2.4 Clinical signs

Animals were observed for clinical signs immediately upon dosing, approximately 1 and 4 hours after dosing and daily thereafter for a total of 14 days.

4.2.5 Body weight

All animals were weighed on allocation to the study (Day -1), immediately prior to dosing (Day 1) and at weekly intervals thereafter (Days 8 and 15).
The animal found dead was weighed when found.

4.2.6 Termination

Surviving animals were killed on Day 15 by carbon dioxide narcosis.

They were subjected to a gross necropsy examination for both external and internal abnormalities. The cranial, thoracic and abdominal cavities were opened to allow examination of their contents. Larger organs were sectioned. Particular attention was paid to the treated site.

4.3 Classification

The results obtained on testing were used to classify the test item according to the requirements of European Directives concerning the classification, packaging and labelling of dangerous substances (67/548/EEC and subsequent revisions).

4.4 Archives

The raw data and documentation generated during the course of this study will be retained at RTC for a period of 5 years after which the Sponsor will be contacted for instructions regarding despatch or disposal of the material.

5. RESULTS

5.1 **Clinical signs** (Table 1)

No mortality occurred in male animals. Clinical signs were limited to dark staining around the eyes, noted on the day of dosing.
One female was found dead on day 14 of the observation period. Erythema and/or desquamation on the treated site were noted from day 4 to day 14 of the observation period. Hunched posture and a thin appearance were noted in one animal on day 15.

5.2 **Body weight** (Table 2)

Changes in body weight in both males and females showed severe reductions in a number of animals.

5.3 **Necropsy** (Table 3)

No abnormalities were found on necropsy of animals on termination of the study.
External abnormalities were limited to a skin/fur staining, noted in the early decedent animal.

6. CONCLUSION

The results of this study indicate that the test item, [redacted], has a slight toxic effect in the rat following dermal exposure over a 24 hour period at a level of 2000 mg/kg. A single animal died and therefore, the LD50 is estimated to be in excess of 2000 mg/kg.

European Directives concerning the classification, packaging and labelling of dangerous substances would indicate the following:-

Classification : Not required
Symbol : None indicated
R Phrase : None indicated

ACUTE DERMAL TOXICITY STUDY IN THE RAT

RTC STUDY NUMBER: 8833-005

TABLE 1 - CLINICAL SIGNS

DOSE LEVEL: 2000 mg/kg

MALES - Number of animals with signs (Number of animals dosed = 5)

Sign observed	Day 1 Time 0	1	2	3	Day 2	3	4	5	6	7
No abnormalities detected	5	5	4	4	5	5	5	5	5	5
Dark staining around eyes	0	0	1	1	0	0	0	0	0	0
MORTALITY	0	0	0	0	0	0	0	0	0	0

Sign observed	Day 8	9	10	11	12	13	14	15
No abnormalities detected	5	5	5	5	5	5	5	5
MORTALITY	0	0	0	0	0	0	0	0

KEY Day 1 : Time 0 : At dosing
Time 1 : Approximately 1 hour after dosing
Time 2 : Approximately 2 hours after dosing
Time 3 : Approximately 4 hours after dosing

ACUTE DERMAL TOXICITY STUDY IN THE RAT

RTC STUDY NUMBER: 8833-005

TABLE 1 - Continued

DOSE LEVEL: 2000 mg/kg

FEMALES - Number of animals with signs (Number of animals dosed = 5)

Sign observed	Day 1 Time 0	1	2	3	Day 2	3	4	5	6	7
No abnormalities detected	5	5	5	5	5	5	3	3	4	4
Erythema - treated site	0	0	0	0	0	0	2	2	1	1
Desquamation - treated site	0	0	0	0	0	0	0	0	1	1
MORTALITY	0	0	0	0	0	0	0	0	0	0

Sign observed	Day 8	9	10	11	12	13	14	15
No abnormalities detected	4	4	4	4	4	4	3	3
Erythema - treated site	1	1	1	0	0	0	0	0
Desquamation - treated site	1	1	1	1	1	1	1	1
Hunched posture	0	0	0	0	0	0	0	1
Thin appearance	0	0	0	0	0	0	0	1
MORTALITY	0	0	0	0	0	0	1	0

KEY Day 1 : Time 0 : At dosing
Time 1 : Approximately 1 hour after dosing
Time 2 : Approximately 2 hours after dosing
Time 3 : Approximately 4 hours after dosing

ACUTE DERMAL TOXICITY STUDY IN THE RAT

RTC STUDY NUMBER: 8833-005

TABLE 2 - BODY WEIGHT

DOSE LEVEL: 2000 mg/kg

Sex	Animal identity number	Body weight (g) on day				Change in body weight (g)
		-1	1	8	15	Days 1 - 15
	12	277	285	275	316	31
M	14	269	273	256	245	-28
A	16	271	278	271	261	-17
L	18	280	289	298	320	31
E	20	283	294	308	335	41
S						
	Mean	276.0	283.8	281.6	295.4	11.6
	S.Dev.	5.9	8.4	21.1	39.8	31.6
	11	209	217	168	-	-
F	13	208	215	214	186	-29
E	15	217	227	247	251	24
M	17	228	235	199	149	-86
A	19	214	219	215	218	-1
L						
E	Mean	215.2	222.6	208.6	201.0	-23.0
S	S.Dev.	8.0	8.3	28.7	43.7	47.3

- = Decedent

ACUTE DERMAL TOXICITY STUDY IN THE RAT

RTC STUDY NUMBER: 8833-005

TABLE 3 - NECROPSY

DOSE LEVEL: 2000 mg/kg

Sex	Animal number	Tissue/ organ	Finding
MALES	12		Terminal kill No abnormalities found
	14		Terminal kill No abnormalities found
	16		Terminal kill No abnormalities found
	18		Terminal kill No abnormalities found
	20		Terminal kill No abnormalities found
FEMALES	11		Early decedent External surfaces Skin, staining generalised brown No abnormalities found
	13		Terminal kill No abnormalities found
	15		Terminal kill No abnormalities found
	17		Terminal kill No abnormalities found
	19		Terminal kill No abnormalities found

REDACTED AS TO TRADE NAMES

RESEARCH TOXICOLOGY CENTRE - ROMA

[redacted]

ACUTE DERMAL IRRITATION STUDY IN THE RABBIT

FINAL REPORT

RTC Study Number: 8835-005

RTC Report Number: 8835-005/T/171/2001

Sponsor:
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Reg. Soc. Trib. di Roma n. 2626/72
Cod. Fisc. 00655120584
Partita IVA 00920611001

RTC Report Number: 8835-005/T/171/2001

COMPLIANCE STATEMENT

We, the undersigned, hereby declare that the following report constitutes a true and faithful account of the procedures adopted, and the results obtained in the performance of this study. The aspects of the study conducted by Research Toxicology Centre S.p.A. were performed in accordance with:

A. Commission Directive 1999/11/EC of 8 March 1999 adapting to technical progress the principles of good laboratory practice as specified in Council Directive 87/18/EEC on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (adoption of the *"OECD principles on Good Laboratory Practice – as revised in 1997"*) and subsequent revisions.

B. Decreto Legislativo 27 Gennaio 1992, n. 120 published in the Gazzetta Ufficiale della Repubblica Italiana 18 Febbraio 1992 (adoption of the Commission Directive of 18 December 1989 adapting to technical progress the Annex to Council Directive 88/320/EEC on the inspection and verification of Good Laboratory Practice (90/18/EEC)) and subsequent revisions.

C. Longobardi, Biol.D.
(Study Director): Date : 08 - 08 - 2002

J. Brightwell, Ph.D.
(Scientific Director): Date : 9.08.2002

RTC Report Number: 8835-005/T/171/2001

QUALITY ASSURANCE STATEMENT

(Relevant to those aspects of the study conducted by Research Toxicology Centre S.p.A.)

Study phases monitored by RTC's QAU according to current relevant Standard Operating Procedures	Quality Assurance Inspections (Day Month Year)		
	Inspection	Report to Study Director	Report to Company Management
PROTOCOL CHECK	17.07.2001	17.07.2001	17.07.2001
PROCESS-BASED INSPECTIONS			
Allocation	21.02.2002	-	19.03.2002
Dose preparation	18.04.2002	-	02.05.2002
Body weight	15.03.2002	-	23.04.2002
Dosing (dermal)	18.04.2002	-	29.04.2002
Clinical observations	11.02.2002	-	13.02.2002
Other routine inspections of a procedural nature were carried out on activities not directly related to this type of study. The relevant documentation is kept on file although specific inspection dates are not reported here.			
FINAL REPORT Review of this report by RTC's QAU found the reported methods and procedures to describe those used and the results to constitute an accurate representation of the recorded raw data.			Review completed 09.08.2002

pp Maria Astolfi

M. M. Brunetti, Biol.D.
(Head of Quality Assurance)

09.08.2002
Date

Contents

1. SUMMARY

The acute dermal irritation of [redacted] was investigated in the rabbit.

A 0.5 ml aliquot of the substance was applied to the prepared dorsal skin of 3 animals for a period of 4 hours. The resulting reaction to treatment was assessed 1, 24, 48 and 72 hours after the end of the exposure period.

No irritation was apparent following a 4 hour period of exposure to the test item.

There was no indication of a systemic effect of treatment.

Body weight changes were not remarkable.

These results indicate that [redacted] has no irritant effect on the skin of the rabbit and European Directives concerning the classification, packaging and labelling of dangerous substances (67/548/EEC and subsequent revisions) would indicate the following:-

Classification : Not required
Symbol : None indicated
R Phrase : None indicated

2. INTRODUCTION

The purpose of this study was to investigate the degree of irritation produced on the intact skin of the rabbit following 4 hours contact with the test item, [redacted]. This allowed hazard assessment as required by European Directives concerning the classification, packaging and labelling of dangerous substances (67/548/EEC and subsequent revisions).

The procedures used were designed to meet the requirements of the test for acute dermal irritation described by OECD guideline Number 404, adopted on 17th July 1992. These methods are in agreement with those of B4 detailed in COM(93)638, a compilation of Council Directive 67/548/EEC. The rabbit was used, being a species indicated in the guidelines for this test. The route of administration is a potential route of exposure during manufacturing, handling or use of the substance.

The study was carried out at: Research Toxicology Centre S.p.A.
Via Tito Speri, 12
00040 Pomezia (Roma)
Italy

On behalf of: AUSIMONT S.p.A.
Via Lombardia, 20
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Italy

The study started on 1st June 2001 with signing of the protocol by the Study Director. The experimental work described in this report started on 8th April 2002 with allocation of animals to the study and ended on 12th April 2002 with termination of the study. The study was completed on the date shown against the Study Director signature at the front of this report.

3. TEST ITEM

Details of the test item received at RTC were as follows:

Name	: [redacted]
Lot or Batch Number	: 90215/92
CAS Number	: 330809-80-8
Expiry date	: February 2004
Purity	: >90% (referred to dry salt)
Concentration of active ingredient	: 20% in water
Received from	: AUSIMONT S.p.A.
Date received	: 11th February 2002
Amount received	: 500 grams
Description	: Colourless liquid
Container	: Opaque plastic container
Storage at RTC	: Ambient condition
RTC reference number	: 6533

Detailed characterisation of the test item was not undertaken at the testing facility. The determination of the identity, strength, purity, composition, stability and method of synthesis and/or derivation of the test item was the responsibility of the Sponsor. A certificate of analysis, supplied by the Sponsor can be found in Addendum 1 of this report. An aliquot of the test item was taken and will be retained within the RTC archives for a period of 10 years prior to disposal.

The test item was used in the condition supplied.

During handling of the substance, precautions were taken to reduce possible operator exposure. These included, but were not limited to, use of a face mask, eye protection and the wearing of gloves.

4. METHODS

Any deviations from the protocol are detailed within the text of the report. No deviations occurred which were considered to have compromised the purpose or conduct of the study. Dated and signed records of all activities relating to the day by day conduct and maintenance of the study were made.

4.1 Animals, husbandry and diet

4.1.1 Animals

Female rabbits of the New Zealand White strain were ordered from, and supplied by, Charles River Italia S.p.A., (Como) and bred by P.O.A.D.A., Mandello Lario, (CO), Italy and were delivered to the testing facility on 28th March 2002. Animals were ordered weighing approximately 2 kg and 9 to 11 weeks of age, nulliparous and non-pregnant.

Animals were examined following arrival and identified in the ear by tattoo with an individual number. An acclimatisation period of at least 10 days was allowed before dosing. The health status of animals was assessed during this time. Following arrival the animals were treated with Pyrantel 6% at a dose level of 0.4 ml/animal.

4.1.2 Housing

Animals were individually housed in stainless steel cages measuring 69 x 45 x 51 cm and equipped with grid floors. Cages were suspended over trays and each tray held an absorbent material which was inspected daily and changed as necessary. Throughout the study each cage was identified by a colour coded label recording the study number, animal number and the details of treatment. This colour coding matched the corresponding colour coded formulation container.

Animal room controls were set to maintain temperature within the range of 17 to 21°C and relative humidity within the range of 40 to 70%. This was a deviation from the study protocol, in which a range of 22 ± 2°C was erroneously indicated. Actual conditions were recorded.

Artificial lighting by fluorescent tubes was set to a 24 hour cycle of 12 hours light/12 hours dark.

4.1.3 Water and diet

Animals were offered drinking water supplied to each cage via water bottles and a commercially available anti-biotic free pelleted laboratory diet (Altromin MSK, Altromin, D-32770 Lage, Postfach 1120, Germany) *ad libitum* throughout the study.

There was no information to indicate that any component present in the drinking water or the diet was at a level likely to interfere with the purpose or conduct of the study.

4.2 Animal selection and preparation

Animals were selected for treatment from available stock. The day before dosing commenced the dorsal surfaces of the trunk of each animal, on both sides of the mid-line, were clipped free of hair using an electric clipper equipped with a suitable blade. Care was taken to avoid damage to the skin.

4.3 Dosing

Each selected animal was removed from its cage and gently restrained. A 0.5 ml aliquot of the test item was spread evenly over a gauze square measuring 2.5x2.5 cm. The gauze square was then placed onto the animal's skin with the test item in direct contact with the skin. A strip of aluminium foil was placed over the treated site and the whole assembly held in place by encircling the trunk of the animal with a length of elastic adhesive bandage, this forming a semi-occlusive barrier.

After a period of 4 hours, the adhesive bandage and gauze patch were removed from the treated site of each animal which was cleaned by gentle swabbing of the skin with cotton wool soaked in water at approximate body temperature.

4.4 Observations

The treated skin site on each animal was examined approximately 1 hour after the end of the exposure period. Additional examinations were performed 24, 48 and 72 hours after dosing.

Animals were examined under standard conditions and any observed irritation, in comparison with adjacent untreated skin, was allocated a numerical value based on the table below.

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 (beet redness) to eschar formation preventing grading of erythema	4

Oedema formation	**Value**
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 mm)	3
Severe oedema (raised more than 1 mm and extending beyond area of exposure)	4

4.5 Body weight

All animals were weighed on preparation (Day -1) and on termination of the study (Day 4).

4.6 Termination

The study was terminated after 72 hours, the objectives having been achieved.

After termination animals were killed by the intravenous injection of a suitable anaesthetic agent. No necropsy examination was undertaken.

4.7 Classification

The results obtained on testing were used to classify the test item according to the requirements of European Directives concerning the classification, packaging and labelling of dangerous substances (67/548/EEC and subsequent revisions).

The numerical scores obtained on assessing irritation at the 24, 48 and 72 hour examinations were summed and a mean calculated for each animal. The values for erythema and eschar formation were calculated separately from those obtained on assessing oedema. When the mean value for either erythema or oedema equalled or exceeded 2.0, in two or more animals, the test item would be considered irritant to the skin. Labelling would then be required with the risk phrase (R 38) "Irritating to the skin" and symbol "Xi".

4.8 Archives

All raw data and documentation generated during the course of this study will be retained at RTC for a period of 5 years after which the Sponsor will be contacted regarding despatch or disposal of the material.

5. RESULTS

5.1 Irritation (Tables 1 and 2)

No irritation or other reaction was apparent on the treated skin of any animal.

5.2 Systemic effects

There was no indication of a systemic effect of treatment.

5.3 Body weight (Table 3)

Changes in body weight during the course of the study were not remarkable.

6. CONCLUSION

The results of this study indicate that the test item, [redacted], has no irritant effect on the skin of the rabbit.

European Directives concerning the classification, packaging and labelling of dangerous substances (67/548/EEC and subsequent revisions) would indicate the following:-

Classification : Not required
Symbol : None indicated
R Phrase : None indicated

ACUTE DERMAL IRRITATION STUDY IN THE RABBIT

RTC STUDY NUMBER: 8835-005

TABLE 1 - IRRITATION - MEAN VALUES

Animal Number	Erythema	Oedema
315	0.0	0.0
317	0.0	0.0
319	0.0	0.0
The mean score recorded for each animal is the average of the individual scores observed at the 24, 48 and 72 hours examinations		

ACUTE DERMAL IRRITATION STUDY IN THE RABBIT

RTC STUDY NUMBER: 8835-005

TABLE 2 - IRRITATION - INDIVIDUAL FINDINGS

Animal Number: 315			
Time of examination	Erythema	Oedema	Additional comments
1 hour	0	0	-
24 hours:	0	0	-
48 hours:	0	0	-
72 hours:	0	0	-

Animal Number: 317			
Time of examination	Erythema	Oedema	Additional comments
1 hour	0	0	-
24 hours:	0	0	-
48 hours:	0	0	-
72 hours:	0	0	-

Animal Number: 319			
Time of Examination	Erythema	Oedema	Additional comments
1 hour	0	0	-
24 hours:	0	0	-
48 hours:	0	0	-
72 hours:	0	0	-

ACUTE DERMAL IRRITATION STUDY IN THE RABBIT

RTC STUDY NUMBER: 8835-005

TABLE 3 - BODY WEIGHT - INDIVIDUAL VALUES

Animal Number	Body weight (kg) on Day:-		Change in body weight (kg)
	Day –1	Day 4	Day –1 to 4
315	2.6	2.7	0.1
317	2.5	2.5	0.0
319	2.8	2.8	0.0

ACUTE DERMAL IRRITATION STUDY IN THE RABBIT

RTC STUDY NUMBER: 8835-005

ADDENDUM 1 - CERTIFICATE OF ANALYSIS OF THE TEST ITEM

AUSIMONT S.p.A.

Bollate, 30 gennaio 2002

Certificato di analisi

Prodotto:	[redacted]
Batch:	90215/92
Concentrazione della soluzione:	20 % peso
PH della soluzione:	6.6

Caratteristiche del precursore acido:

Peso equivalente:	534
Metodo:	titolazione acidimetrica